Patterns of psychotropic drug prescribing to children and adolescents attending Australian general practices from 2011 to 2018

A thesis submitted

by

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Abstract

Prescribing of psychotropic drugs to children and adolescents has increased worldwide over several decades despite concerns about the safety and effectiveness of these drugs in paediatric populations. To date, no studies have examined psychotropic prescribing to children and adolescents in Australian primary care settings. This thesis aims to examine patterns of psychotropic prescribing from 2011 to 2018 for children aged 0-18 years, using electronic health records in the large primary care database, MedicineInsight.

This thesis consisted of three main studies. Firstly, trends in the prevalence of five classes of psychotropics were examined: antidepressants, antipsychotics, attention deficit hyperactivity disorder (ADHD) drugs, anxiolytics and sedatives/hypnotics. The neurohormone melatonin was examined separately. The second study examined patterns of antipsychotic prescribing, focusing on off-label prescribing (for conditions not approved by Australia's drug regulatory body) comparing 2011 to 2017. An examination of prescribing by social disadvantage was included, and an analysis of psychotropic co-prescribing. The third study examined the extent to which patients receiving antipsychotics were undergoing guideline-recommended monitoring for adverse events. Health monitoring included weight, waist circumference, blood pressure, blood lipids, glucose and liver function. The extent of off-label prescribing for the other four psychotropic classes was also briefly examined.

Three of the five classes of psychotropics demonstrated an increase in prescribing from 2011 to 2018. The largest increase was for ADHD drugs (+9.6%, 95% CI [8.8, 10.5] annual; overall 95.8%), followed by antipsychotics (+6.2%, 95% CI [5.1, 7.2] annual; overall +62.8%) and antidepressants (+4.5%, 95% CI [4.0, 5.0] annual; overall +42.8%). The neurohormone, melatonin, showed the highest increase in prescribing (+24.7%, 95% CI [23.7, 25.8] annual; overall +606.7%). Anxiolytic prescribing remained stable, while sedative/hypnotic prescribing declined significantly (-6.5%, 95% CI [-8.0, -5.0] annual; overall -40.2%) For the antidepressants, antipsychotics and ADHD drugs there was a monotonic increase across IRSAD quintiles, with more patients receiving prescriptions as socio-economic disadvantage increased.

Off-label antipsychotics prescribing increased from 69.8% of patients in 2011 to 79.7% in 2017. Antipsychotics were mainly prescribed to children and adolescents with depression/anxiety diagnoses in both years (26.8% of patients, 2011; 30.8%, 2017). 70% of

all patients were co-prescribed another psychotropic with the antipsychotic in both years. Off-label prescribing of antidepressants and melatonin was also prevalent in general practice, and largely guideline-concordant, although near 100% off-label.

Monitoring of health parameters in patients receiving antipsychotics was low. Within 12 months of incident prescription, 55.9% had at least one parameter measured at least once. Weight was measured most frequently (39.1%), followed by blood pressure (29.0%) and glucose (12.9%). Using target trial methodology to compare antipsychotic users to non-users, a significant but small increase in monitoring of patients starting antipsychotics was observed. Antipsychotic users recorded an average 1.157 visits with any kind of monitoring occurring within 12 months, compared to 0.691 for non-users.

This thesis highlights problematic psychotropic prescribing to children and adolescents in Australian primary care settings. Public health initiatives are needed to curb the trends in psychotropic prescribing in the paediatric population and improve health outcome monitoring.

Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint award of this degree.

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I acknowledge the support I have received for my research through the provision of an Australian Government Research Training Program Scholarship.

Signed:

___ _____

Julie Klau (PhD candidate)

Date: 5 May 2024

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I came to this PhD rather late in my career. The wealth of knowledge gathered from a lifetime of experiences, and a passion for improving health outcomes for children with mental disorders, led me to work as a research assistant with the then recently-formed Critical and Ethical Mental Health group (CEMH), led by Professor Jon Jureidini at the Robinson Research Institute at the University of Adelaide. A few years later I embarked on this PhD thesis.

The list of acknowledgements is long.

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Publications included in this thesis

Published

1. Trends in prescribing of psychotropics to children and adolescents (Chapter 4)

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1. Cardiometabolic monitoring in children and adolescents using antipsychotics

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Other related publications during candidature but not included in the thesis

1. Effects of inadequate blinding of trial participants on depression outcomes in adolescents.

Jureidini J, Moncrieff J, Klau J, Aboustate N, Raven M (2024). Treatment guesses in the Treatment for Adolescents with Depression Study: Accuracy, unblinding and influence on outcomes. *Australian and New Zealand Journal of Psychiatry* 58(4): 355-64.

Conference presentations and awards arising from this thesis

1. 2021 Florey Postgraduate Research Conference, Adelaide, Australia

   Oral presentation “More kids being prescribed psychotropic drugs” (see Appendix 15).

2. 2022 Florey Postgraduate Research Conference, Adelaide, Australia

   Oral presentation “Antipsychotic prescribing patterns in children and adolescents in Australian general practice” (see Appendix 16).

Awards

2022 awarded the Vernon Roy East Prize for mental health research.

Abbreviations

Abbreviations for mental and physical conditions

ADHD	Attention deficit hyperactivity disorder
AN	Anorexia nervosa
ARFID	Avoidant restrictive food intake disorder
ASD	Autism spectrum disorder
ASWPD	Advanced sleep-wake phase disorder
BED	Binge eating disorder
BN	Bulimia nervosa
CD	Conduct disorder
CDD	Childhood disintegrative disorder
DBD	Disruptive behaviour disorder
DSWPD	Delayed sleep-wake phase disorder
ED	Eating disorder
FEP	First episode psychosis
GAD	Generalised anxiety disorder
ISWRD	Irregular sleep-wake rhythm disorder
LD	Learning disorder
MDD	Major depressive disorder
MetS	Metabolic syndrome
N24SWD	Non-24-hour sleep-wake rhythm disorder
OCD	Obsessive-compulsive disorder
ODD	Oppositional defiant disorder
PD	Personality disorder
PDD	Pervasive developmental disorder
PTSD	Post-traumatic stress disorder
SAD	Social anxiety disorder
SUD	Substance use disorder
T2DM	Type 2 diabetes mellitus
TRD	Treatment resistant depression

Abbreviations for treatments

CBT	Cognitive behaviour therapy
FGA	First-generation antipsychotic
FPS	Focussed psychological strategies
IPT	Interpersonal psychotherapy
SGA	Second-generation antipsychotic
SNRI	Selective serotonin noradrenaline reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant

Other abbreviations

AACAP	American Academy of Child and Adolescent Psychiatry
AAP	American Academy of Pediatrics
ABS	Australian Bureau of Statistics
AGREE	Appraisal of guidelines for research and evaluation
AIPW	Augmented inverse probability weighting
APA	American Psychiatric Association
ASGS	Australian Statistical Geography Standard
ATC	Anatomical Therapeutic Chemical
BAP	British Association of Psychopharmacology
CABF	Child and Adolescent Bipolar Foundation
CAMHW	Child and Adolescent Mental Health and Wellbeing
CANMAT	Canadian Network for Mood and Anxiety Treatments
CDC	Centers for Disease Control
CEBM	Centre for Evidence Based Medicine
CHIP	Children's Health Insurance Program
COI	Conflict of interest
CPA	Canadian Psychiatric Association
CPG	Clinical practice guideline
CPP	Clinical practice point
DAG	Directed acyclic graph
DSM	Diagnostic and Statistical Manual of Mental Disorders
DUSC	Drug Utilisation Sub Committee
EHR	Electronic health record
EMA	European Medicines Agency
FDA	Food and Drug Administration
FGA	First-generation antipsychotic
GLAD-PC	Guidelines for Adolescent Depression in Primary Care
GP	General practitioner
GPMHSC	General Practice Mental Health Standards Collaboration
GPP	Good practice point
GRADE	Grading of recommendations, assessment, development and evaluations
HbA1c	HbA1c haemoglobin A1c

HCP	Health care professional
HDL	High-density lipoprotein cholesterol
HSD	Highly specialised drugs
ICD-10	International Classification of Diseases [Version 10]
IER	Index of Economic Resources
IRSAD	Index of Relative Socio-economic Advantage and Disadvantage
ISBD	International Society for Bipolar Disorders
LDL	Low-density lipoprotein cholesterol
MBS	Medicare Benefits Schedule
MHRA	Medicines and Healthcare products Regulatory Agency
MHST	Mental health skills training
MHTP	Mental health treatment plan
NHMRC	National Health and Medical Research Council
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NP	Nurse practitioner
NPS	National Prescribing Service
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PI	Product information
RACGP	Royal Australian College of General Practitioners
RACP	Royal Australasian College of Physicians
RANZCP	Royal Australian and New Zealand College of Psychiatrists
RCHM	Royal Children's Hospital Melbourne
RCT	Randomised controlled trial
RIAT	Restoring Invisible and Abandoned Trials
SDH	Social determinants of health
SIGN	Scottish Intercollegiate Guidelines Network
TADS	Treatment for adolescents with depression study
TGA	Therapeutic Goods Administration
UHR	Ultra-high risk
WHO	World Health Organization
WSFBP	World Federation of Societies of Biological Psychiatry

1 Introduction

1.1 Background

Prescriptions for psychotropic medications to children and adolescents have been on the rise worldwide in recent decades [1-7]. This is despite ongoing concerns about the efficacy and safety of these drugs in paediatric populations [1-11]. Studies have also found psychotropic prescribing rates have increased more rapidly in children and adolescents compared to adults [12, 13], raising concerns about overmedicating young people with mild psychological problems [12].

There is limited research on prescribing trends of psychotropic drugs to children and adolescents in Australia, and none specific to primary care. To address this knowledge gap, this thesis examines the management of paediatric patients aged 0-18 years who were prescribed psychotropic agents from 2011 to 2018 using a large database of electronic health records (EHRs) from Australian general practices, MedicineInsight.

The present chapter briefly describes the Australian health system, prevalence of child and adolescent mental disorders, and government regulation of paediatric medications in Australia (Chapter 1). Chapter 2 extensively summarises and compares Australian and international treatment guidelines for mental disorders in children and adolescents, with a focus on the use of psychotropics. Chapter 3 addresses methodological considerations. This is followed by three papers examining patterns of prescribing in Australia, specifically: trends in prescribing of all psychotropics to children and adolescents in Australian primary care (Chapter 4), off-label prescribing patterns for one class – antipsychotics (Chapter 5), and rates of monitoring for cardiometabolic health outcomes for patients receiving antipsychotics (Chapter 6). Chapter 7 examines diagnostic patterns in MedicineInsight and contrasts the findings with the most recent survey of Child and Adolescent Mental Health and Wellbeing (CAMHW) and international studies.

This thesis examined prescribing in relation to both approvals of the Australian regulatory body, the Therapeutic Goods Administration (TGA), and Australian and international clinical practice guidelines. The findings are presented in Chapter 8 and discussed further in the general discussion (Chapter 9). Finally, Chapter 9 brings together all findings and explores the implications for future research and health policies.

1.2 Mental health of children and adolescents in Australia and internationally

Public health surveillance of mental disorders in children and adolescents can be used to monitor trends and highlight areas of need [14]. Information on the prevalence of paediatric mental disorders in Australia is sparse, and to date, no studies have reported the prevalence of recorded mental disorders in Australian general practice. In this section, findings from the most recent Australian Child and Adolescent Mental Health and Wellbeing survey (CAMHW) are summarised and compared to international findings. Changes in prevalence over the last few decades are also discussed.

1.2.1 Australian statistics

The prevalence of mental health disorders in children and adolescents in Australia is commonly cited using information from the second CAMHW survey [15] that was conducted between 2013/2014 (see Table 1.1). The CAMHW survey is an Australian Government Department of Health funded initiative designed to assess the prevalence of common mental disorders in children and adolescents based on the Child Behaviour Checklist. The 2013/2014 survey interviewed parents and carers of 6,310 children and adolescents aged 4-17 years and included a self-report questionnaire component for those aged 11-17 years. 12-month prevalence rates were reported for seven disorders: major depressive disorder (MDD), anxiety disorder (social phobia, separation anxiety disorder, generalised anxiety disorder [GAD], obsessive-compulsive disorder [OCD]), conduct disorder (CD), and attention-deficit/hyperactivity disorder (ADHD).

1.2.2 International statistics

Surveys similar to the CAMHW are regularly performed in the United States and England. In the US, there are at least nine useful surveillance systems for monitoring the prevalence of mental disorders in children, which were summarised by two Centers for Disease Control (CDC) reports in 2013 [16] and 2019 [14]. Prevalences from the 2019 CDC report by Bitsko and colleagues [14] are reported in Table 1.1. Despite such regular and comprehensive surveying in the US, however, monitoring of mental disorder prevalences in children is considered poor, with no comprehensive surveillance system providing a reliable estimate of numbers of children with mental disorders [14]. There are also a number of disorders that are not reported, such as bipolar disorder, OCD and some other specific anxiety disorders [14].

The most recent English mental health survey sampled 2-19-year-olds on the National Health Service (NHS) patient register in 2016 [17]. Similar to the CAMHW, young people and their

parents were interviewed face-to-face, and an anonymous self-completed questionnaire was included for 11-19-year-olds. The survey included the DABWA (Development and Well-Being Assessment) module [18] that allowed assessment of less common childhood mental disorders [17, 18]. Information was collected by trained lay interviewers and further assessed by clinical raters with reference to the International Classification of Disease 10th Revision (ICD-10) [17]. These prevalence data for 2017 are summarised in Table 1.1.

Other research teams have carried out systematic reviews and meta-analyses of published papers on the international prevalence of mental disorders in children and adolescents [19-21]. A meta-analysis by Polanczyk et al. (2015) analysed 41 studies from 27 countries with publication dates ranging from 1988 to 2012 (data collection occurred between 1983 and 2006) [21]. This study found a worldwide pooled prevalence of 13.4% for any mental disorder. Further, variability in prevalence estimates between countries was not explained by geographic location or year of data collection [21]. Another more recent systematic review and meta-analysis of 11 high-income countries by Barican and colleagues [19] also found a similar prevalence rate of 12.7% (Table 1.1). This meta-analysis included studies published from 2003 to 2020.

In both the Barican and Polanczyk meta-analyses, the researchers selected studies with representative sampling, use of standardised diagnostic instruments (e.g., derived according to Diagnostic and Statistical Manual [DSM] or ICD standards), reporting a minimum of three diagnostic groups of disorders, and including an assessment of functional impairment [19, 21].

Survey studies chosen for inclusion in Table 1.1 used similar robust methodologies to the Australian CAMHW survey, with reference to DSM and ICD diagnostic codes and including assessments of functional impairment or severity. The time periods covered were also similar. Two comprehensive meta-analyses of studies are also included. Rates from all included studies in Table 1.1 are remarkably similar and appear relatively stable across time period and country.

Table 1.1 Summary of Australian and international studies reporting on the prevalence of mental disorders in children and adolescents

Author	**CAMHW survey (Lawrence et al. (2015))[1]**					**NHS Digital (Sadler et al. (2018))[2]**	**CDC (Bitsko et al. (2022))[3,a]**	**Barican et al. (2022)[4]**	**Polanczyk et al. (2015)[5]**
Age range	4-17 years					5-19 years	3-17 years	4-18 years	6-18 years
Time period	2013/2014					2017	2013-2019	1993-2017	1983-2006
Population	Australia					England	United States	High-income countries	All countries
Prevalence period	30 day %	12 month %	12 month % mild	12 month % moderate	12 month % severe	Unspecified[b]	Varied	Most 12-month	Varied
Any disorder	9.3	13.9	8.3	3.5	2.1	12.8[c]	13.9[d,e] [2017]	12.7	13.4
Schizophrenia						<0.1		0.1	
Bipolar disorder						<0.5		0.3	
Behavioural disorders[f]						4.6			
Disruptive behaviour disorders							8.9 [7.0][e]	4.6	5.7
Oppositional defiance disorder						2.9		3.3	3.6
Conduct disorder	2.1	2.1	1.2	0.5	0.4	1.7		1.3	2.1
Autism spectrum disorder						1.3	3.1 [2.9][e]	0.4	
Attention-deficit/hyperactivity disorder	5.9	7.4	4.9	1.8	0.8	1.6	9.8 [8.7][e]	3.7	3.4
Any "emotional" disorder[g]						8.1			
Any depressive disorder						2.1	4.4 [3.4][e]	1.5	2.6
Major depressive disorder	0.7	2.8	0.6	1.0	1.2	1.5		1.3	1.3
Dysthymia						0.6		0.2	1.3
Any anxiety disorder	3.4[h]	6.9[h]	3.7[h]	1.9[h]	1.3[h]	7.2[i]	9.4 [7.8][e,j]	5.2[k]	6.5[l]

Author	CAMHW survey (Lawrence et al. (2015))[1]					NHS Digital (Sadler et al. (2018))[2]	CDC (Bitsko et al. (2022))[3,a]	Barican et al. (2022)[4]	Polanczyk et al. (2015)[5]
Prevalence period	30 day %	12 month %	12 month % mild	12 month % moderate	12 month % severe	Unspecified[b]	Varied	Most 12-month	Varied
Specific phobia						0.8		3.4	
Social phobia	1.1	2.3				0.8		1.2	
Separation anxiety disorder	1.7	4.3				0.7		1.6	
Reactive attachment disorder									
Generalised anxiety disorder	1.1	2.2				1.5		0.9	
Panic disorder						1.1		0.1	
Agoraphobia						0.5		0.1	
Post-traumatic stress disorder						0.6		0.1	
Obsessive-compulsive disorder	0.5	0.8				0.4		0.3	
Other less common disorders[m]						2.1			
Eating disorders						0.4		0.2	
Substance use disorders							4.1	2.3	

Abbreviations: CAMHW, Child and Adolescent Mental Health and Wellbeing; CDC, Centers for Disease Control; NHS, National Health Service.

References included in this table:

1. Lawrence et al. (2015) The mental health of children and adolescents: report on the second Australian child and adolescent survey of mental health and wellbeing. Canberra: Department of Health. [15]

2. Sadler et al. (2018) Mental health of children and young people in England, 2017: trends and characteristics. Leeds (UK): NHS Digital. [17]

3. Bitsko et al. (2022) Mental health surveillance among children - United States, 2013-2019. [14]

4. Barican et al. (2022) Prevalence of childhood mental disorders in high-income countries: a systematic review and meta-analysis to inform policymaking. [19]

5. Polanczyk et al. (2015) Annual research review: a meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. [21]

Notes:

a. Nine surveillance systems examining child and adolescent mental health were used in this analysis: 1). Autism and Developmental Disabilities Monitoring Network (ADDM), 2). National Health and Nutrition Examination Survey (NHANES), 3). National Health Interview Survey (NHIS), 4). National Survey of Children's Health (NSCH), 5). National Survey on Drug Use and Health (NSDUH), 6). National Violent Death Reporting System (NVDRS), 7). National Vital Statistics System (NVSS), 8). School-Associated Violent Death Surveillance System (SAVD-SS), 9). Youth Risk Behavior Survey (YRBS).

b. The NHS digital survey did not specify the prevalence period. The survey used the Development and Wellbeing Assessment tool based on DSM-IV and ICD-10 criteria. Developers of the DABWA believed it preferable to focus on the present and recent past when assessing prevalence of mental disorders, mainly focussing on the previous month. (see Goodman et al. (2008), [18, p.647]).

c. The prevalence figure for 2017 comprises disorders included in previous surveys in 1999 and 2004, plus body dysmorphic disorder (BDD) and a few low prevalence conditions including bipolar affective disorder, both added in 2017.
d. The US mental health surveillance report did not give a figure for the prevalence of any disorder. For comparison, an estimate was obtained from a paper by Tkacz and Brady (2021) [22], examining mental health prevalence in children 4-17 years in the US, using the MarketScan commercial claims database. As the report by Bitsko et al. (2018) used nine different surveillance systems this figure may not be a good comparison.
e. Format x[y] shows the weighted prevalence for "Ever" (x) having the disorder (parent ever told by health care provider child had the problem) and [y] – "current" weighted prevalence (parent reported child currently had problem).
f. Behavioural disorders include conduct disorder (CD), oppositional defiant disorder (ODD), unsocialised and socialised CD, other CD.
g. Any "emotional" disorder includes separation anxiety disorder, different phobias (specific phobia, social phobia, agoraphobia), obsessive-compulsive disorder (OCD), panic disorder, post-traumatic stress disorder (PTSD), generalised anxiety disorder (GAD) and other anxiety disorders, depressive disorders, bipolar affective disorder, and body dysmorphic disorder.
h. Anxiety disorders in this category were social phobia, separation anxiety disorder, GAD or OCD.
i. Anxiety disorders in this category were: separation anxiety disorder, different phobias, OCD, panic disorder, PTSD, GAD, or other anxiety disorders.
j. Anxiety was defined as "anxiety problems", as measured by the NSCH survey.
k. Anxiety disorders in this category were: separation anxiety disorder, specific phobia, social anxiety disorder, GAD, panic disorder, agoraphobia. Six of the 14 studies in the meta-analysis also included PTSD and/or OCD.
l. This metanalysis covered a wide range of countries, methodologies and timespans. No list of included diagnoses in the "any anxiety disorder" was given.
m. Other less common disorders include autism spectrum disorder, eating disorder, tic disorder, selective mutism and psychosis.

1.2.3 Changes in prevalence of mental disorders in children and adolescents

Data on Australian trends in prevalence of childhood mental disorders remains lacking. Only two CAMHW surveys of the population have assessed prevalence, one each in 1998 and 2013/2014 [15]. The earlier 1998 survey examined only five disorders (MDD, dysthymic disorder, ADHD, CD, and eating disorders), whereas the 2013/2014 survey examined seven disorders (CD, ADHD, major depressive disorder [MDD], social phobia, separation anxiety disorder, GAD, and OCD). Only three disorders were common across both periods, limiting the interpretation of changes in prevalence over time. The prevalence of MDD in 6-17-year-olds increased from 2.1% in 1998 to 3.2% in 2013/2014, while conduct disorder (2.7% to 2.1%) and ADHD decreased (9.8% to 7.8%) (Table 1.2) [15].

In other high-income countries such as the UK and US, surveys have included a broader range of disorders, observing similar small changes in the prevalence of mental disorders across two decades. The Health and Social Care Information Centre in the UK, also known as NHS Digital, surveyed children in 1999, 2004 and 2017 [17] (Table 1.2). The NHS Digital survey is considered the most comprehensive analysis of changes in mental disorder prevalence over time [23]. Trend analyses were restricted to 5-15-year-olds within the same geographic regions, observing the same diagnoses [17] (Table 1.2). The NHS Digital report observed a slight upward trend for all recorded mental disorders, from 9.7% in 1999, to 10.1% in 2004 and 11.2% in 2017 [17]. For “emotional disorders”, which included depressive and anxiety disorders, prevalence was stable between 1999 (4.3%) and 2004 (3.9%) but increased to 5.8% in 2017. On the other hand, behavioural disorders (e.g., oppositional defiant disorder [ODD], conduct disorder [CD]), and hyperactivity disorders, remained relatively stable over time. From 2004 to 2017, autism spectrum disorders (ASD) (1% to 1.3%) and eating disorders (0.1% to 0.2%) both recorded increases in their prevalence. The information summarised in Tables 1.1 and 1.2 suggests similar prevalence rates are observed internationally, with approximately 13%, or one in eight children 5-18 years experiencing a mental disorder within a 12-month period, and similar small changes over time.

Although mental disorders are the most common reason for general practitioner (GP) visits and identified as an important area for federal government action for all age groups [24], information on the prevalence of paediatric mental disorder diagnoses in primary care in Australia has not previously been reported. This thesis examines the prevalence of mental disorders in children and adolescents attending general practice from 2011 to 2018 using a large EHR primary care database.

Table 1.2 Summary of changes in Australian and international prevalence of child and adolescent mental disorders

Source	CAMHW survey (Lawrence et al. (2015))[1]			NHS Digital (Sadler et al. (2018))[2]				CDC (Bitsko et al. (2022))[3]		
Age range	1998	2013/14	Change %	5-15 years[a]	5-15 years[a]	5-15 years[a]	Change %	3-17 years	3-17 years	Change %
Time period	6-17 years	6-17 years		1999	2004	2017		2005-2011	2013-2019	
Prevalence period	12 month %	12 month %		undefined[b]	undefined[b]	undefined[b]		Varied	Varied	
Any disorder[c]	12.5	11.1	-11.2%	9.7	10.1	11.2	15.5%[d]	11.0[e] [2012]	13.9[e] [2017]	26.4%
Behavioural disorders[f]				5.4	6.2	5.5	1.9%	4.6 [3.5][g]	8.9 [7.0][g]	93.5%[100.0][g]
Conduct disorder	2.7	2.1	-22.2%							
Autism spectrum disorder					1.0	1.3	30.0%[h]	1.2 [1.1][g]	2.8 [2.5][g]	133.3% [127.3][g]
Attention-deficit/hyperactivity disorder	9.8	7.8	-20.4%	1.5	1.5	1.9	26.7%	8.4 [6.8][g]	9.7 [8.5][g]	15.5% [25.0][g]
Any "emotional" disorder[h]				4.3	3.9	5.8	34.9%[i]			
Any depressive disorder								3.9 [2.1][g]	4.4 [3.4][g]	12.8% [61.9][g]
Major depressive disorder	2.1	3.2	52.4%							
Any anxiety disorder								4.7 [3.0][g,j]	9.4 [7.8][g,j]	100.0% [160.0][g]
Eating disorders					0.2	0.4	100.0%[k]			

Abbreviations: CAMHW, Child and Adolescent Mental Health and Wellbeing; CDC, Centers for Disease Control; NHS, National Health Service.

References included in this table:

1. Lawrence et al. (2015) The mental health of children and adolescents: report on the second Australian child and adolescent survey of mental health and wellbeing. Canberra: Department of Health.[15]
2. Sadler et al. (2018) Mental health of children and young people in England, 2017: trends and characteristics. Leeds (UK): NHS Digital.[17]
3. Bitsko et al. (2022) Mental health surveillance among children - United States, 2013-2019. [14]

Notes:

a. Disorders were assessed in 5-15-year-olds in 1999, 5-16-year-olds in 2004, and 5-19-year-olds in 2017. To examine trends the age group was restricted to 5-15 years. Disorders excluded from trend analyses include all disorders added since 1999, - body dysmorphic disorder, bipolar affective disorder, mania (emotional disorders), attachment disorder, feeding disorder, sleep disorder, eliminating disorder (other less common disorders).

b. The NHS digital survey did not specify the prevalence period. The survey used the Development and Wellbeing Assessment tool based on DSM-IV and ICD-10 criteria. Developers of the DABWA believed it preferable to focus on the present and recent past when assessing prevalence of mental disorders, mainly focussing on the previous month. (see Goodman et al. (2008), [18, p.647]).

c. For trend analyses, "any disorder" included all disorders measured for ach time period. CAMHW included depression, ADHD and conduct disorders; NHS Digital included behaviour disorders (defined in footnote e), autism spectrum disorders, ADHD and any "emotional" disorder (defined in footnote g); the US surveillance report only specified "behavioural or conduct problem" and "anxiety problem" without recording a specific diagnosis.

d. While the confidence intervals around the 1999 and 2017 rates of any disorder overlapped t-tests indicated an increase in the prevalence of any disorder over this period. However, there was no significant difference in prevalence rates between 2004 and 2017.

e. The US mental health surveillance report did not give a figure for the prevalence of any disorder. For comparison, an estimate was obtained from a paper by Tkacz and Brady (2021), examining mental health prevalence in children 4-17 years in the US, using the MarketScan commercial claims database. As the report by Bitsko et al. (2018) used nine different surveillance systems this figure may not be a good comparison.

f. For NHS Digital, behavioural disorders included oppositional defiant disorder (ODD), conduct disorder (CD), unsocialised CD, socialised CD and other CD.

g. Format x[y] shows the weighted prevalence for "Ever" (x) having the disorder (parent ever told by health care provider child had the problem) and [y] – "current" weighted prevalence (parent reported child currently had problem).

h. Any "emotional" disorder includes separation anxiety disorder, different phobias, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, generalised anxiety and other anxiety disorders, and depressive disorders. Disorders included for the first time in 2017 are excluded (bipolar affective disorder and body dysmorphic disorder).

i. Rates of "emotional" disorders were stable between 1999 and 2004 but increased significantly between 2004 and 2017.

j. Anxiety was defined as "anxiety problems", as measured by the National Survey of Children's Health.

k. Eating disorders were not measured in 1999. Trends could only be examined from 2004 to 2017. The sample size for eating disorders was too small to reliably detect any changes.

1.3 Australian regulation of medicines

This section provides a background on the operations of the TGA, the federal body responsible for the approval and regulation of medicines in Australia [25]. The TGA is comparable to the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA). Australian drug approval processes and safety monitoring mechanisms are briefly described, with special reference to paediatric drug approvals (see Section 1.3.2).

To obtain approvals for supply or sale of drugs within Australia, drug sponsors (usually pharmaceutical companies) submit applications to the TGA. Applications also require the submission of a Product Information (PI) document that details all product indications, requested dosages for approval, and a summary of safety and efficacy information available about the product [25]. If the sponsor is seeking paediatric approval, the PI must also include a separate section on children that reports on the outcomes of any testing in paediatric populations. Applications require that sponsors similarly provide a Consumer Medicine Information leaflet detailing the safety and efficacy of a medicine in layman's terms and include approved dosages, expected and possible side-effects, and interactions with other medications or foods [25].

The TGA carries out extensive reviews of medicine applications, considering available evidence on the efficacy and safety of the product for the health condition and age group for which the approval is sought. If the medicine is approved for use in the indicated population, it will be included on the Australian Register of Therapeutic Goods. The TGA also provides the applicant with a letter of approval that outlines federal requirements for the provision of regular Periodic Safety Update Reports (PSURs) [26]. Product PSURs are typically required annually for three years post-registration [26]. Additionally, sponsors are required to inform the TGA of any safety updates as soon as any new information is available to them [25].

1.3.1 Pharmacovigilance requirements for TGA-approved products

After market approval, the TGA continues to evaluate the safety and effectiveness of drugs as new evidence emerges. This is achieved using five main pharmacovigilance tools: risk management plans, reporting of adverse events, periodic safety update reports, the Pharmacovigilance Inspection Program of adverse event reporting, and environmental scans (see Table 1.3 for a description of pharmacovigilance tools) [27].

Table 1.3 Summary of pharmacovigilance methods used by the TGA for post-market surveillance of approved products

Pharmacovigilance tool	Description of method	Source of information
Risk Management Plan (RMP)	Summary of the known important safety information about the therapeutic product (safety specifications). Plans to identify and characterise known or potential safety concerns (pharmacovigilance plan) and to minimise any identified or potential safety risk (risk minimisation plan). High-risk medicines may require an assessment of benefit.	Sponsors[a]
Adverse event (AE) reporting	Reports on harmful and unintended responses to medicines marketed in Australia or in clinical trials. Expedited reporting of serious unexpected clinical trials adverse events. Reports regarding deficiencies in labelling, instructions or packaging.	Sponsors[a], health professionals, patients, consumers, and clinical trial sponsors and organisations
Periodic Safety Update Report (PSUR)/ Periodic Benefit-Risk Evaluation Report (PBRER)	A comprehensive and critical analysis of new or emerging information on the risks of the product, and, where pertinent, on its benefit in approved indications, to enable an appraisal of the product's overall benefit-risk profile. Such reports are required for specific medicines as a condition of approval.	Sponsors[a]
Pharmacovigilance Inspection Program (PVIP)[b]	Inspection of a medicine sponsor to assess whether they are meeting their pharmacovigilance responsibilities.	Sponsors[a]
Environmental scanning	Collection and review of scientific and medical literature, media reports and regulatory news from Australia and overseas to identify safety issues that require further investigation.	Media, academia, governments, industry and consumers

Source. Adapted from Therapeutic product vigilance Version 1.4, accessed from www.tga.gov.au [27]
Notes:
a. Sponsors are agents requesting approval for a medication that they supply and import into Australia or export from Australia. In most cases, this is the pharmaceutical company that manufactures the drug.
b. The TGA use a risk-based approach to prioritise pharmacovigilance inspections. Risk is assessed based on aspects relating to the sponsor's, product, pharmacovigilance systems, previous inspections, and any other factors deemed relevant by the TGA.

1.3.2 Regulation of paediatric drugs

In paediatric populations, ethical constraints and regulations restrict studies that examine drug efficacy and safety [28-30]. This results in a poor evidence base to guide clinicians when treating children [31, 32] and additional risk for paediatric patients using medications [33, 34]. In the US, concerns about the quality of the evidence base for drugs used in children prompted the introduction of new legislation in 2002 (Pediatric Research Equity ACT), encouraging pharmaceutical companies to test new drugs in paediatric populations if they are likely to be used in children or adolescents [32]. Similarly, in 2007, the EMA introduced regulations that encouraged higher-quality, ethical research on medicines used in children while attempting to minimise unnecessary or high-risk trials [35]. In both jurisdictions,

pharmaceutical companies are granted a six-month patent extension for the drug for undertaking paediatric trials.

In Australia, the TGA requires an additional form to be completed when regulatory approval is sought for medicines to be used in children or adolescents (the "paediatric development program") [36]. This application for paediatric drug approval requires adherence to standards in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use paediatric guideline, which requires submission of data generated in paediatric populations [37]. The application must also detail any submissions and approvals lodged with the EMA and FDA. Therefore, the Australian approval process for paediatric drugs is influenced by EMA and FDA approvals and is more comprehensive than that for drugs to be used in adult populations.

1.4 The Australian health system

Australia has a universal health insurance scheme, Medicare, providing a range of free or low-cost healthcare services to all citizens and permanent residents [38, 39]. Medicare consists of three major parts: medical services, public hospitals, and medicines. Medical services subsidised by the government are listed in the Medicare Benefits Schedule (MBS) and include GP and specialist consultations, laboratory testing, and imaging [40]. The MBS has a "safety net" that annually caps out-of-pocket expenses for patients, reducing the financial burden for patients with high medical costs. Medicines are similarly capped through the Pharmaceutical Benefits Scheme, discussed in the next section.

1.5 The Pharmaceutical Benefits Scheme (PBS)

The PBS subsidises TGA-approved medicines for most health conditions, aiming to ensure patients have access to affordable medicines, irrespective of their financial position [38, 39]. However, not all TGA-approved medicines are PBS-listed [38]. To be listed on the PBS schedule and therefore subsidised, an independent body of the Australian Government Department of Health and Aged Care, the Pharmaceutical Benefits Advisory Committee (PBAC), assesses evidence on the safety and effectiveness of the medication (available through the TGA) and the cost-effectiveness of subsidising the drug compared to other indicated treatments available for a particular health condition [38]. If successfully PBS-listed, the Australian government reimburses community pharmacies for PBS-approved medications. Medications are not subsidised without PBS registration, or where prescribed

for a non-approved indication (off-label prescribing, see Section 1.6), or if a branded, more expensive medication is prescribed when alternative generic medications are available [38].

1.6 Off-label prescribing

1.6.1 What is off-label prescribing?

Off-label prescribing is most often defined as the use of a drug for a medical condition for which it has not been officially approved by regulatory authorities (off-label by indication), as well as prescribing for an age group for which a medicine has not been approved (off-label by age), which is particularly common in children and adolescents [29, 41]. Prescribing can also occur off-label by contraindication if a medication is prescribed against recommendations of regulatory authorities [29]. Off-label by dose or mode of administration occurs when a drug is used outside of approved procedures [41]. For the purposes of this thesis, off-label was defined as prescribing for a non-TGA-approved indication or when the age of the paediatric patient was below the recommended age for approved prescribing. The off-label algorithm is described in more detail in Chapter 5 (Supplementary Table S4).

1.6.2 Paediatric off-label prescribing

Off-label psychotropic prescribing in children and adolescents is common [13, 31, 42-48] and appears to be on the increase worldwide [46, 49-51]. Off-label prescribing is influenced by four main factors: the specific drug or drug class, the healthcare professional, the patient and/or their carer, and the difficulties in conducting clinical trials in paediatric populations (clinical trial factor) [52]. These four factors are intricately interlaced (see Figure 1.1). The clinical trial factor is addressed to some extent by the regulations encouraging clinical trials in children, discussed in Section 1.3. However, despite international efforts to conduct more drug trials in paediatric populations, off-label use of drugs in children remains problematic, as the evidence base is still limited [52].

Medical practitioners can legally prescribe drugs for off-label indications, but such use should still reflect sound evidence-based treatment [53]. The absence of TGA approval does not always translate to an absence of evidence altogether [53], but using medicines off-label requires a more thorough assessment of the evidence for both risks and benefits prior to prescribing [31]. Due to the added risks involved in off-label prescribing (see Section 1.7), the Royal Australian College of Psychiatrists (RANZCP) encourages health practitioners to actively note the reasons for the prescription and justify their decision with quality evidence

[41, 53, 54]. Reasons for choice of drug should be clearly explained to the patient and their carer and consent to off-label treatment noted in patient records [41, 53, 54].

Figure 1.1 illustrates additional influences on off-label prescribing, including availability of non-drug alternative treatments, poor and difficult-to-access guidelines, and unethical drug promotion practices by pharmaceutical companies [52]. Relationships may be even more complex than depicted with causal actions in more than one direction.

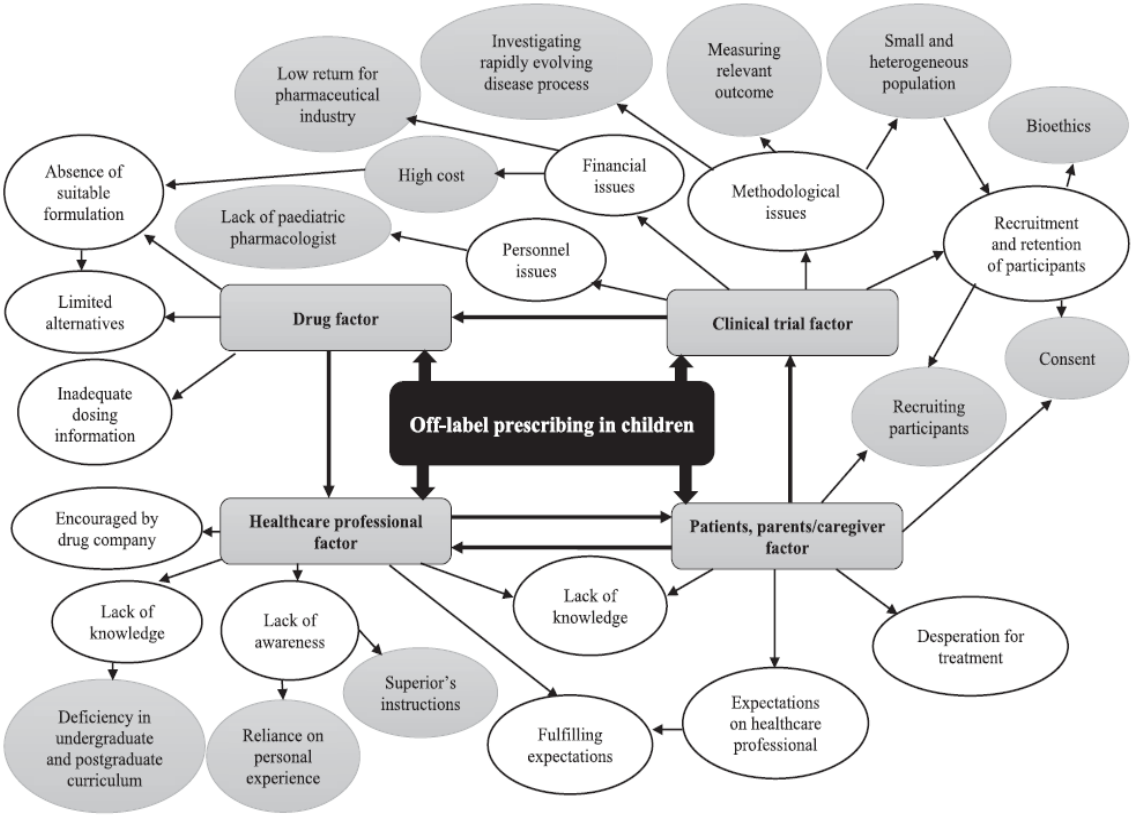


Figure 1.1 A concept map of factors causing off-label prescribing in children.
Source: Balan et al. (2017). [52, p.1220].

1.6.3 Summary of Australian and international studies examining off-label psychotropic prescribing in children and adolescents

Psychotropic drugs are among the most widely prescribed drugs for off-label indications in children and adolescents [55-57]. Several international studies [55, 56, 58] and one Australian study [59] have found drugs indicated for ADHD are rarely prescribed for non-ADHD conditions, with one Danish study reporting a small 2.7% off-label rate [55]. On the other hand, paediatric off-label prescribing rates for antidepressants and antipsychotics are much higher: in Europe, around 50% of antidepressants and up to 95% of antipsychotics are

prescribed off-label [57]. A systematic review of off-label prescribing of antipsychotics found rates varied from 36% to 93% in children and adolescents, depending on the approvals in different countries and sample characteristics [48].

Antipsychotics are also prescribed for a broader range of off-label conditions than other psychotropics, including diagnoses of borderline personality disorder, OCD, depression, post-traumatic stress disorder (PTSD), and stuttering [46, 56, 60]. One US study found that second-generation antipsychotics (SGAs) have been used off-label for a wider variety of disorders than the other four classes of psychotropics in their analysis (antidepressants/anxiolytics, mood stabilisers, benzodiazepines (excluding anxiolytics), and stimulants) [56]. Antipsychotics have also been actively promoted by pharmaceutical companies for off-label uses for both adults and children in the US, raising particular concerns about broadening use of this class of psychotropics [31]. Although promotion of off-label uses is illegal in Australia, the influence of international promotions may indirectly influence prescriber behaviour: prescribing trends in other countries can have a significant impact on Australian prescriber behaviour, both through TGA drug approval processes (see Section 1.3.2) and through the influence of international clinical practice guidelines (see Chapter 2).

Literature searches yield only a small number of Australian studies of paediatric patients prescribed antipsychotics where reasons for prescriptions were reported, allowing an analysis of off-label prescribing practices [59, 61-63]. All of these studies had small sample sizes, ranging from 60 patients in a retrospective case note audit in a South Australian hospital to a chart review of 248 patients attending a mental health service in Queensland [59]. None of these studies provided data that was representative of the national Australian population, with one study restricted to adolescents [61] and another located in a specialist eating disorder clinic [63].

The Drug Utilisation Sub Committee (DUSC) of the PBAC examined the utilisation of PBS-subsidised antipsychotics in children and adolescents from 2010 to 2012 [64]. The DUSC report highlighted concerns about off-label prescribing and called for further investigation into an unexpectedly high use of quetiapine and risperidone in 5-19-year-olds [64]. The report also flagged concerns about the possible off-label uses of quetiapine for insomnia and/or ADHD [64].

In response to the research gaps highlighted in the DUSC report, this thesis examines the pattern of off-label antipsychotic prescribing in detail (Chapter 5). Off-label prescribing of other classes of psychotropics is also discussed more generally in relation to TGA approvals and guideline recommendations in Chapter 8.

1.7 Health risks associated with psychotropic use in paediatric populations

Children and adolescents are particularly vulnerable to the effects of psychotropic medications. Compared with the adult population, young patients can experience increased severity and rates of adverse effects, and there are unknown risks to their developing brains [10]. They are also more vulnerable to the metabolic and extrapyramidal effects (e.g., tardive dyskinesia, dystonia, akathisia) of these drugs [65-70], including alterations in glucose and lipid metabolism, hyperprolactinaemia, and long QT syndrome [70-72].

Although concerns exist about the effects of all psychotropics in children and adolescents, the prescribing of antidepressants, antipsychotics, and stimulants has been controversial. In the first decade of the 21st century, black box warnings have been issued by the FDA for antidepressants [73, 74] and stimulants [74, 75] for children and adolescents. Initially, a black box warning was issued for children and adolescents exposed to antidepressants for an increased risk of suicidal ideation and suicidal behaviour in October 2004, which was expanded to include young adults up to 24 years in 2007 [73, 74]. A black box warning was then issued for stimulants in August 2006, concerning serious cardiovascular events and sudden death in both children and adults [75]. In 2004, the FDA issued a warning regarding the cardiometabolic adverse effects of second generation antipsychotics (SGAs), which was expanded to include first generation antipsychotics (FGAs) in 2008 [76]. The TGA has also issued safety warnings for antidepressants in April and October 2004 [77, 78] and June 2005 [79] and a warning regarding hyperglycaemia with the use of SGAs in June 2004 [80].

There are also concerns about delayed growth in children prescribed stimulants [81] and fluoxetine (an antidepressant) [82]. In 2015, Correll and colleagues reviewed the association between using antipsychotics, antidepressants, and mood stabilisers and the risk of developing physical disease [8]. They observed an increased risk for a broad range of conditions, including overweight/obesity, dyslipidaemia, diabetes, blood disorders, respiratory illnesses, and movement and seizure disorders. Dose-dependent effects and added risks with polypharmacy increased the effect of antipsychotics on most diseases, especially for vulnerable groups, including the young.

There are additional risks when using medications off-label [31, 33]. According to Stroup and Gray (2018), when antipsychotics are prescribed for "off-label uses, for which the evidence of antipsychotic benefits is often unclear, side effects are vitally important because the ratio of benefits to risks is lower" [34, p.341]. This is particularly problematic in paediatric populations where off-label use is high [33, 82]. There is also evidence that adverse events can be more severe when used off-label for a wide range of drugs used in adults and children [83-86]. Therefore, monitoring the context (e.g., medical conditions) and extent of off-label drug prescribing is critical to ensure safe use of medications in paediatric populations.

Following an examination of off-label antipsychotic prescribing in Chapter 5, Chapter 6 examines the monitoring of metabolic adverse effects associated with these drugs. Therefore, a detailed summary of adverse effects associated with antipsychotics is presented in Section 1.7.1.

1.7.1 Adverse effects associated with antipsychotic drugs

Antipsychotics are a potent class of drug associated with a wide range of adverse effects. FGAs were developed in the 1950s [87, 88] and are potent sedatives that can cause irreversible movement disorders such as tardive dyskinesia [8, 88], neuroleptic malignant syndrome [88], and hyperprolactinaemia [88, 89]. SGAs are sometimes referred to as atypical antipsychotics and were introduced in the 1980s [88]. SGAs were initially heralded as superior to FGAs as they had a 5- to 6-fold lower risk for tardive dyskinesia [8]. However, these newer SGAs were associated with serious metabolic and endocrine effects [69, 87] and still caused movement disorders, though less severely than FGAs [90]. Correll (2008) considered the antipsychotic-related metabolic and endocrine adverse effects observed in paediatric patients to be particularly "worrisome", as "they occur in the context of important physical and psychological development, a phase of life during which obesity and metabolic abnormalities may lead to accelerated detrimental cardiovascular downstream effects" [69 p.196].

1.7.1.1 Antipsychotic-induced weight gain (AIWG) and cardiometabolic health

Weight gain associated with antipsychotic use is well documented [69, 72, 87, 90] and can occur rapidly in children and adolescents [9]. A Bayesian meta-analysis of 41 short-term trials (3-12 weeks) in children and adolescents examined weight changes in several SGAs [90]. Comparing each drug to placebo, odds ratios ranged from 3.77 for ziprasidone to 15.1

for olanzapine. Table 1.4 summarises the results from this meta-analysis, comparing the potential for weight gain and metabolic effects for five SGAs. In a US study of 505 antipsychotic-naïve Medicaid youth aged 4-19 years, significant weight gain was observed in just 10.8 weeks for olanzapine (average 8.6 kg), quetiapine (6.1 kg), risperidone (5.4 kg), and aripiprazole (4.5 kg) [9].

Table 1.4 Short-term (3-12 weeks) adverse effects of different second-generation antipsychotics compared to placebo observed in children and adolescents

	Aripiprazole	Olanzapine	Quetiapine	Risperidone	Ziprasidone
Weight gain (OR, credible CI)	4.44[2.0, 8.88]	15.1[6.56, 31.1]*	6.2[2.61, 13.56]*	6.03[3.02, 11.4]*	3.77[0.37, 16.27]*
Weight gain (kg)-mean(sd)	0.89(0.32)	3.99(0.42)	1.74(0.38)	2.02(0.32)	-0.1(0.7)
Glucose (mg/dL) (OR, credible CI)	2.21[-0.63,5.09]	2.09[0.13,4.32]*	1.64[-0.4, 3.7]	3.7[1.08, 6.42]*	-1.24[-5.7, 3.23]
Cholesterol (mg/dL) (OR, credible CI)	2.65[-2.11, 7.34]	4.46[1.24, 7.73]*	10.77[6.6, 14.95]*	0.91[-3.22, 5.08]	0.47[-5.64, 6.56]
Triglycerides (mg/dL) (OR, credible CI)	0.03[-8.9, 8.98]	20.18[9.85, 30.53]*	19.5[11.84, 27.17]*	5.57[-3.38, 14.51]	-1.52[-12.31, 9.34]
Prolactin (ng/dL)[a]	-	15.6[4.39, 41.1]*	3.16[0.13, 15.9]	38.63[8.62, 125.6]*	9.35[1.24, 37.03]*
Sedation (%)[b]	6.07[2.79, 12.22]*	8.49[3.97, 16.59]*	5.44[2.91, 9.26]*	7.33[4.63, 11.19]*	8.72[2.71, 21.97]*
Extrapyramidal syndrome[c]	3.79[2.17, 6.17]*	6.36[2.43, 13.84]*	2.54[0.88, 6.07]	3.71[2.18, 6.02]*	20.56[3.53, 68.94]*

* $p<0.05$

Source: Cohen et al. (2012). [90].

a. Percentage of patients judged to have clincally significant hyperprolactinaemia.

b. Percentage of patients reporting somnolescence or sedation.

c. Percentage of patients with clinically significant extrapyramidal syndrome or akithisia.

Similarly, metabolic disorders are commonly associated with antipsychotic use. Developing Type 2 diabetes mellitus (T2DM) is a well-documented risk for young people using SGAs [89, 91, 92], with one study reporting a 3-fold increase in T2DM in children and adolescents using antipsychotics [91].

Metabolic syndrome (MetS) has also been associated with antipsychotic use in adults [93] and children and adolescents [94, 95]. MetS is a collection of risk factors associated with an increased risk of experiencing cardiovascular events and developing T2DM [96, 97], and includes increased adiposity, especially abdominal obesity (measured by waist circumference), elevated triglycerides, high blood pressure, hyperglycaemia and reduced "good" cholesterol (high density lipoproteins [HDLs]) [98]. In a small sample of Danish young people aged 7-19 years [95], researchers found significant adverse changes in most indicators of MetS in a group of children and adolescents that occurred within 12 months of

initiating SGA treatment. At commencement, none of these patients had any signs of metabolic syndrome, but by 12 months, 20% recorded abnormal ranges across all except blood pressure readings.

A recent study by Koskinen and colleagues (2017) found that childhood MetS from the age of five years predicted the development of adult MetS [99]. From eight years of age, childhood MetS predicted adult T2DM and subclinical atherosclerosis [99]. These findings raise concerns that antipsychotic use in childhood could be placing children at increased risk of lifelong health problems and premature mortality [99].

1.7.1.2 Antipsychotic-induced hyperprolactinaemia

Hyperprolactinaemia is a well-documented adverse outcome associated with antipsychotic use in adults and children [89]. Antipsychotics block the dopamine-D2 receptors in the pituitary gland, which can result in increased prolactin levels and flow-on effects on oestrogen and testosterone concentrations [100]. Hyperprolactinaemia can cause gynecomastia in males, galactorrhea and amenorrhea in females, as well as reduced bone mineral density that may increase the lifetime risk of osteoporosis [8, 100-102]. As children and adolescents have a higher density of dopamine D2-receptors in their central nervous system, they may be particularly vulnerable to these adverse effects [100, 103].

Antipsychotic agents vary in their effect on prolactin levels, with all FGAs and some of the newer SGAs causing concerning increases in prolactin [89], in particular risperidone [100]. Raffin and colleagues summarised the effects of six SGAs on a variety of antipsychotic-related adverse effects, including hyperprolactinaemia [104, Table 3, p.94]. An extract of the table is reproduced below in Table 1.5.

Table 1.5 Summary of adverse effects of SGA use reported in short-term controlled studies

	Aripiprazole	Clozapine	Olanzapine	Quetiapine	Risperidone	Ziprasidone
↗ Weight	+	++++	++++	+++	++	+/−
↗ Glucose	+/−	?	+	+/−	++	0
↗ Cholesterol	0	?	+++	++++	0	0
↗ Triglycerides	0	+++	++++	++++	+/−	0
Hyperprolactinemia	0	?	+++	+/−	++++	++

Source: Raffin et al. (2014). [104, p.94].

1.7.1.3 Cardiometabolic monitoring guidelines

Given the well-documented adverse effects associated with antipsychotic use and the rapidity with which they can occur, several countries have introduced guidelines for recommended metabolic monitoring of children and adolescents prescribed antipsychotics

[72, 105-107]. Because guidelines recommended varying monitoring frequencies [108], Dinnissen and colleagues summarised all guideline recommendations that were mentioned in at least half of the child and adolescent guidelines available in English or Dutch in 2012 [108;Table 1, p.14]. An adapted version that highlights the parameters related to MetS is presented in Table 1.6.

Table 1.6 Summary of guideline recommendations for monitoring health outcomes in children and adolescents who are prescribed antipsychotics

Parameter	Monitoring schedule					
	Baseline	Week 4	Week 8	3 months	Annually	"Regularly"
Weight	yes	yes	yes	yes	Yes	
Height/BMI	yes	yes	yes	yes	yes	
Waist circumference	yes				yes	
Glucose	yes			yes	yes	
Lipids	yes			yes	yes	
Blood pressure	yes			yes	yes	
Prolactin						Yes

Note: Monitoring schedule represents the lowest recommended frequencies of monitoring.
Adapted from: Dinnissen et al. (2021) [108, Table 1, p.14].

There are some inconsistencies in guidelines with respect to the importance of monitoring prolactin levels [102]. Two American guidelines [69, 105] and one Australian guideline [109] recommend testing only if paediatric patients are "symptomatic" for hyperprolactinaemia. Other guidelines [72, 106, 107] recommend baseline and regular follow-up monitoring in children and adolescents. There is evidence that levels of prolactin are not closely related to symptoms [69, 72, 103, 110], especially in children [72]. Although there is some evidence that prolactin levels initially increase rapidly and then normalise within 12 months [89, 94], researchers often recommend adopting a more conservative approach, suggesting clinicians regularly monitor in the absence of symptoms until long-term studies establish the effects of hyperprolactinaemia on puberty and long-term health outcomes [72, 102].

1.7.2 Off-label melatonin prescribing

Melatonin is included in the ATC category of sedatives/hypnotics (ATC classification N05C), but is considered a non-traditional psychotropic [111] or neurohormonal drug by some researchers [112]. Several international studies have reported marked increases in the

prescribing of melatonin to children and adolescents over the last two decades [58, 113-117]. A Swedish study of 0-17-year-olds found a large 15-fold increase in girls and a 20-fold increase in boys prescribed melatonin from 2006 to 2017 [115]. Similarly, an Australian study of paediatricians noted a marked increase in melatonin prescribing from 2008 to 2013 [111]. No studies to date have examined paediatric melatonin prescribing in Australian general practice. Therefore, in this thesis, patterns of melatonin prescribing were examined separately to other sedatives/hypnotics.

1.8 Socio-economic factors in psychotropic prescribing practices

An important area of research into child and adolescent health outcomes includes consideration of negative social, economic, and environmental circumstances that place individuals at higher risk of developing physical and mental disorders [118, 119]. The risk factors associated with exposure to negative circumstances include family financial stress, socio-economic inequality, low education levels, and unemployment, and are referred to as the social determinants of health (SDH) [118-121]. Risk factors can be classified as "proximal", such as an individual's gender, race, income, or employment status; or "distal", including neighbourhood deprivation and macroeconomic factors [119]. Figure 1.2 highlights proximal and distal causes associated with five domains of the SDH of mental disorders and how they are linked to the Sustainable Development Goals endorsed by the United Nations member states in 2015 [119].

There is a well-established socio-economic gradient related to health outcomes in both developing and high-income countries [122, 123]. Those living with the highest levels of socio-economic disadvantage also experience the highest rate of illness across their lifespan and premature mortality [122]. Social inequities affect children's health and developmental trajectory, increasing the risk of disease and mental health later in life [122].

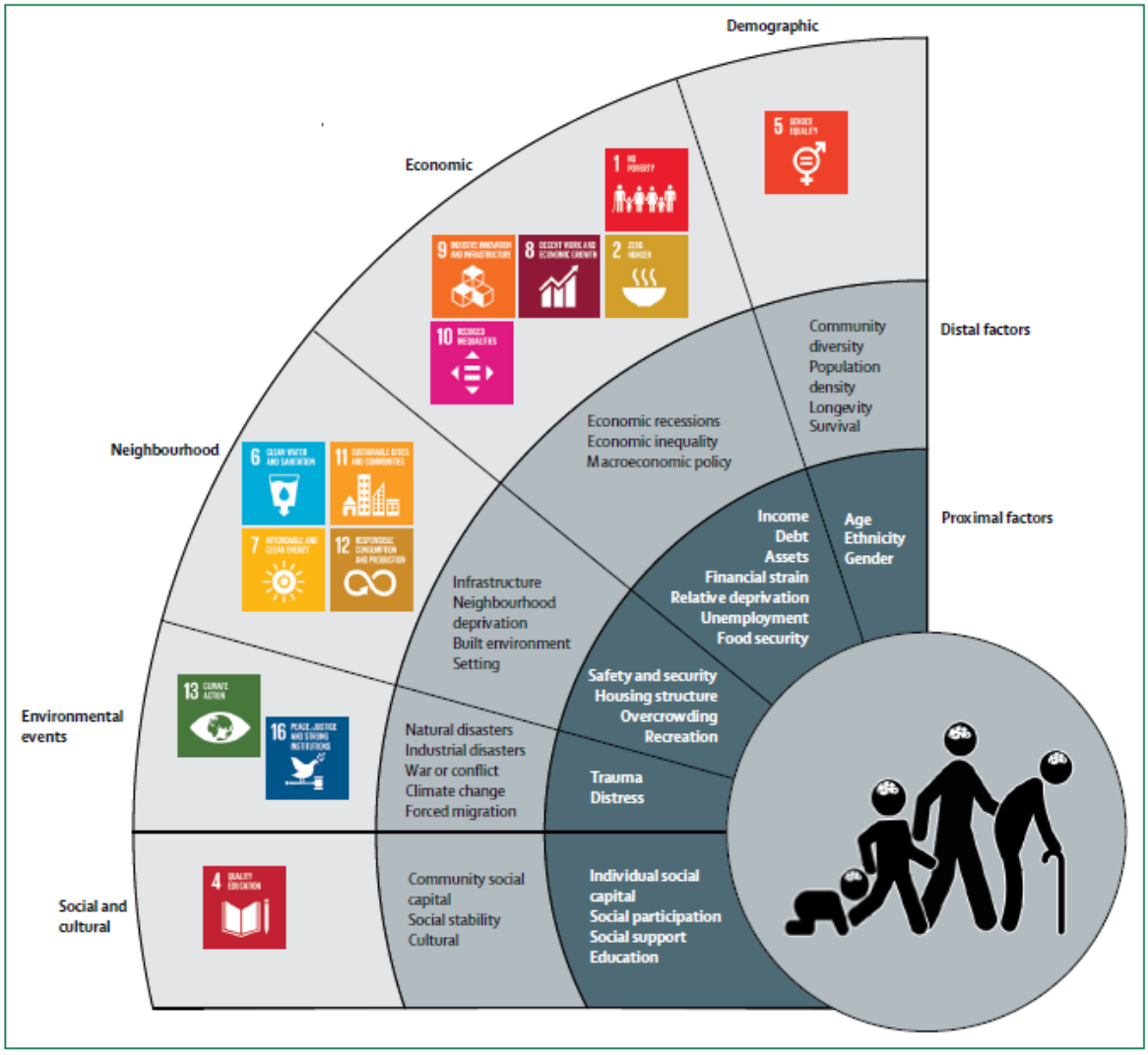


Figure 1.2 A summary of proximal and distal social determinants of mental disorders.
Source: Lund et al. (2018). [119, p.359].

Studies examining paediatric and adult populations have largely found evidence of a social gradient whereby residing in socially disadvantaged geographical areas is associated with higher rates of both mental disorders and psychotropic prescribing [47, 124-130]. For example, a study of antidepressant [47] and anxiolytic and hypnotic/sedative prescribing [127] in 6-18-year-olds captured in a Welsh GP database between 2003 and 2013 found patients in socio-economically disadvantaged areas were more likely to be diagnosed with depression and anxiety, and also more likely to be prescribed psychotropics than patients in the most socio-economically advantaged areas. A French study looking at socio-economic status and antipsychotic prescribing in 0-17-year-olds found the proportion of patients with antipsychotic prescriptions was 10-times higher in low-income families compared to the general population [124]. Notably, this study used an individual-level socio-economic indicator rather than an area-level socio-economic indicator. Overall, international studies

appear to show prescribing of psychotropic drugs to be more prevalent in more disadvantaged children and adolescents, irrespective of whether socio-economic disadvantage is measured on an individual level or by area of residence [47, 124, 127].

Australian studies examining socio-economic disadvantage are sparse and contradictory [125, 129, 131], with only one study including children [129]. Page et al. (2009) [129] examined PBS-dispensed antidepressants in all age groups and found that adults aged over 30 years living in the most socio-economically disadvantaged areas were more likely to be prescribed antidepressants than those in the least disadvantaged areas, but found the opposite for people aged 0-19 years. For children and adolescents, antidepressant prescribing was statistically significantly lower in the low socio-economic group (p for trend, <0.001) compared to higher socio-economic groups. This study used the Index of Economic Resources (IER), which includes a measure of an area's access to economic resources [132] as the measure of socio-economic deprivation. Another Australian study by Butterworth and colleagues (2013) [125] examined socio-economic differences in self-reported antidepressant use in a sample of young adults aged 24 to 48 years, using data from wave 2 (2003 to 2005) of a longitudinal survey study. In line with results for adults in the Page et al. study and international studies discussed earlier, they found an inverse socio-economic gradient associated with antidepressant use, such that socio-economically disadvantaged people were more likely to be prescribed antidepressants. Moreover, this finding was not attributed to higher rates of diagnosed depression, suggesting a preference for prescribing pharmacological rather than non-pharmacological treatments to patients living in more disadvantaged areas. Only one other Australian study of 16-85-year-olds examined socio-economic disadvantage and psychotropic prescribing [131]. This study found no association between disadvantage and self-reported use of antidepressants, anxiolytics, or hypnotics [131].

The relationship between socio-economic differences, mental disorders, and psychotropic prescribing practices is markedly under-researched for all age groups in Australia and almost non-existent in children and adolescents. This thesis will explore the relationship of social disadvantage to psychotropic prescribing using the Index of Relative Socio-economic Advantage and Disadvantage (IRSAD). IRSAD is an area-level factor that incorporates a range of socio-economic factors in addition to income [132] and is described in detail in Chapter 3.

1.9 Knowledge gap

There is a dearth of information on psychotropic prescribing to children and adolescents in Australia. Although some studies using PBS data have identified rising trends in prescribing of psychotropics at the population level [4, 12], very few studies address the reasons for prescribing, which allows an estimation of the extent of off-label prescribing. Furthermore, those studies that do address indications for prescribing are small, chart reviews in limited clinical settings [59, 61, 62] and unrepresentative of the general population. Analysis of trends by sociodemographic factors is also lacking, with only one paper addressing the issue in an Australian paediatric population, again using PBS data [129].

PBS data is also limited to those drugs approved for subsidy through the PBS and cannot assess off-label prescribing, which occurs in the majority of paediatric psychiatric settings. The dataset used in the current thesis, MedicineInsight, is a large general practice dataset that includes all prescriptions written by GPs and provides information on patient diagnoses, allowing an analysis of off-label prescribing. Pathology results included in the dataset also allow for an analysis of health monitoring, previously only examined in small samples in hospitals or community mental health settings. Using this GP dataset, the following gaps in the research literature on Australian psychotropic prescribing to children and adolescents are addressed:

1) Trends in prescribing in Australian primary care settings
2) Examining both private and PBS-subsidised medicines to provide a more comprehensive picture of prescribing practices
3) Sociodemographic factors associated with prescribing in Australian primary care
4) Diagnoses associated with antipsychotic prescriptions in Australian primary care
5) Off-label prescribing of psychotropics in Australian primary care
6) Monitoring of health outcomes for patients prescribed antipsychotics in Australian primary care
7) The prevalence of child and adolescent mental disorder diagnoses in Australian primary care.

1.10 Thesis aims and research questions

The overarching aim of this thesis is to examine psychotropic prescribing patterns to children and adolescents attending general practices across an 8-year period, from 2011 to 2018.

1.10.1 Thesis structure

Chapter 1 – Introduction

Chapter 1 provides a background to this thesis. The chapter describes the Australian health system, the prevalence of mental disorders in children and adolescents, and the concept of off-label prescribing and how it relates to paediatric populations. It discusses the controversial role of psychotropic drug prescribing in children and adolescents, especially in relation to antipsychotic prescribing, and the importance of the social determinants of health.

Chapter 2 – A summary of clinical practice guidelines

Chapter 2 provides an extensive overview of clinical practice guidelines to contextualise thesis findings. It discusses how clinical practice guidelines are formulated and addresses some of the controversies relating to guideline recommendations. Chapter 2 then summarises all available clinical practice guidelines for all mental disorders in children and adolescents, with an emphasis on when and how psychotropic medications are recommended, suggested, or contra-indicated. There were few Australian guidelines specific to children and adolescents, so international resources, GP specific journals, and adult guidelines are also summarised where necessary.

Chapter 3 - Methodology

Chapter 3 outlines the methodological approach in this thesis. The chapter includes a description of the database (MedicineInsight) used in all analyses and an explanation of the data extraction process. The rationale for the specific statistical methods and variables used throughout the thesis is also addressed in Chapter 3.

Chapters 4 through 6 – three papers

Chapters 4 to 6 comprise three main papers arising from this thesis. The first published paper examines the prevalence of prescribing for all the main classes of psychotropics, including trends over the 8-year period (Chapter 4). The second published paper examines off-label prescribing and diagnoses associated with antipsychotic prescriptions (Chapter 5). The third paper comprises a manuscript under peer review at the time of thesis submission, which examines how effectively adverse health outcomes are being monitored in general practice when antipsychotics are prescribed (Chapter 6).

Chapter 7 – Prevalence of mental disorder in Australian general practice

Chapter 7 serves as a supplementary examination of the prevalence of mental disorder diagnoses recorded in MedicineInsight over the 8-year period and contrasts this to Australian and international findings.

Chapter 8 – Examination of off-label prescribing and guideline concordance

Chapter 8 summarises findings on the extent of off-label prescribing for all the main classes of psychotropics examined in this thesis and discusses the results with respect to TGA approvals and guideline recommendations summarised in Chapter 2. It highlights discrepancies between the two sources of recommendations.

Chapter 9 – General Discussion

Chapter 9 consolidates findings from Chapters 4 through 8 in the form of a discussion. The key findings of this thesis are briefly summarised, including overall trends in paediatric psychotropic prescribing, off-label psychotropic prescribing, and metabolic monitoring for children and adolescents receiving antipsychotics. These findings are examined in the context of the Australian healthcare system, highlighting areas where current practices and policies require review. The social determinants of paediatric mental disorders are also examined in relation to published literature. Finally, this chapter addresses the methodological contribution of this thesis for future studies using general practice EHRs.

Chapter 10 – Conclusion and recommendations

Chapter 10 provides a synopsis of the thesis, highlighting key points, areas of future research need and implications for public health policy.

1.10.2 Thesis research questions

Thesis research questions are stated below, according to which thesis Chapter addresses them.

Chapter 4 - Trends in prescription of psychotropic medications to children and adolescents in Australian primary care from 2011 to 2018 (peer-reviewed publication):

1) What is the rate of prescribing for the five main classes of psychotropic drugs (antidepressants, antipsychotics, ADHD drugs, anxiolytics, sedatives/hypnotics) and melatonin in a cohort of children and adolescents in Australian primary care from 2011 to 2018?

2) Is there an increasing trend in prescribing across the study period from 2011 to 2018?

3) How do psychotropic prescribing trends differ by age, gender, and socio-economic level?

4) Which drugs are most commonly prescribed, by age group, in a selected year: 2018?

Chapter 5 - Antipsychotic prescribing patterns in children and adolescents attending Australian general practice in 2011 and 2017 (peer-reviewed publication):

1) Is there a change in the prescribing rate of antipsychotics to children and adolescents with mental health diagnoses in 2017, compared to 2011?

1a). Which diagnoses exhibit increases, decreases, or no change?

2) Does the proportion of patients with mental health diagnoses who are prescribed antipsychotics vary by sociodemographic characteristics from 2011 to 2017?

3) Has the rate of off-label prescribing of antipsychotics changed from 2011 to 2017?

4) What sociodemographic characteristics are associated with antipsychotic prescribing?

5) Which antipsychotics were most commonly prescribed for each diagnostic category in each year?

6) What is the extent of co-prescribing of other classes of psychotropics with antipsychotics in each year?

Chapter 6 – Cardiometabolic monitoring in children and adolescents prescribed antipsychotics in Australian primary care (manuscript under peer review):

1) How frequently are children and adolescents monitored for antipsychotic-related adverse effects within 12 months following their first antipsychotic prescription?

2) Are children and adolescents receiving antipsychotic prescriptions monitored more often than patients not receiving antipsychotics?

Chapter 7 – Prevalence of paediatric mental disorders in Australian general practice

1) Has the prevalence of mental disorder diagnoses changed in Australian general practice from 2011 to 2017?

Chapter 8 – Off-label prescribing and guideline concordance:

1) Is prescribing of psychotropics concordant with TGA approvals?

2) Is prescribing of psychotropics concordant with clinical guideline recommendations?

2 Chapter 2 Clinical Guidelines for Child and Adolescent Mental Health

2.1 Preface

There are few GP guidelines relating to mental health available from the Royal Australian College of General Practitioners (RACGP), with none specific to children and adolescents (https://www.racgp.org.au). GPs must therefore rely on other resources to guide paediatric treatment. This chapter summarises Australian and international guidelines for child and adolescent mental disorders applicable to the study period 2011 to 2018. The recommended treatment options for different disorders are summarised and also presented in more detail in Appendices 2 to 13. While this thesis focuses on pharmacological treatments, most guidelines emphasise non-pharmacological as first-line treatments for paediatric mental disorders. Therefore, both approaches are summarised in this chapter, with a greater emphasis on pharmacological treatments.

This chapter also briefly discusses some limitations of clinical practice guidelines. Children and adolescents are considered "therapeutic orphans"; that is, patients for whom there are limited or no drug trials conducted for ethical reasons (e.g., pregnant women due to the risk of harm to the unborn child; children due to major physiological and hormonal changes occurring during childhood and adolescence) or due to pharmaceutical company reluctance to run expensive trials for drugs with an anticipated small sales volume [33]. The paucity of clinical drug trials conducted in paediatric populations limits the amount of evidence on which to base guidelines [33]. There are also concerns with the quality of studies included in guidelines [33]. Efficacy and safety reported in clinical drug trials have been criticised [133], and there remains major controversy about the quality of guidelines due to conflicts of interest (COIs) [134, 135]. Despite these limitations, clinical practice guidelines are an important source of information to help clinician's guide treatment choices [136].

2.2 Introduction

Clinical practice guidelines (CPGs) are intended to promote good health and reduce harm from misuse of medical treatments by providing health professionals with evidence-based advice on best treatment practices for health conditions [137-139]. In Sections 2.2.1 to 2.2.3, processes and standards for the development of CPGs are discussed.

2.2.1 The Australian National Health and Medical Research Council (NHMRC)

In Australia, the National Health and Medical Research Council (NHMRC) is the national body responsible for the assessment and approval of guidelines, although there is no legal requirement that guidelines be submitted for approval.

The NHMRC lists nine standards that must be met for guideline approval (Table 2.1) [140], emphasising recommendations must be based on the best available evidence, relevant and useful, peer-reviewed, open for public review, and free of COIs. The NHMRC does not approve guidelines published or funded by industry groups.

Table 2.1 NHMRC standards for clinical practice guidelines

Standard	Description	Main points to address
Standard 1	Be relevant and useful for decision making	1. Address a health issue of importance 2. Clearly state the purpose of the guideline and the context in which it will be applied 3. Be informed by public consultation 4. Be feasible to implement
Standard 2	Be transparent	1. The details of all processes and procedures used to develop the guideline 2. The source of evidence 3. The declarations of interest of members of the guideline development group and information on how any conflicts of interest were managed 4. All sources of funding for the guideline
Standard 3	Be overseen by a guideline development group	1. Be composed of an appropriate mix of expertise and experience, including relevant end users 2. Have clearly defined, documented processes for reaching consensus
Standard 4	Identify and manage conflicts of interest	1. Require all interests of all guideline development group members to be clarified 2. Establish a process for determining if a declared interest represents a conflict of interest, and how a conflict of interest will be managed
Standard 5	Be focused on health and related outcomes	1. Be developed around explicitly defined clinical or public health questions 2. Address outcomes that are relevant to the guideline's expected end users 3. Clearly define the outcomes considered to be important to the person/s who will be affected by the decision, and prioritise these outcomes
Standard 6	Be evidence informed	1. Be informed by well conducted systematic reviews 2. Consider the body of evidence for each outcome (including the quality of that evidence) and other factors that influence the process of making recommendations including benefits and harms, values and preferences, resource use and acceptability 3. Be subjected to appropriate peer review
Standard 7	Make actionable recommendations	1. Discuss the options for action 2. Clearly articulate what the recommended course of action is, and when it should be taken 3. Clearly articulate what the intervention is so it can be implemented 4. Clearly link each recommendation to the evidence that supports it 5. Grade the strength of each recommendation
Standard 8	Be up-to-date	1. Ensure that the recommendation is based on an up to date body of evidence 2. Propose a date by which the evidence and the guideline should be updated. This may be specific to each recommendation.

Standard	Description	Main points to address
Standard 9	Be accessible	1. Be easy to find 2. Ideally be free of charge to the end user 3. Be clearly structured, easy to navigate and in plain English 4. Be available online

Source: NHMRC Standards for Guidelines (https://www.nhmrc.gov.au/guidelinesforguidelines/standards) [140]

The NHMRC and many international guideline organisations [141-144] use the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system and the Oxford Centre for Evidence-Based Medicine (CEBM) list of levels of evidence, to assess the quality and strength of evidence from systematic reviews to classify recommendations as high, moderate, low, or very low quality. A summary of evidence grading prepared from documents from the NHMRC [145] and the Oxford CEBM [146] is presented in Table 2.2. In general, a "high" rating is based on good quality randomised controlled trials (RCTs) and represents evidence that is unlikely to be contradicted by future studies, resulting in a strong recommendation [142]. Moderate evidence includes quasi-experimental studies or cohort studies. The lowest level is expert opinion and clinical experience, often referred to as Good Practice Points (GPPs) or Clinical Practice Points (CPPs).

Table 2.2 Summary of Levels of evidence and strength of recommendations for interventions

Quality of evidence[a]	Definitions of quality[b]	Levels defined[c]	Consistency of evidence[a]
High quality – excellent (several Level I quality studies or Level II studies with low risk of bias)	Further research is very unlikely to change our confidence in the estimate of effect	**Level I:** • one or more systematic reviews with homogeneity of RCTs • Individual RCT with narrow CI • all or none case series **Level II**: • one or more RCTs: independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation • systematic review of cohort studies with homogeneity • ecological studies	Studies are consistent, with very large clinical effect and generalizable
Moderate quality – Good (one or two good quality Level II studies or Level III studies with low risk of bias.)	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate	**Level II**: • one or more RCTs: independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation • systematic review of cohort studies with homogeneity • ecological studies **Level III-1** • a pseudo-randomised controlled trial • systematic review of case-control studies with homogeneity **Level III-2**: a comparative study with concurrent controls • non-randomised trial • cohort study • case-control study Interrupted time series with control group **Level III-3**: a comparative study without concurrent controls • Historical control study • Two or more single arm study • Interrupted time series without a parallel control group	Studies are mostly consistent, with substantial clinical impact, with a body of evidence similar to the target population in the guideline
Low quality – Satisfactory (level III studies with low risk or Level I or II studies with moderate risk of bias)	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate	**Levels I to III**: see above	Some inconsistency in studies, with moderate clinical impact. The study population differs from the target population, but it is clinically sensible to apply the evidence
Very low quality – Poor (Level IV studies or Levels I to III with high risk of bias)	Any estimate of effect is very uncertain	**Levels I to III**: see above **Level IV:** • Case series • Cohort studies of persons at different stages of disease	Evidence is inconsistent with small or restricted clinical impact. The study population is different to the target population, and it is hard to judge generalisability of findings.
Good Practice Points – Very poor			Recommendation is based on clinical experience and expert opinion

Abbreviations: CI, confidence interval; RCT, randomised controlled trial.
Notes:

a. Derived from Table 3 (Body of Evidence Matrix) in the NHMRC document "NHMRC additional levels of evidence and grades for recommendations for developers of guidelines: Stage 2 Consultations (2008-2009)" [145].

b. Refer to BOX 2 in Guyett et al (2008) GRADE: an emerging consensus on rating quality of evidence and strength of recommendations.

c. Derived from NHMRC Evidence Hierarchy [145] and Oxford Centre for Evidence-based Medicine – Levels of Evidence (March 2009) [146].

2.2.2 Quality of guidelines

CPGs provide the best summaries of currently available evidence and can be a useful guide for clinicians [136]. Procedures adopted by guideline committees use respected systems such as the GRADE system and AGREE II checklist (Appraisal of Guidelines Research and Evaluation) to ensure a high standard for endorsing guidelines [142]. Checklists assess for appropriate randomisation techniques, effectiveness of blinding of participants and researchers, selective reporting of outcomes, and incomplete outcome data [147, 148]. AGREE II also includes an assessment of stakeholder involvement and editorial independence. When these internationally recognised systems, such as GRADE, AGREE, and the CEBM evidence levels are used, the quality of CPGs has been found to be superior [149]. Vitry and Zhang [149] examined a sample of 17 Australian guidelines for chronic conditions using the AGREE instrument and found those not approved by the NHMRC were of significantly lower quality than approved guidelines.

2.2.2.1 Bias in guidelines

While use of the GRADE and AGREE checklists can assist in generating reliable, evidence-driven guidelines, the quality and usefulness of guidelines is still questionable [134, 150-154]. Labelling evidence as level “I” or “IV”, or “C”, or “D”, does not negate the “air of certainty” provided by the term “evidence”, nor give a good indication of the quality of the research that underpins the recommendation [155].

COIs are recognised as a major source of bias in CPGs [134], but even when a number of measures are taken to address them, a risk of bias remains [135, 156]. Disclosure of conflicts can worsen bias in some instances [134, 157, 158], shifting the issue from “secrecy of bias” to “openness of bias” [134, p.810]. Extensive lists of COIs can falsely give the impression that financial influences are being adequately handled [159]. Disclosing conflicts can sometimes even be perceived as a sign of expertise, making disclosers feel liberated and exonerated, leading some to feel licenced to behave immorally through a phenomenon called “moral licensing” [158].

There are also biases that are largely invisible to the reader, such as publication bias [152]. Results of industry trials are often published more rapidly than non-industry trials [153, 160], with a strong bias toward publishing trials demonstrating positive results while omitting trials showing negative results [152]. For example, of 74 trials that were submitted to the FDA between 1987 and 2004 in support of approvals or labelling changes for

antidepressants, 38 showed a positive statistical result, of which 37 were published [161]. For the other 36 trials showing non-significant results, three were published as negative results, 11 published with the results inaccurately presented in a positive light, and 22 never published [161]. This publication bias inflated treatment effect sizes for antidepressants. The overall effect size calculated using the FDA combined published and unpublished studies dataset was 0.31, whereas limiting the review to only articles published in journals inflated the effect size to 0.41, an increase of 32% [161]. This imbalance biases any results from systematic literature reviews and meta-analyses that form the foundation of the highest level of evidence in published guidelines [162].

An example of how poor-quality evidence has informed the approval of the antidepressant fluoxetine for treating childhood depression, which is currently recommended in all national and international guidelines, is described in Appendix 1.

2.2.3 Usefulness of guidelines in general practice

Although CPGs provide the best evidence-based advice, drawn from extensive literature reviews and a range of expert opinions, they are intended to be used as guides only [163]. According to the Australian Code of Conduct for doctors, published by the Medical Board of Australia, “No code or guidelines can ever encompass every situation or replace the insight and professional judgement of good doctors.” [163, p.5]. Similarly, other clinical practice guidelines emphasise that recommendations are not mandatory [141, 164] and do not override a health professional’s personal responsibility for medical decisions, which need to consider the individual circumstances and preferences of the patient [165]. Nonetheless, guidelines have substantial authority and an air of certainty, leading physicians to believe that they should use the guidelines to avoid malpractice [135]. As Mangin (2012) points out, guidelines can have a powerful influence over medical practice but may not be “fit for purpose in primary care” [155, p.160] and may even cause harm.

A recent 2019 study examined the effect of the introduction of the National Institute for Health and Care Excellence (NICE) depression guidelines for children in 2005 on antidepressant prescribing practices in primary care in the UK between 2000 and 2010 [166]. The guideline strongly emphasised first-line psychosocial therapies, so researchers hypothesised its advice would lead to a reduction in prescribing of antidepressants to children and adolescents, especially following the warnings by regulatory authorities in the US and UK in 2003 about increased risks for suicide and self-harm in children and youth.

Contrary to hypotheses, following the publication of the NICE guideline, there was a steady increase in prescribing from 2005 to 2010, but only for the three drugs specifically recommended as second-line treatments in the guideline: fluoxetine, citalopram, and sertraline. Despite the NICE guideline being replete with cautions and limitations of using antidepressants in children and adolescents, it appeared the inclusion of the drug recommendations in the guideline was interpreted by clinicians as an endorsement for their effectiveness and safety.

Despite the limitations discussed above and in Section 2.2.2, however, CPGs remain an important resource for GPs [136]. Section 2.2.4 describes the search strategy used to source relevant guidelines for analyses of guideline-concordant prescribing in this thesis. Summaries of guideline recommendations for child and adolescent mental disorders, focusing on psychotropic drug prescribing, are provided in Section 2.3.

2.2.4 Guideline search strategy

The aim of this project was to examine the prescribing of psychotropic medications to children and adolescents in Australia. NHMRC-approved guidelines, now accessed from the Guidelines International Network International Guidelines Library (https://g-i-n.net/), were located first. Secondly, the RANZCP website (https://www.ranzcp.org/clinical-guidelines-publications) was searched. Overall, very few Australian resources from these organisations listed guidelines specific to children and adolescents, so the search was expanded to include international registers of guidelines.

The National Guideline Clearinghouse website, a useful resource for US and international guidelines, ceased as of 16 July, 2018 due to funding cuts [167]. However, other free internet resources provide comprehensive lists of international medical guidelines [167]. The Turning Research Into Practice (TRIP) [168] medical database (https://www.tripdatabase.com/) was the most comprehensive resource at the time of writing this chapter and, as recommended by Gerberich et al. (2019) [167], was used in searches in this thesis. PubMed, Medline, and professional organisation websites, such as the RANZCP, were also searched.

Two living guidelines were also included in searches: the eTG Complete (https://tgldcdp.tg.org.au/) and BMJ Best Practice (https://bestpractice.bmj.com/) guidelines. Guideline recommendations are traditionally based on extensive systematic reviews of the available evidence at a particular point in time and published as a static document valid for several years [137]. Given the increasingly rapid expansion in medical

knowledge, guideline recommendations can become outdated by the time they are ready for publication [169]. Living guidelines continuously update as new evidence emerges rather than waiting for the next scheduled complete guideline review [169, 170].

The following sources were searched for all guidelines relating to mental disorders for children and adolescents:

1. PubMed and Medline using:
    a. Advanced search feature "guideline" filter
    b. Using guideline as a keyword
    c. Following up with "similar article" and "cited by" listing for each article located in PubMed
2. TRIP medical database guidelines filter (all guidelines, including Australian and New Zealand guidelines)
3. Websites of organisations identified in prior searches (e.g., NICE, American Academy of Child and Adolescent Psychiatry [AACAP])
4. Reference lists in all documents that were identified by searches described in points 1 to 3
5. Living guidelines: BMJ Best Practice point of care guidelines and eTG Complete Australian guidelines[a]
6. Where search strategies listed in points 1 to 5 failed to locate any guidelines, further searches were performed in Australian general practice journals (e.g., Australian Family Physician, Australian Journal of General Practice).

2.2.4.1 Guidelines discussed in this chapter

This chapter summarises available guidelines that were applicable during the study period 2011 to 2018. Many guidelines described in the summaries in this chapter are out of date but have been included because they are the most current for their respective organisations and are still influential. For example, some guidelines issued by AACAP are over 10 years old but are still referenced in some recent Australian and international publications and by the RANZCP and may, therefore, have influence on current prescribing practices in Australia.

[a]. eTG Complete guidelines were accessed from 2019 to 2022 but covered years prior to these dates that were applicable to the study period. It was not possible to determine the publication dates for the guidelines, so they have been referenced as the year of access.

2.3 Guidelines in use in Australia

At the time of writing, the only CPG approved by the NHMRC for the treatment of mental disorders in children or adolescents was the *beyondblue* guideline for depression in adolescents and young adults aged 13-24 years [171]. This guideline was valid for a portion of the study period (2011 to 2016). Australian organisations, including *beyondblue* and Orygen, have created several guidelines for treating mental disorders, but there are few CPGs overall directed at treating children up to 18 years. In the absence of reliable evidence summaries published by Australian health organisations, health care providers (HCPs) may refer to international guidelines. For example, the Australian *beyondblue* guidelines [171] for bipolar disorder refer HCPs to the Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines [172] and the British Association for Psychopharmacology (BAP) guidelines [173]. In many cases, where child and adolescent guidelines lack paediatric evidence, both national and international guidelines will refer HCPs to adult guidelines [171, 174-186]. Therefore, where relevant, international and adult guidelines have also been summarised.

The following guidelines summaries present, analyse, and compare information available to GPs from locally published resources and from respected international organisations, including NICE in the UK and AACAP in the US. The guidelines are summarised under the main categories of depressive disorders, bipolar disorder, ADHD, disruptive behaviour disorders (DBDs), anxiety disorders, psychotic disorders, ASD, eating disorders (EDs), sleep disorders, and enuresis (bedwetting) disorders. A section on “other disorders” includes diagnoses for conditions where there is minimal evidence for children and adolescents and includes substance use disorders (SUDs), personality disorders (PDs), and learning disorders (LDs). For convenience, for Sections 2.3.1 to 2.3.10, a list of guidelines that have been summarised for each disorder is tabled at the beginning, followed by a summary of TGA-approved drug treatments for the disorder. At the end of each section, advice on monitoring for adverse drug effects is also summarised. Historical guideline changes noted up to the end of the study period that may have influenced prescribing practices are also summarised.

2.3.1 Depressive disorders

The guidelines summarised in this section on managing depressive disorders in children and adolescents are listed in Table 2.3.

Table 2.3 Australian and international guidelines for management of depressive disorders in children and adolescents

Country	Organisation	Year	Title	Reference
Australia	*beyondblue*	2011	Clinical Practice Guidelines: Depression in adolescents and young adults.	McDermott B, Baigent M, Chanen A, et al. (2011) *Clinical Practice Guidelines: Depression in adolescents and young adults*. [171]
Australia	eTG Complete	2019	Major depression in children and adolescents.	eTG Complete (2019) *Major depression in children and adolescents*. (accessed 2 Jun 2019). [191]
Australia	RANZCP	2015	Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders.	Malhi GS, Bassett D, Boyce P, et al. (2015) Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. [192]
UK	NICE	2005	Depression in children and young people: Identification and management – cg28.	NICE (2005) *Depression in children and young people: Identification and management.* (accessed 11 Jul 2019). [194]
UK	NCCMH, commissioned by NICE	2005	National Clinical Practice Guideline Number 28 full guideline: Depression in children and young people: Identification and management in primary, community and secondary care.	National Collaborating Centre for Mental Health (2005) Depression in Children and Young People: Identification and management in primary, community and secondary care. Full guideline. [199]
US	AACAP	2007	Practice parameter for the assessment and treatment of children and adolescents with depressive disorders.	Birmaher B, Brent D, Bernet W, et al. (2007) Practice parameter for the assessment and treatment of children and adolescents with depressive disorders. *Journal of the American Academy of Child and Adolescent Psychiatry* 46(11): 1503-1526. [188]
US	GLAD-PC	2007	Guidelines for Adolescent Depression in Primary Care (GLAD-PC): Part II. Treatment and Ongoing Management.	Cheung AH, Zuckerbrot RA, Jensen PS, et al. (2007) Guidelines for Adolescent Depression in Primary Care (GLAD-PC): II. Treatment and Ongoing Management. [198]
UK	BMJ Best Practice	2018	Depression in children.	BMJ Best Practice (2018) *Depression in children*. (accessed 12 Jun 2019). [189]
UK	BAP	2015	Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines.	Cleare A, Pariante CM, Young AH, et al. (2015) Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines. [200]

Country	Organisation	Year	Title	Reference
US	TMAP	2007	Texas Children's Medication Algorithm Project: update from Texas Consensus Conference Panel on Medication Treatment of Childhood Major Depressive Disorder.	Hughes CW, Emslie GJ, Crismon ML, et al. (2007) Texas Children's Medication Algorithm Project: update from Texas Consensus Conference Panel on Medication Treatment of Childhood Major Depressive Disorder. [193]
Canada	British Columbia GPAC	2010	Anxiety and Depression in Children and Youth – Diagnosis and Treatment.	Guidelines and Protocols Advisory Committee (2010) *Anxiety and Depression in Children and Youth – Diagnosis and Treatment*. (accessed 20 May 2020). [196]

Abbreviations organisations/institutions: AACAP, American Academy of Child and Adolescent Psychiatry; BAP, British Association for Psychopharmacology; eTG Complete, Electronic Therapeutic Guidelines Complete; GPAC, Guidelines and Protocols Advisory Committee; GLAD-PC, Guidelines for Adolescent Depression in Primary Care; NCCMH, National Collaborating Centre for Mental Health; NICE, National Institute for Health and Clinical Excellence; RANZCP, Royal Australian and New Zealand College of Psychiatrists; TMAP, Texas Medication Algorithm Project.

2.3.1.1 TGA-approved psychotropic drugs for treatment of depression in children and adolescents

No psychotropic drugs have been approved by the TGA for the treatment of depression in children and adolescents.

2.3.1.2 Introduction

Clinical depression is a mood disorder where sufferers experience feelings of sadness, hopelessness, and loss of interest in activities that previously brought enjoyment [187]. The treatment of depression is implemented in three phases: acute, continuation, and maintenance [188, 189]. Non-pharmacological options are considered first-line in a majority of international guidelines.

In the following section, the only NHMRC-approved Australian guideline and other Australian resources are briefly described (Section 2.3.1.3). A description of depression by severity and phase of illness is then discussed in Section 2.3.1.4, including both Australian and international guidelines. Detailed summaries of recommendations for treatment of acute depression (Appendix 2) and recurrent, chronic, and treatment-resistant depression (Appendix 3) are included in the Appendices.

2.3.1.3 Australian guidelines for depression

There are several guidelines for the treatment of child and adolescent depression available for clinician reference in Australia and New Zealand, including *beyondblue* [171], Orygen [190] and an online resource, Electronic Therapeutic Guidelines Complete (eTG Complete) [191].

Beyond Blue (previously *beyondblue*) is an independent, not-for-profit Australian national depression initiative that was established in 2000. *beyondblue* published clinical guidelines for treating depression in adolescents and young adults [171], which were officially approved by the NHMRC in 2011. Although now outdated, the *beyondblue* guidelines would have been considered current for 5 years from publication in 2011 [171], so would be applicable for some of the analysis period in this thesis (2011 to 2016). They are the only Australian paediatric mental disorder guidelines that have received approval from the NHMRC, so they have been given prominence in the discussion of depression treatments in this chapter.

The *beyondblue* guidelines are intended for use in young people aged 13-24 years, with each recommendation graded for the quality and type of supporting evidence based on the NHMRC grading system (see Tables 2.1 and 2.2 and *beyondblue* guidelines [171, p.94]). Due to the broad age range in these guidelines, only some recommendations and practice points apply to young people aged up to 18 years. Only grades A and B are listed as recommendations, as lower grades were considered inadequate to guide treatment, needing to be applied with caution. Grade A (high) is defined as good quality evidence that can be trusted to guide practice, while Grade B (moderate) represents a trusted source of evidence that can be used to guide practice in most situations [171].

Seven of the eight recommendations are relevant to the treatment of adolescents, and all are graded B, with recommendations 5 to 8 relating to antidepressant medications (see Table 2.4). The only A-grade recommendation relates to psychosocial preventive measures, which were found to be ineffective (and are not recommended). Nineteen of 32 GPPs that are relevant to the treatment of adolescents aged 13-18 years are also listed in Table 2.4, of which 10 are related to antidepressant treatment (GPPs 19-28). GPPs are informal recommendations that have no solid support from published literature and are generated by a consensus of expert opinion.

Table 2.4 Recommendations in the 2011 Australian *beyondblue* guidelines for treatment of depression in adolescents and young adults

Recomm-endation[a]	Recommendation text	Evidence Grade[b]
1	Psychosocial interventions of the types investigated to date are not currently recommended for universal prevention of depressive symptoms or major depressive disorder in the adolescent population. More research is needed to identify effective approaches.	A
2	For children who experience a family-related risk factor for depression, family-focused interventions should be considered for the prevention of major depressive disorder in adolescence.	B
3	Cognitive behavioural interventions should be considered for short-term symptom reduction in adolescents with identified depressive symptoms who do not meet diagnostic criteria for major depressive disorder.	B
4	Cognitive behavioural therapy (CBT) or interpersonal psychotherapy (IPT) should be considered as first-line treatment for adolescents with major depressive disorder.	B
5	Prescription of the selective serotonin reuptake inhibitor (SSRI) fluoxetine should be considered for acute, short-term reduction of depressive symptoms in adolescents with moderate to severe major depressive disorder, where psychological therapy has not been effective, is not available or is refused, or if symptoms are severe.	B
6	CBT may be added to/continued with SSRI therapy, to reduce the risk of suicidal thinking and improve functioning in adolescents with major depressive disorder.	B
7	Tricyclic antidepressants should not be used for treating major depressive disorder in adolescents.	B
8	Young people should be monitored for the onset of or increase in suicidal thinking following initiation of SSRIs.	B
GPP 10	Health professionals, young people and parents/carers must be aware of the dangers of not treating episodes of moderate to severe depression. Depression is the major risk factor for suicide.	
GPP 11	Development of the management plan should be person-centred, involving consideration of physical, mental, family, social, spiritual and cultural factors relevant to the young person.	
GPP 12	Treatment decisions should be based on the findings of assessments, taking into account the severity of symptoms, response to any previous treatments and co-occurring conditions, as well as the young person's circumstances, preferences and resources.	
GPP 14	The length of treatment required for effective remission varies. Depressive conditions may require up to 36 weeks of active treatment.	
GPP 17	CBT and IPT should be provided by professionally trained CBT/IPT therapists who have experience in working with young people. It is important that the therapy is applied in line with evidence-based practice manuals. Continuing maintenance of therapy skills is essential.	
GPP 19	SSRIs are not recommended for treating young people with mild depression.	
GPP 20	Prescription of an SSRI must occur within the context of an ongoing therapeutic relationship and management plan.	
GPP 21	To enable informed consent to pharmacological treatment, young people must be given information on adverse effects (including the possibility of emergence or escalation of suicidal thinking) and the need for ongoing monitoring during treatment.	
GPP 22	Pharmacological treatments need to be prescribed by those trained to do so, who are very familiar with the range of adverse effects and able to appropriately monitor the young person. Where necessary, expert advice should be sought before prescribing, or the young person should be referred to a mental health service or psychiatrist.	
GPP 23	Close monitoring of symptom severity and adverse effects is required for young people taking an SSRI, especially during the first 4 weeks.	
GPP 24	A protocol for managing suicidal thinking must be in place for every young person who is taking an SSRI, including baseline assessment and regular monitoring for suicidal thinking.	

Recommendation[a]	Recommendation text	Evidence Grade[b]
GPP 25	Health professionals should be aware of the risk that a manic episode may be precipitated following initiation of SSRIs. For young people with depressive episodes and a history of mania or mixed presentations, a mood stabiliser may be required.	
GPP 26	If a young person does not respond to an adequate treatment dose (psychological therapy and/or pharmacological treatment) after an appropriate period of time, the diagnosis should be reviewed and consideration given to co-occurring conditions, drug or alcohol misuse or ongoing adverse circumstances.	
GPP 27	While there is a small evidence base, current good clinical practice suggests continuing medication therapy for 6 months post-remission.	
GPP28	Where SSRI medication is warranted, a combined SSRI plus CBT/IPT approach appears to provide the most effective care. If a moderate to severe depressive disorder fails to respond to combined therapy, specialist advice or a second opinion should be sought.	
GPP 29	If discontinuation of treatment is planned, consideration needs to be given to factors that may contribute to relapse and recurrence.	
GPP 30	Complex presentations may require a longer assessment phase and multiple interventions delivered by different health professionals. Overall case management by one health professional is advisable.	
GPP 31	Electroconvulsive therapy (ECT) may be considered in rare cases, such as treating severe depression with psychotic features where other approaches have not been successful.	
GPP 32	If inpatient care is required, admission should be to an environment designed for young people wherever possible.	

Abbreviation: GPP, good practice point.
Source: McDermott et al. (2011) [171, pp.viii-xiii]
Notes:
a. Only recommendations and GPPs relevant to adolescent treatment were included in this table.
b. Grades of evidence: Grade A: excellent evidence - at least one systematic review or several randomised controlled trials (RCTs) with low risk of bias; Grade B: good evidence -pseudo-randomised controlled trials, case-control and cohort studies with low risk of bias; Grade C: satisfactory evidence - lower quality RCTs with moderate risk of bias and some cohort studies; Grade D: poor evidence - case series and studies from categories A to C with high levels of bias.

Other Australian resources include eTG Complete [191], RANZCP CPGs for mood disorders [192], and Orygen guidelines for treating depression in young people [190]. eTG Complete is an Australian online therapeutic guideline resource accessible to health care professionals and maintained by Therapeutic Guidelines Ltd, an independent not-for-profit organisation located in Melbourne (https://tgldcdp.tg.org.au/). The guideline available at the time of writing was accessed in April 2019.

The RANZCP guidelines were prepared by the College's Mood Disorders Committee in consultation with international experts and published in 2015, but they are predominantly adult guidelines with limited reference to treatment in children and adolescents. Orygen guidelines [190], published in 2017, summarise recommendations from the 2005 (updated 2015) NICE guidelines and have therefore not been separately discussed.

2.3.1.4 Australian and international depression guidelines by severity and phase of illness

2.3.1.4.1 Mild and sub-syndromal depression

In most countries, first-line therapy for children and adolescents with mild, uncomplicated depression with low levels of psychosocial impairment is “watchful waiting” [193, 194] or “active monitoring” [188, 189, 195, 196], recommended for up to eight weeks. Guideline recommendations for mild and sub-syndromal depression suggest no treatment unless symptoms worsen significantly [165, 188, 189, 193, 195, 197]. Similarly, Australian *beyondblue* [171], eTG Complete [191], and RANZCP [192] guidelines recommend non-pharmacological options as first-line treatment.

BMJ Best Practice guidelines suggest active monitoring as first-line treatment for all levels of depression but also allow the addition of medication (e.g., melatonin, antihistamines) at any stage to address symptoms associated with depression, such as insomnia or agitation [189]. Appendix 2 compares guideline recommendations.

2.3.1.4.2 Moderate and severe depression

When depression is diagnosed as moderate or severe, cognitive behaviour therapy (CBT) or interpersonal therapy (IPT) is recommended as first-line therapy in the *beyondblue* guidelines (Recommendation 4; Table 2.4), with the addition of a selective serotonin reuptake inhibitor (SSRI) antidepressant (fluoxetine) only when therapy has been tried and found ineffective, or therapy is unavailable or is refused by the young person, or where symptoms are particularly severe (Recommendation 5; Table 2.4). Australian eTG Complete guidelines also recommend adding fluoxetine for moderate or severe depression if there has been an inadequate response to non-drug therapy [191]. Second-line pharmacological options include other SSRIs (sertraline, citalopram) [171, 191] or mirtazapine [171].

Venlafaxine and paroxetine are not recommended due to reports of increased hostility and suicide-related events [191]. Tricyclics are mostly considered too ineffective and dangerous for children and adolescents [171, 191], although eTG Complete limits this contraindication to young people less than 16 years old.

International guidelines provide similar advice, where all except US Guidelines for Adolescent Depression in Primary Care (GLAD-PC) recommend non-pharmacological options as first-line treatments for moderate and severe depression (Appendix 2). GLAD-PC guidelines are arguably the most positive towards pharmaceutical treatments and recommend fluoxetine as a first-line option for moderate or severe depression [198] and

allow a wide range of other SSRI options, including citalopram, escitalopram, fluvoxamine, sertraline, and paroxetine [198] (refer to Table 3 of the 2007 GLAD-PC guidelines [198, p.e1320]).

In the case of severe, unresponsive depression, two guidelines allow for treatment augmentation with antipsychotics as a last option: the BMJ Best Practice guidelines for depression in children [189] and RANZCP clinical practice guidelines for mood disorders [192, p.1169].

2.3.1.4.3 Depression with psychotic symptoms and other comorbid disorders

Depression commonly occurs with other conditions (*beyondblue*, p.5) [171]. If depression is associated with psychotic symptoms, *beyondblue* guidelines strongly recommend referral to specialised services [171, p.49]. Otherwise, psychotic symptoms are addressed only within the context of bipolar disorder, which will be discussed in the following section (Section 2.3.2). Other Australian [192] and international guidelines [188, 189, 194] recommend the addition of a second-generation antipsychotic (SGA) if an antidepressant medication is not adequately controlling symptoms.

For other comorbid conditions, consideration needs to be given to which condition is causing the most impairment or distress, with priority given to the treatment of the most severe or disabling condition [188, 189, 193].

2.3.1.4.4 Continuation, maintenance treatment, recurrent and treatment resistant depression (TRD)

There is minimal advice on continuation, maintenance phases, recurrent, or TRD in Australian or international guidelines (Appendix 3). A few guidelines suggest there is no evidence for continuation [199] or maintenance [171, 194, 199] in children and adolescents, but others suggest drugs be continued from 6 months [171, 188, 189, 193, 194, 196, 198, 200] to life [193]. The lack of evidence in children and adolescents resulted in two guidelines basing recommendations on adult guidelines [198, 200]. Drug recommendations are similar to those included in the treatment of acute depression (Appendix 2), but treatment-resistant depression (TRD) also includes non-SSRIs duloxetine and trazodone as options [189]. Trazodone, a serotonin receptor antagonist and reuptake inhibitor, is recommended to be used with extreme caution due to hepatotoxicity [189].

2.3.1.4.5 Adverse events

There is a well-established link between use of SSRI antidepressants in children and adolescents and a risk of emergent or worsening suicidal thinking, hostility, self-harm, and agitation [201]. This is recognised in the majority of guidelines for childhood depressive disorders [171, 188, 189, 191, 192, 194, 198, 200]. eTG Complete guidelines recommend that the young person and their family be advised of the risk for emergent suicidality and that health professionals monitor patients closely for the first two months on antidepressants [191].

Guidelines also warn of the development of mania if antidepressants are being prescribed for a young person with undiagnosed bipolar disorder [171, 192]. If SGAs are used, health care providers are advised to also monitor closely for weight gain, metabolic syndrome and extrapyramidal symptoms [192].

2.3.1.4.6 Changes in treatment recommendations

There have not been any major changes in recommended treatments across the study period.

2.3.2 Bipolar Disorders

The guidelines summarised in this section on managing bipolar disorder in children and adolescents are listed in Table 2.5.

Table 2.5 Australian and international guidelines for management of bipolar disorders in children, adolescents and adults

Country	Organisation	Year	Title	Reference
Australia	*Beyondblue* (adolescent)	2011	Clinical Practice Guidelines: Depression in adolescents and young adults.	McDermott B, Baigent M, Chanen A, et al. (2011) *Clinical Practice Guidelines: Depression in adolescents and young adults*. [171]
Australia	eTG Complete (child)	2019	Juvenile bipolar disorder.	eTG complete (2019) *Juvenile bipolar disorder*. (accessed 2 Jun 2019). [174]
Australia	eTG Complete (adult)	2019	Bipolar disorder.	eTG complete (2019) *Bipolar disorder*. (accessed 2 Jun 2019). [205]
Australia	RANZCP (adult)	2015	Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders.	Malhi GS, Bassett D, Boyce P, et al. (2015) Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. [192]
Australia	RANZCP (adult)	2004	Australian and New Zealand clinical practice guidelines for the treatment of bipolar disorder.	RANZCP (2004) Australian and New Zealand clinical practice guidelines for the treatment of bipolar disorder. [204]
Australia	Article in AFP (adult)	2013	Bipolar disorder.	Mitchell P (2013) Bipolar disorder. *Australian Family Physician* 42: 616-619. [208]
Canada	CANMAT (adult)	2013	Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2013 guidelines for the management of patients with bipolar disorder.	Yatham LN, Kennedy SH, Parikh SV, et al. (2013) Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. [185]
Canada	CANMAT (adult)	2018	Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder.	Yatham LN, Kennedy SH, Parikh SV, et al. (2018) Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. [186]
US	AACAP (child and adolescent)	2007	Practice parameter for the assessment and treatment of children and adolescents with bipolar disorder.	McClellan J, Kowatch R, Findling RL, et al. (2007) Practice parameter for the assessment and treatment of children and adolescents with bipolar disorder. [181]

Country	Organisation	Year	Title	Reference
US	CABF (child and adolescent)	2005	Treatment guidelines for children and adolescents with bipolar disorder.	Kowatch RA, Fristad M, Birmaher B, et al. (2005) Treatment guidelines for children and adolescents with bipolar disorder. [180]
UK	NICE – cg185 (adult)	2014	Bipolar disorder: assessment and management.	NICE (2014) *Bipolar disorder: assessment and management*. (accessed 4 Jun 2018). [184]
UK	BAP (adult)	2016	Evidence-based guidelines for treating bipolar disorder.	Goodwin GM, Haddad PM, Ferrier IN, et al. (2016) Evidence-based guidelines for treating bipolar disorder: Revised third edition recommendations from the British Association for Psychopharmacology. [177]
International	WFSBP (adult)	2017	Guidelines for the Biological Treatment of Bipolar Disorders: Acute and long-term treatment of mixed states in bipolar disorder.	Grunze H, Vieta E, Goodwin GM, et al. (2017) The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Acute and long-term treatment of mixed states in bipolar disorder. [178]

Abbreviations organisations/institutions: AACAP, American Academy of Child and Adolescent Psychiatry; AFP, Australian Family Physician; BAP, British Association for Psychopharmacology; CABF, Child and Adolescent Bipolar Foundation; CANMAT, Canadian Network for Mood and Anxiety Treatments; eTG Complete, Electronic Therapeutic Guidelines Complete; NICE, National Institute for Health and Care Excellence; RANZCP, Royal Australian and New Zealand College of Psychiatrists; WFSBP, World Federation of Societies of Biological Psychiatry.

2.3.2.1 Approved psychotropic drugs

Table 2.6 TGA-approved psychotropic drugs for bipolar disorders in children and adolescents

Medicine	Medicine Name	Age range	Indications
Quetiapine	Seroquel	10-17 years	Monotherapy for treatment of acute mania associated with bipolar 1 disorder
Lithium	Lithicarb	>11 years	Acute treatment and prophylaxis of mania
Lithium	Quilonium-SR[a]	>11 years	Treatment of acute episodes of mania and hypomania, and for prophylaxis of recurrent manic-depressive illness

Notes:
a. Quilonium -SR is gluten free lithium carbonate.

2.3.2.2 Introduction

Bipolar disorder is a condition characterised by episodes of mania or hypomania interspersed with depressive episodes [184]. It has a peak age of onset in late adolescence (15-19 years) [184], but is increasingly being diagnosed in children as young as 6 years [174] or even preschoolers [202]. The condition includes bipolar I, bipolar II, mixed affective, and rapid cycling disorders [181, 203], but CPGs address predominant symptoms, divided into manic/mixed or depressive, with each requiring different treatment strategies [180, 181,

184, 186, 204, 205]. Bipolar disorder treatment also includes a maintenance stage, which can be lifelong [177, 180, 181].

In children, irritability, rather than mania or elevated mood, is considered a core feature of child-onset bipolar disorder [202, 206], and there is some difficulty distinguishing the diagnosis from other childhood conditions such as ADHD and ODD [206]. The issue of bipolar disorder diagnosis in children remains controversial, with concerns about iatrogenic harm caused by the diagnosis in children and adolescents [202, 207].

Unlike treatment for depression, there is no recommendation for a period of "watchful waiting" for bipolar disorder, and psychological therapies are not generally recommended by guidelines except in conjunction with medications [171, 177, 181, 192, 204, 208]. Most guidelines make explicit reference to the use of adult guidelines when child and adolescent recommendations result in inadequate improvement [171, 174, 177, 178, 180, 181, 184-186]. Therefore, where minimal recommendations have been made for children and adolescents, adult guideline recommendations are included. Summaries of treatment guidelines are detailed in Appendix 4.

2.3.2.3 Australian guidelines

Australian guidelines provide little information on treatment strategies for bipolar disorders in children and adolescents. The *beyondblue* guidelines provide no recommendations and only eight good practice points [171] (Table 2.7): The guidelines include little evidence on the management of bipolar disorder in young people and suggest that clinicians consult the CANMAT and International Society for Bipolar Disorders (CANMAT-ISBD) and BAP guidelines [171, p.71].

Table 2.7 Good practice points in the 2011 Australian *beyondblue* guidelines for treatment of bipolar disorder in adolescents and young adults

GPP 33	Psychoeducation and psychological interventions to improve management and assist with coping skills and psychosocial functioning are valuable adjuncts to pharmacological treatment**.**
GPP 34	Considerations in decision-making about pharmacological treatments include past history of mania or family history of bipolar disorder, severity of symptoms, need for short-term stabilisation, previous dosage regime and adherence to treatments, and reasons for any non-adherence.
GPP 35	Serious agitation may require adjunctive medication, consistent with local prescribing protocols. If the patient is less unwell, lithium can be the initial drug of choice.
GPP 36	Short-term medication is generally required for acute mania, preferably with rapid-acting anti-mania medications.
GPP 37	Medication used for short-term stabilisation (e.g. for agitation) should be tapered and discontinued.
GPP 38	If symptoms are severe or the young person does not respond to treatment, combination pharmacological treatment is justified.
GPP 39	Specialist input should be sought for the care of young women with bipolar disorder who are considering pregnancy, pregnant or in the postpartum period.
GPP 40	A consistent, long-term, flexible relationship between the young person, his or her parents/carers and one health professional is ideal for outpatient care in young people whose condition has been stabilised. Young people's family members should feel comfortable contacting the health professional to report escalations of symptoms or other emergencies.

Source: McDermott et al. (2011) [171, p.xiii].

Similarly, 2019 eTG Complete juvenile bipolar disorder guidelines [174] and 2015 RANZCP mood disorder guidelines [192] provide little information on treatment for paediatric patients. In agreement with most international bipolar disorder guidelines for children and adolescents [171, 177, 178, 180, 181, 184-186], the eTG Complete guidelines for bipolar disorder in children also recommend adult guidelines as a secondary resource [174].

Because both Australian guidelines for childhood bipolar disorder provided minimal guidance [174, 192], with *beyondblue* providing only GPPs and the initial eTG Complete guidelines providing a minimal one-page summary of diagnosis and treatment recommendations [174], an additional search for any articles published in GP journals was carried out. An article published in the Australian Family Physician (AFP) in 2013 relating to treatment of bipolar disorder in the adult population was located that made similar treatment recommendations to other Australian resources. The AFP was a peer-reviewed journal published by the RACGP (now published under the name Australian Journal of General Practice). The journal aimed to provide relevant evidence-based information to Australian GPs to help guide treatment choices and provide high-quality patient care (https://www1.racgp.org.au/ajgp/about-the-journal). The journal was a highly respected and

influential journal, with readership levels ranging from 67% in 2009 [209] to 72% in 2017 [210].

2.3.2.4 International guidelines

Only two international guidelines described in Table 2.5 are specific to young patients: the 2007 AACAP Practice Parameter for the Assessment and Treatment of Children and Adolescents With Bipolar Disorder [181] and the 2005 Child and Adolescent Bipolar Foundation (CABF) Treatment Guidelines for Children and Adolescents With Bipolar Disorder [180]. Although both of these are outdated, they have been included for reference as they specifically refer to the paediatric population. Other international guidelines that recommend referral to adult guidelines have been summarised in Appendix 4, with separate sections for the adult and child/adolescent populations.

2.3.2.5 Australian and international guidelines by polarity and phase of illness

2.3.2.5.1 Treatment of acute manic and mixed episodes

Lithium, sodium valproate, and SGAs are the most commonly suggested medications for treatment of manic and mixed episodes of bipolar disorder (Appendix 4), with an overall shift from lithium to SGAs as a first-line treatment since the early 2000s (see Section 2.3.2.7).

This move toward SGAs in favour of traditional mood stabilisers, such as lithium and carbamazepine, is also reflected in Australian resources. According to both Australian guidelines [192, 205], the most consistent evidence is for the use of SGAs to treat mania. The AFP article addressing adult bipolar disorder treatment also recommended prescribing SGAs, especially risperidone and olanzapine, but also included the FGA haloperidol for the treatment of manic episodes [208].

2.3.2.5.2 Treatment of acute depressive episodes

For bipolar depressive episodes, evidence for children remains limited. As with treatment for mania, most guidelines suggest referring to adult treatment guidelines for clinical guidance [171, 174, 177, 178, 180, 181, 184-186]. However, there are some caveats when using adult guidelines to treat bipolar depression in children and adolescents. While lamotrigine has been shown to be effective in adult studies, there are significant safety concerns for young people and a black box warning for children aged under 16 years due to an increased risk of Stevens-Johnson syndrome [180, p. 225]. Antidepressants are also deemed unsuitable as they can cause a switch to mania in bipolar disorder patients [177, 178, 180, 181, 184, 186,

192, 205] and, as previously mentioned, can induce or exacerbate suicidal ideation in children and adolescents (see Section 2.3.1.4.5).

Due to the limited evidence for bipolar depression and concerns with antidepressants causing a manic switch, AACAP 2007 child and adolescent guidelines [181] recommend lithium, valproate (for children aged 12 years and over), and antipsychotics. NICE guidelines for bipolar disorder (child/youth section) are similar to those for depression, starting with psychological interventions for at least three months [165, p.39] and allowing addition of medications if response is inadequate and the bipolar depression is moderate to severe. The article in the AFP general practice journal also recommended quetiapine and the olanzapine-fluoxetine dual therapy [208], as did guidelines in the UK [184], US [181], and Canada [185].

2.3.2.5.3 Maintenance

Maintenance or prophylactic treatment is recommended, as there is a high risk of relapse [177, 192] (see Appendix 4 for individual guideline recommendations). Medication that is successful in stabilising acute episodes is recommended to be used in the continuation and maintenance phases [165, 177, 180, 192, 205]. The predominant polarity of the disorder (manic or depressive) is also taken into consideration when choosing medication, which can be continued from six months [192, p.1170] to lifelong [177, 180, 181]. However, there are no well-controlled studies of medications for maintenance treatment in children and adolescents [192]. Lithium has the most evidence on efficacy in adults, although a rapidly developing evidence base supports the preferential use of SGAs for maintenance treatment [192, 208].

2.3.2.6 Adverse Events

All guidelines mention the importance of monitoring for adverse events with pharmacological treatment, with the option of changing to alternate medications or treatments with less impact for the individual concerned if possible. Regular testing is important for patients taking SGAs, but especially important for patients taking lithium due to its well documented toxicity and narrow therapeutic index [211]. Monitoring is also important for patients on multiple medications due to the potential for drug interactions [177, 192]. Figure 2.1 summarises the ISBD 2009 guidelines for monitoring of medication-related adverse events in patients with bipolar disorder [211].

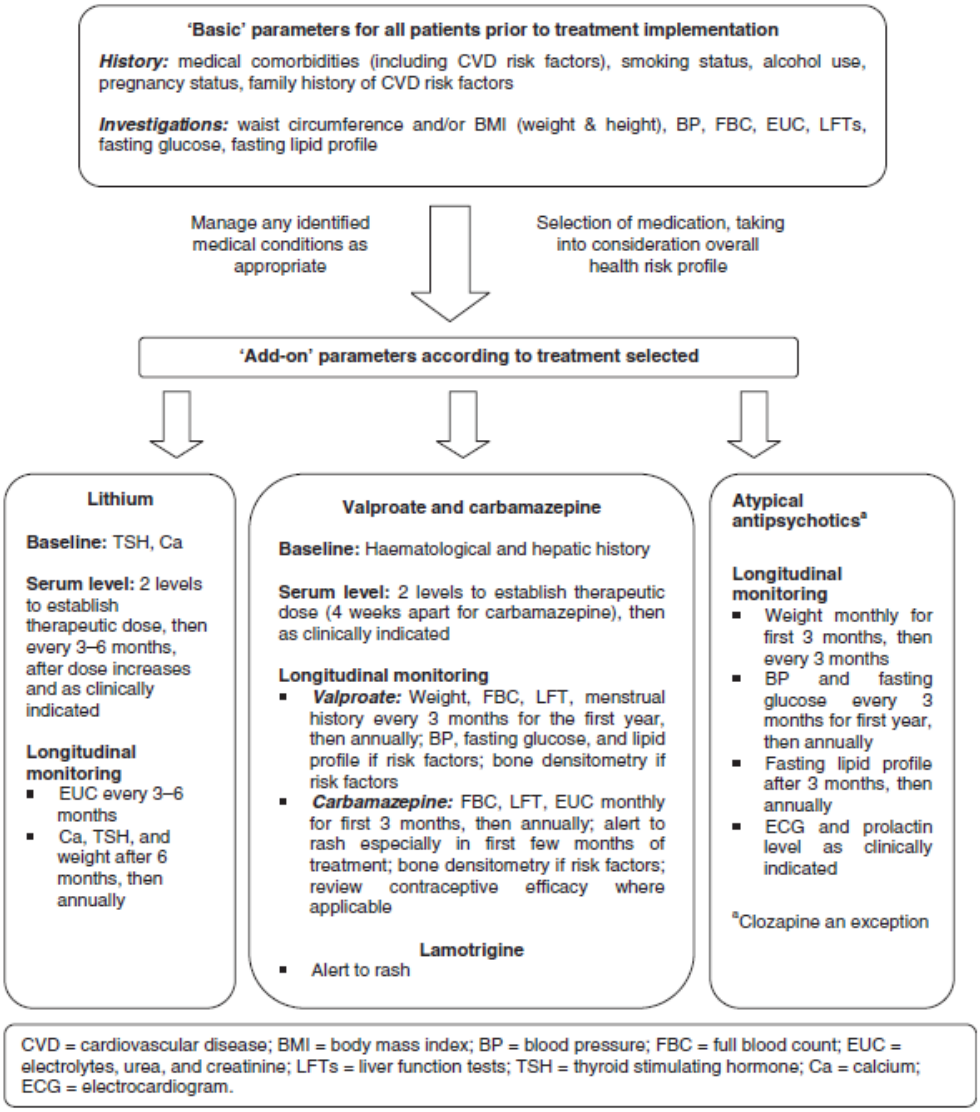


Figure 2.1 International Society for Bipolar Disorders recommended safety monitoring guideline (2009**).**
Source: Ng (2009). [211, p.562].

2.3.2.7 Changes in treatment recommendations

While mood stabilisers, anticonvulsants (e.g., valproate, carbamazepine), and SGAs remain the main medications used to treat bipolar disorder, recommendations for which drugs to prescribe as first-line treatments have changed. In the early 2000s, RANZCP guidelines recommended lithium, valproate, carbamazepine, and only one SGA (olanzapine) as first-line treatments for the manic phase of bipolar disorder in adults [204]. In the updated 2015 guidelines, SGAs dominate as first-line options [192]. Many other guidelines have also increasingly included SGAs as first-line options, in particular olanzapine, quetiapine, and risperidone [171, 177, 181, 192, 212]. As increasing evidence emerged about problems with valproate causing foetal abnormalities, the drug was removed as a first-line option in the CANMAT 2018 guidelines [186], and it appears less frequently as first-line in many post-2011

guidelines [177, 178, 184, 205]. Similarly, as more evidence has emerged about problems with olanzapine and ziprasidone, these SGAs have been relegated to second-line options in the 2018 CANMAT guidelines [186, p.135]. Lurasidone has been added as a first-line option for children and adolescents with bipolar depression in the CANMAT 2018 guidelines [186].

2.3.3 Attention Deficit Hyperactivity Disorder (ADHD)

The guidelines summarised in this section on managing ADHD in children and adolescents are listed in Table 2.8.

Table 2.8 Australian and international guidelines for management of ADHD in children and adolescents

Country	Organisation	Year	Title	Reference
Australia	NHMRC	2012	Clinical Practice Points on the diagnosis, assessment and management of attention deficit hyperactivity disorder in children and adolescents.	NHMRC (2012) *Clinical Practice Points on the diagnosis, assessment and management of attention deficit hyperactivity disorder in children and adolescents*. (accessed 13 Sep 2019).[215]
Australia	RACP	2009	Australian Guidelines on Attention Deficit Hyperactivity Disorder (ADHD) – Draft.	RACP (2009) *Australian Guidelines on Attention Deficit Hyperactivity Disorder (ADHD). Draft guidelines* (accessed 20 Jul 2018). [214]
Australia	eTG Complete	2019	Attention deficit hyperactivity disorder.	eTG complete (2019) *Attention deficit hyperactivity disorder*. (accessed 2 Jun 2019).[217]
US	AACAP	2007	Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder.	Pliszka S (2007) Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. [231]
US	AAP	2011	Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents.	AAP (2011) ADHD: Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. [223]
US	TMAP	2006	The Texas Children's Medication Algorithm Project: revision of the algorithm for pharmacotherapy of attention-deficit/hyperactivity disorder.	Pliszka SR, Crismon ML, Hughes CW, et al. (2006) The Texas Children's Medication Algorithm Project: revision of the algorithm for pharmacotherapy of attention-deficit/hyperactivity disorder. [232]
UK	NCCMH, commissioned by NICE	2009	The full NICE guideline on diagnosis and management of ADHD in children, young people and adults: ng72.	National Collaborating Centre for Mental Health (2009) Attention deficit hyperactivity disorder: The NICE guideline on diagnosis and management of ADHD in children, young people and adults: ng72. Leicester, UK: The British Psychological Society and The Royal College of Psychiatrists. (accessed 3 Sep 2018) [221]
UK	NICE	2018	Attention deficit hyperactivity disorder: diagnosis and management.	NICE (2018) *Attention deficit hyperactivity disorder: diagnosis and management*. (accessed 3 Sep 2018). [229]

Country	Organisation	Year	Title	Reference
Scotland	SIGN	2009	Management of attention deficit and hyperkinetic disorders in children and young people: A national clinical guideline.	SIGN (2009) *Management of attention deficit and hyperkinetic disorders in children and young people: A national clinical guideline*. (accessed 26 Sep 2019). [222]
UK	BMJ Best Practice	2018	Attention deficit hyperactivity disorder in children.	BMJ Best Practice (2018) *Attention deficit hyperactivity disorder in children*. (accessed 18 Oct 2018). [230]
UK	BAP	2014	Evidence-based guidelines for the pharmacological management of attention deficit hyperactivity disorder: update on recommendations from the British Association for Psychopharmacology.	Bolea-Alamanac B, Nutt DJ, Adamou M, et al. (2014) Evidence-based guidelines for the pharmacological management of attention deficit hyperactivity disorder: update on recommendations from the British Association for [225]
Canada	CPS	2018	ADHD in children and youth: Part 2-Treatment.	Feldman ME, Charach A and Belanger SA (2018) ADHD in children and youth: Part 2-Treatment. [227]
Canada	CADDRA	2011	Canadian ADHD Practice Guidelines, Third Edition.	CADDRA (2011) Canadian ADHD Practice Guidelines, Third Edition. Ontario, Canada: Canadian Attention Deficit Hyperactivity Disorder Resource Alliance (CADDRA). [233]
Canada	CADDRA	2018	Canadian ADHD Practice Guidelines, Fourth Edition.	CADDRA (2018) Canadian ADHD Practice Guidelines, Fourth Edition. Ontario, Canada: Canadian Attention Deficit Hyperactivity Disorder Resource Alliance (CADDRA). [226]
Kutcher et al.	International	2004	International consensus statement on attention-deficit/hyperactivity disorder (ADHD) and disruptive behaviour disorders (DBDs): clinical implications and treatment practice suggestions.	Kutcher S, Aman M, Brooks SJ, et al. (2004) International consensus statement on attention-deficit/hyperactivity disorder (ADHD) and disruptive behaviour disorders (DBDs): clinical implications and treatment practice suggestions. [228]

Abbreviations organisations/institutions: AACAP, American Academy of Child and Adolescent Psychiatry; AAP, American Academy of Pediatrics; BAP, British Association for Psychopharmacology; CADDRA, Canadian Attention Deficit Hyperactivity Disorder Resource Alliance; CPS, Canadian Paediatric Society; eTG Complete, Electronic Therapeutic Guidelines Complete; NCCMH, National Collaborating Centre for Mental Health; NHMRC, National Health and Medical Research Council; NICE, National Institute for Health and Care Excellence; RACP, Royal Australian College of Physicians; SIGN, Scottish Intercollegiate Guidelines Network; TMAP, Texas Medication Algorithm Project.

2.3.3.1 Approved psychotropic drugs

Table 2.9 TGA-approved psychotropic drugs for ADHD in children and adolescents

Medicine	Medicine Name	Age range	Indications
Methylphenidate[c]	Ritalin 10	>5 years	ADHD
Methylphenidate - LA[c]	Ritalin-LA/ Concerta	>5 years	ADHD
Lisdexamphetamine[a,c]	Vyvanse	>5 years	ADHD
Dexamphetamine[c]	Aspen dexamphetamine	>2 years	ADHD
Guanfacine[b]	Intuniv	>5 years	ADHD
Atomoxetine	Strattera	>5 years	ADHD

Notes:
a. Lisdexamphetamine was approved for treating ADHD in children and adolescents on 23 October 2013.
b. Guanfacine was approved for treatment of ADHD on 22 August 2017.
c. In Australia, stimulants are classified as Schedule 8 drugs that require strict monitoring. They are rarely initiated by GPs.

2.3.3.2 Introduction

ADHD is the most prevalent mental disorder diagnosed during childhood in Australia [213], defined as "a pattern of inattention and/or hyperactivity-impulsivity symptoms that persist for at least 6 months" [214, p.vii]. ADHD symptoms are not consistent with the developmental level of the child and cause significant impairment in the child's functioning at school and in social situations [214]. The diagnosis, however, remains controversial in children, as it can be difficult to distinguish symptoms from normal developmental stages [215]. As discussed in the following section, medication is the predominant treatment modality for ADHD.

2.3.3.3 Australian guidelines

During the study period, there were no Australian guidelines for ADHD approved by the NHMRC[b]. A draft document was funded by the Department of Health in June 2009 for preparation by the Royal Australian College of Physicians (RACP)[c] [214], but the document was not endorsed by the NHMRC due to concerns about conflicts of interest of major contributors to the draft document [215, 216]. Subsequently, the NHMRC published clinical practice points (CPPs) in June 2012, designed to be an interim measure to assist clinicians in the treatment of adult and paediatric ADHD patients [215]. Appendix 5 summarises the Australian and international guidelines and includes the 2009 draft document, which remained on the NHMRC website until the end of 2013, and the RACP website until 2019.

The NHMRC CPPs were based on expert consensus, with reference to UK NICE guidelines, Scottish Intercollegiate Guidelines Network (SIGN) guidelines, and American Academy of Pediatrics (AAP) guidelines in the US [215]. The CPPs suggest psychosocial or family interventions as first-line options for all children and adolescents. For children under 7 years, the emphasis is on environmental interventions and parent training, with medication to be used very rarely and with extreme caution in the young preschool cohort. Environmental interventions include strategies such as implementing structures and routines, using visual reminders (e.g., sticky notes, calendars), finding suitable, non-distracting areas, and in the school setting, the use of classroom management strategies, such as smaller class sizes [214]. For school-aged children and adolescents, psychological therapies and behavioural modifications are also suggested. The CPP medication recommendations were restricted to two TGA-approved stimulants, methylphenidate and dexamphetamine. CPPs were therefore

b. New NHMRC-approved guidelines for ADHD were published on 30 July 2022. [539]
c. The RACP is a college for medical specialists, which is distinct from the RACGP for general practitioners.

limited in scope, excluding many medication recommendations that were listed in the RACP 2009 draft guidelines.

The other main source of guidance for treating paediatric ADHD in Australia is the eTG Complete guidelines [217], accessed in 2019. eTG Complete guidelines state children as young as 4 years can benefit from stimulants, but stress that any child under 4 years should be prescribed medication only in rare situations, with an emphasis on parent training and behavioural interventions for preschoolers [217]. eTG Complete guidelines also include non-stimulants in their recommendations, such as atomoxetine, approved in Australia to treat children with ADHD since 2004 [218], as well as clonidine, a non-stimulant alpha-agonist/antihypertensive drug, which is available in Australia but not approved by the TGA for ADHD [219].

2.3.3.4 International guidelines

Given the lack of NHMRC-approved Australian guidelines for ADHD treatment, the role of international guidelines has become influential in the Australian context. Indeed, the NHMRC CPPs were developed to "complement, not replace, existing guidelines" [220, p.4], with specific reference to the NICE [221], SIGN [222], and AAP CPGs [223]. The RANZCP Position Statement Number 55 (Attention Deficit Hyperactivity Disorder in Childhood and Adolescence) also provides little advice and refers readers to the NHMRC CPPs and the RACP 2009 draft guidelines for guidance [224]. Therefore, relevant international guidelines for the treatment of children and adolescents with ADHD have also been summarised in Appendix 5.

2.3.3.5 ADHD Treatment recommendations by age group

2.3.3.5.1 Treatment for pre-schoolers

Most guidelines recommend parent training as first-line treatment for pre-schoolers [221-223, 225-229]. NICE guidelines also recommend a period of up to 10 weeks of "watchful waiting" [221, 229]. Medications are cautioned against in very young children in all guidelines, although, in agreement with the eTG Complete guidelines, AAP guidelines state medications are not necessarily contraindicated for 4-5-year-olds [223, p.1016]. If it is deemed necessary to prescribe medications, stimulants are first-line therapy, and immediate-release formulations are preferred, as dosages in long-acting formulations are considered too high for preschoolers [230-232] (Appendix 5).

2.3.3.5.2 Treatment for school-aged children

For children of school age and adolescents (mostly classified as 6-18 years), psychological therapies are also commonly recommended as first-line treatments [222, 226, 230, 231, 233]. When medications are prescribed, methylphenidate and amphetamine-based stimulants are considered first-choice, with some guidelines also including mixed salt amphetamines[d] and the pro-drug lisdexamphetamine amongst first-line options [225, 226, 230, 231, 233]. Following an initial trial of one stimulant, most guidelines recommend an alternative stimulant as a second-line option before trialling non-stimulant options such as atomoxetine, guanfacine, or clonidine [217, 222, 227, 230-233].

2.3.3.5.3 Treatment of ADHD with comorbidities

Comorbid conditions for children with ADHD are considered the norm rather than the exception [215, 228]. Fifty to ninety percent of children diagnosed with ADHD have at least one comorbid disorder, with almost half having two or more comorbidities [226, p.14]. Among these, behavioural disorders (e.g., ODD, CD) and anxiety are particularly prevalent [214, 217, 222, 226, 231].

Despite the near ubiquitous existence of comorbidities with ADHD, NHMRC CPPs contain no specific guides for their treatment, only providing generic advice that they "may require specific treatment strategies" [215, p.16]. Therefore, as with treatment for ADHD symptoms, the NHMRC CPPs recommend referring to NICE [221], SIGN [222], and AAP [223] guidelines when treating ADHD with comorbidity [215].

2.3.3.6 Adverse events

In Australia, stimulant medications are classified as Schedule 8 controlled substances [215]. Schedule 8 classification requires strict monitoring through state legislation, which requires that drugs be authorised, prescribed, documented, and destroyed in specific ways [234].

Stimulant medications used in the treatment of ADHD are associated with a range of adverse events, including the risk of growth retardation [226]. Although there is some debate as to whether there is an impact on final adult height, all guidelines, with the exception of the 2006 TMAP medication algorithm, recommend regular monitoring of growth and medication "holidays". A medication holiday is a temporary discontinuation of stimulants, usually at a

d. Mixed salt amphetamines are not prescribed in Australia.

time when it would be the least disruptive, such as weekends or during school vacations [226].

Adverse effects of stimulants also include increased heart rate and blood pressure [227]. Although these changes are considered too mild to significantly affect young people with ADHD [227, p.468], there have been reports of sudden deaths from stimulants in both adults and children, with proportionally more reported in children [231, p.911]. There are also concerns with the development or exacerbation of tics [226, 231, 232], suicidal ideation [226, 231, 232], psychosis [215, 217, 230, 231], or drug abuse or diversion [215, 226, 229, 230]. Drug diversion is the use of prescription drugs for non-prescribed or illegal purposes [215, 226, 229, 230]. If prescribed atomoxetine [217, 222, 226, 227, 230-232] or adjunct antidepressants for comorbid depression [214, 222, 232], suicidal ideation needs to be monitored closely in young people.

2.3.3.7 Changes in treatment recommendations

ADHD guidelines were first published by the American Association of Pediatrics in 1991 [235]. These initial and brief, two-page guidelines advocated for multimodal treatment for ADHD in children and adolescents, emphasising the importance of psychoeducation and therapy for families and considering medication for children aged six years or older. Stimulants were considered first-line medications, with imipramine and desipramine[e] considered second-line. Neuroleptics (antipsychotics) were considered too risky and ineffective to use in the treatment of ADHD.

The general advice since 1991 has not changed, but the number of medications used in the treatment of ADHD has increased substantially in all international guidelines, as well as the evidence base for treatment of comorbid conditions (Appendix 5). Additions include a range of longer-acting stimulant formulations, the pro-drug lisdexamphetamine, and the non-stimulants atomoxetine, guanfacine[f] and clonidine. The tricyclic antidepressant desipramine has lost favour as an alternative and was specifically contra-indicated in the 2007 AACAP guidelines due to reports of sudden death in children [231]. TCAs in general were relegated as options for rare use [229, 230], due to well-documented issues with adverse effects [236].

SGAs were never recommended for the treatment of ADHD symptoms, but from the early 2000s they were increasingly suggested for use in patients with comorbid aggression or

e. Desipramine was withdrawn from the Australian market in 2003.
f. Guanfacine was not approved as a treatment for ADHD in Australia until 22 August 2017.

conduct disorders [214, 225, 226, 228-230, 232], tics [232], bipolar disorder [226], learning disorders [225] or ASD [225, 226].

Only the NICE (2018), BAP (2014), BMJ Best Practice (2018), and CADDRA (2018) guidelines remain current, although other outdated guidelines continue to be referenced in these documents (e.g., AACAP 2007 guidelines are referenced in the BMJ Best Practice [230] and CADDRA 2018 [226] guidelines).

2.3.4 Disruptive Behaviour Disorders

The guidelines summarised in this section on managing disruptive behaviour disorders and aggression in children and adolescents are listed in Table 2.10.

Table 2.10 Australian and international guidelines for management of disruptive or aggressive behaviours in children and adolescents

Country	Disorder	Organisation	Year	Title	Reference
Australia	DBD	eTG Complete	2019	Disruptive behaviour disorders in children and adolescents.	eTG complete (2019) *Disruptive behaviour disorders in children and adolescents*. (accessed 1 Jun 2019). [237]
Australia	ODD	AFP article	2008	Oppositional defiant disorder.	Fraser A and Wray J (2008) Oppositional defiant disorder. [240]
UK	ASD & CD	NICE	2013	Antisocial behaviour and conduct disorders in children and young people: recognition and management.	NICE (2013) *Antisocial behaviour and conduct disorders in children and young people: recognition and management*. (accessed 25 Nov 2019). [244]
US	CD	AACAP	1997	Practice parameters for the assessment and treatment of children and adolescents with conduct disorder. American Academy of Child and Adolescent Psychiatry.	Steiner H (1997) Practice parameters for the assessment and treatment of children and adolescents with conduct disorder. American Academy of Child and Adolescent Psychiatry. [247]
US	ODD	AACAP	2007	Practice parameter for the assessment and treatment of children and adolescents with oppositional defiant disorder.	Steiner H and Remsing L (2007) Practice parameter for the assessment and treatment of children and adolescents with oppositional defiant disorder. [239]
Canada	DBD	CPS	2017	Screening for disruptive behaviour problems in preschool children in primary health care settings.	Charach A, Belanger SA, McLennan JD, et al. (2017) Screening for disruptive behaviour problems in preschool children in primary health care settings. [241]
Canada	ADHD with (ODD or CD)	Consensus group of Canadian paediatric specialists	2015	Canadian guidelines on pharmacotherapy for disruptive and aggressive behaviour in children and adolescents with attention-deficit hyperactivity disorder, oppositional defiant disorder, or conduct disorder.	Gorman DA, Gardner DM, Murphy AL, et al. (2015) Canadian guidelines on pharmacotherapy for disruptive and aggressive behaviour in children and adolescents with attention-deficit hyperactivity disorder, oppositional defiant disorder, or conduct disorder. [242]
US	Aggression	T-MAY – Part I	2012	Treatment of maladaptive aggression in youth: CERT guidelines I. Engagement, assessment, and management.	Knapp P, Chait A, Pappadopulos E, et al. (2012) Treatment of maladaptive aggression in youth: CERT guidelines I. Engagement, assessment, and management. [243]

Country	Disorder	Organisation	Year	Title	Reference
US	Aggression	T-MAY – Part II	2012	Treatment of maladaptive aggression in youth: CERT guidelines II. Treatments and ongoing management.	Scotto Rosato N, Correll CU, Pappadopulos E, et al. (2012) Treatment of maladaptive aggression in youth: CERT guidelines II. Treatments and ongoing management. [246]
US	Aggression	T-MAY survey	2011	Experts' recommendations for treating maladaptive aggression in youth.	Pappadopulos E, Rosato NS, Correll CU, et al. (2011) Experts' recommendations for treating maladaptive aggression in youth. [245]

Abbreviations organisations/institutions: AACAP, American Academy of Child and Adolescent Psychiatry; AAP, American Academy of Pediatrics; AFP, Australian Family Physician; CERT, Centre for Education and Research on Mental Health Therapeutics; CPS, Canadian Paediatric Society; eTG Complete, Electronic Therapeutic Guidelines Complete; NICE, National Institute for Health and Care Excellence; T-MAY, Treatment of Maladaptive Aggression in Youth.
Abbreviations disorders: ADHD, attention deficit hyperactivity disorder; CD, conduct disorder; DBD, disruptive behaviour disorder; ODD, oppositional defiant disorder.

2.3.4.1 Approved psychotropic drugs

Table 2.11 TGA-approved psychotropic drugs for disruptive behaviours and aggression in children and adolescents

Medicine	Medicine Name	Age range	Indications
Haloperidol	Serenace	>2 years	Severely aggressive or hostile children
Periciazine	Neulactil	>6 years	Severe impulsiveness, aggression
Risperidone	Risperdal	>5 years	Treatment of conduct disorders or other disruptive behaviour disorders

2.3.4.2 Introduction

Disruptive behaviour disorders (DBDs) include oppositional defiance disorder (ODD), conduct disorder (CD), and aggressive or destructive behaviours alone or within the context of other childhood disorders such as ADHD, pervasive developmental disorders (PDDs), and ASD [237, 238]. ODD is diagnosed most often in children less than 11 years of age and includes hostile, defiant behaviours and disobedience to authority figures, while CD is mostly diagnosed in children and adolescents from 11 years of age and includes aggressive and destructive behaviours directed toward people, animals, and property [238]. The presence of ODD in young children often precedes CD in adolescence and antisocial behaviours in adulthood [238, 239]. Recommendations from different guidelines focusing on ODD, CD, or aggression are summarised in Appendix 6.

2.3.4.3 Australian guidelines

The Australian-produced eTG Complete guidelines describe DBDs and treatment priorities in three short paragraphs, mentioning three important principles of treatment [237]. Firstly, non-pharmacological treatment is the recommended first-line treatment. Secondly, there

should be a careful assessment and treatment of comorbid conditions, and thirdly, the scope for pharmacological treatment is limited [237]. There are no other Australian clinical guidelines for the treatment of DBD, CD, or ODD in children and adolescents.

There is also little information published in general practice publications. An article published in the Australian Family Physician (AFP) in 2008 [240] highlighted the importance of psychosocial strategies and the lack of research on drug treatments for ODD, except in the presence of comorbid ADHD, where it was suggested that stimulants, atomoxetine or clonidine, may improve ODD symptoms. As mentioned in Section 2.3.2.3, AFP was an influential journal read by around 70% of GPs in Australia during the study period.

2.3.4.4 International guidelines

The absence of detailed Australian guidelines for behavioural disorders in children and adolescents leaves health practitioners with only international guidelines to recommend treatment choices. Appendix 6 summarises the available guidelines. A few international guidelines were identified from the US, UK, and Canada.

Guidelines for behavioural disorders unanimously recommend psychosocial therapies as first-line treatment [238, 239, 241-246], with an emphasis on parent training for younger children and a combination of family interventions and behavioural therapies for adolescents [238, 246].

All guidelines, as well as the Australian AFP article [240], also mention the importance of assessing for other mental health disorders, as there is a high rate of comorbidity with other childhood conditions, in particular ADHD [237-240, 242, 245, 247]. Where there is a psychiatric comorbidity, it is recommended that health practitioners follow the guidelines for the comorbid condition first [239, 242, 245]. If behavioural problems persist, the addition of medication is recommended [242, 246], with the most frequent recommendation being for SGAs, in particular risperidone [238, 242, 246].

The 2013 NICE guideline [238, 244] aptly summarises the recommendations found in most clinical practice guidelines for DBDs. The NICE guideline suggests a limited role for drugs for the routine management of behaviour problems in children and young people with CD [238, p.36, 244, p.327], but recognise that CD comorbid with severe aggression and anger problems may benefit from treatment with SGAs [238, 239, 242, 245, 246]. For CD or ODD

comorbid with ADHD, it states children and young people may benefit from ADHD drugs such as methylphenidate or atomoxetine [238, p.36, 239, 240, 242, 244, p.327].

2.3.4.5 Adverse events and monitoring

Although most guidelines recommend monitoring for the effectiveness of medications on symptoms of behavioural disorders [238, 239, 241, 242, 245, 246], few have addressed the monitoring of adverse effects of medications, particularly if antipsychotics are prescribed. Only NICE [238] and T-MAY [246] guidelines mentioned detailed adverse event profiles for antipsychotics, and only NICE guidelines provided specific recommendations of tests that need to be regularly performed for adverse effects [238]. T-MAY guidelines made only generic recommendations that clinicians should monitor for metabolic outcomes and perform laboratory tests where "clinically relevant" while assessing lifestyle factors such as diet and exercise [246, p.1583].

Similarly, Canadian guidelines [242] only listed an overall estimation of the adverse effect burden for various medications as low, moderate, or high, and suggested that careful monitoring is required if using antipsychotics. Notably, the two Australian references mentioned in Table 2.10 and Appendix 6 made no mention of the need to monitor adverse effects [237, 240].

2.3.4.6 Changes in treatment recommendations

Guidelines for DBDs in children and adolescents are few. There was only one earlier version of AACAP guidelines for CDs in children and adolescents published in 1992 [248], and recommendations did not differ from its 1997 version [247]. There were no other guideline changes for CD, ODD, or aggressive behaviours during the study period.

2.3.5 Anxiety disorders

The guidelines summarised in this section on managing anxiety disorders are listed in Table 2.12.

Table 2.12 Australian and international guidelines for management of anxiety disorders in children, adolescents and adults

Country	Disorder	Organisation	Year	Title	Reference
Australia	OCD, Separation Anxiety Disorder, GAD	eTG Complete (child and adolescent)	2019	Anxiety disorders in children and adolescents.	eTG complete (2019) *Anxiety disorders in children and adolescents*. (accessed 19 Jun 2019). [251]
Australia	Anxiety, OCD	Article in Australian Prescriber (child and adolescent)	2005	Prescribing psychotropic medication to children in general practice.	Hazell P (2005) Prescribing psychotropic medication to children in general practice. [253]
US	GAD, Separation Anxiety Disorder, Phobias, Panic disorder	AACAP (child and adolescent)	2007	Practice parameter for the assessment and treatment of children and adolescents with anxiety disorders.	Connolly SD and Bernstein GA (2007) Practice parameter for the assessment and treatment of children and adolescents with anxiety disorders. [256]
US	PTSD	AACAP (child and adolescent)	2010	Practice parameter for the assessment and treatment of children and adolescents with posttraumatic stress disorder.	Cohen JA, Bukstein O, Walter H, et al. (2010) Practice parameter for the assessment and treatment of children and adolescents with posttraumatic stress disorder. [255]
US	OCD	AACAP (child and adolescent)	2012	Practice parameter for the assessment and treatment of children and adolescents with obsessive-compulsive disorder.	Geller D, March J, Walter H, et al. (2012) Practice parameter for the assessment and treatment of children and adolescents with obsessive-compulsive disorder. [254]
US	Panic disorder	APA (adult: minor section child and adolescent)	2009	Practice Guideline for the treatment of patients with panic disorder.	APA (2009) *Practice Guideline for the treatment of patients with panic disorder*. [258]
US	OCD	APA (adult: minor section child and adolescent)	2007	Practice Guideline for the treatment of patients with obsessive-compulsive disorder.	APA (2007) *Practice Guideline for the treatment of patients with obsessive-compulsive disorder*. [257]
UK	GAD, SAD, phobias, OCD, PTSD, Panic	BAP (adult: minor section child and adolescent)	2005	Evidence-based guidelines for the pharmacological treatment of anxiety disorders: recommendations from the British Association for Psychopharmacology	Baldwin DS, Anderson IM, Nutt DJ, et al. (2005) Evidence-based guidelines for the pharmacological treatment of anxiety disorders: recommendations from the British Association for Psychopharmacology. [268]

Country	Disorder	Organisation	Year	Title	Reference
UK	Anxiety, OCD, PTSD	BAP (adult: minor section child and adolescent)	2014	Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines.	Baldwin DS, Anderson IM, Nutt DJ, et al. (2014) Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology. [259]
UK	GAD	BMJ Best Practice (all ages)	2018	Generalised anxiety disorder.	BMJ Best Practice (2018) *Generalised anxiety disorder*. (accessed 18 Oct 2018). [261]
UK	SAD	BMJ Best Practice (all ages)	2018	Social anxiety disorder.	BMJ Best Practice (2018) *Social anxiety disorder*. (accessed 18 Oct 2018). [262]
UK	OCD	BMJ Best Practice (all ages)	2017	Obsessive-compulsive disorder.	BMJ Best Practice (2017) *Obsessive-compulsive disorder*. (accessed 6 Jan 2020). [260]
UK	SAD, BDD	NICE (adult: minor section child and adolescent)	2013	Social anxiety disorder: recognition, assessment and treatment – cg159.	NICE (2013) *Social anxiety disorder: recognition, assessment and treatment – cg159*. (accessed 3 September 2018). [266]
UK	PTSD	NICE (adult: minor section child and adolescent)	2005	Post-traumatic stress disorder: management – cg26.	NICE (2005) *Post-traumatic stress disorder: management*. (accessed 11 Jul 2019). [197]
UK	OCD	NICE (adult: minor section child and adolescent)	2005	Obsessive-compulsive disorder and body dysmorphic disorder: treatment – cg31.	NICE (2005) *Obsessive-compulsive disorder and body dysmorphic disorder: treatment*. (accessed 1 Jan 2020). [263]
Canada	All anxiety disorders	British Columbia GPAC (children and youth)	2010	Anxiety and Depression in Children and Youth – Diagnosis and Treatment.	BCAC (2010) *Anxiety and Depression in Children and Youth – Diagnosis and Treatment*. (accessed 20May 2019) [196].
Canada	All anxiety disorders	CPA (all ages)	2006	Clinical practice guidelines. Management of anxiety disorders.	CPA (2006) Clinical practice guidelines. Management of anxiety disorders. [264]
Canada	OCD, PTSD	Expert consensus (adult: minor section child and adolescent)	2014	Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders.	Katzman MA, Bleau P, Blier P, et al. (2014) Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. [265]

Abbreviations organisations/institutions: AACAP, American Academy of Child and Adolescent Psychiatry; APA, American Psychological Association; BAP, British Association of Psychopharmacology; CPA, Canadian Psychiatric Association; eTG Complete, Electronic Therapeutic Guidelines Complete; GPAC, Guidelines and Protocols Advisory Committee; NICE, National Institute for Health and Care Excellence.
Abbreviations disorders: BDD, body dysmorphic disorder; GAD, generalised anxiety disorder; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; PTSD, post-traumatic stress disorder; SAD, social anxiety disorder.

2.3.5.1 Approved psychotropic drugs

Table 2.13 TGA-approved psychotropic drugs for anxiety disorders in children and adolescents

Medicine	Medicine Name	Age range	Indications
Periciazine	Neulactil	>6 years	Severe anxiety
Fluvoxamine	Luvox	>7 years	Obsessive-compulsive-compulsive disorder
Sertraline	Zoloft	>5 years	Obsessive-compulsive-compulsive disorder
Diazepam	Antenex (tabs) Orion (Oral liquid)	> 6 months	Anxiety disorders or for the short-term relief of anxiety symptoms
Oxazepam	Serepax	>15 years	Anxiety disorders, anxiety associated with depression Short term relief of anxiety symptoms Relief of tremor, confusional states or anxiety associated with alcohol withdrawal
Lorazepam	Ativan	>15 years	Anxiety disorders, anxiety associated with depression Short term relief of anxiety symptoms

2.3.5.2 Introduction

The DSM-IV-TR (2000) [249] and DSM-5 (2013) [187] define anxiety disorder as “excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance)”. In children, symptoms will often manifest as crying, tantrums, clinging behaviour, or shrinking from social situations [196].

Anxiety disorders in children and adolescents include separation anxiety disorder, social anxiety disorder (SAD; also referred to as social phobia), specific phobias, generalised anxiety disorder (GAD), and panic disorder [187, 249]. Post-traumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD), which have been included under separate sections in the DSM-5 (2013) [187], were included under the category of anxiety disorders in the previous edition of the DSM-IV-TR [249]. For convenience, all disorders included in anxiety disorders in the DSM-IV-TR edition have been listed under anxiety disorders in this thesis.

2.3.5.3 Australian guidelines

At the time of writing[g], the only guideline produced in Australia that specifically addresses anxiety disorders in children and adolescents is the eTG Complete guideline “Anxiety disorders in children and adolescents” [251]. RANZCP guidelines for anxiety make little reference to children and adolescents, simply stating that there is evidence of efficacy for

g. The Melbourne Children’s Campus Mental Health Strategy Anxiety Guideline Development Group published a clinical practice guideline for anxiety in children and young people in October 2023 [250].

SSRI medications and that GPs should obtain advice before prescribing to young people [252, p.1155]. Therefore, a search for other resources available to Australian GPs was performed. An article by Hazell [253] gave some minor information on the prescribing of psychotropic medications to children. Therefore, this article was also included in the summary of anxiety disorder guidelines in Table 2.12 and Appendix 7. The SSRIs, in particular fluvoxamine, sertraline, and fluoxetine, feature prominently in the treatment of anxiety disorders in Australian resources [251, 253].

2.3.5.4 International guidelines

The only guidelines to extensively and exclusively report on the treatment of child and adolescent anxiety disorders are published by the US organisation, the American Academy of Child and Adolescent Psychiatry (AACAP) [254-256]. The majority of other anxiety disorder guidelines are for adults, with sections referring to treating young people [196, 197, 257-266]. In cases where references to children contained only generic advice and referred the reader to the recommendations for adults, a summary of the adult guidelines has also been included in Appendix 7.

For child and adolescent anxiety, first-line options in all guidelines recommend non-pharmacological interventions (Appendix 7). When appropriate psychological interventions are unavailable, or when patients or their carers are unwilling or unable to engage in therapy, medication is often recommended [197, 254, 260, 263, 267]. Similar to Australian resources, three SSRIs (fluvoxamine, sertraline, and fluoxetine) feature prominently in medication options. All guidelines also recommend medication be combined with psychosocial therapies when available.

Although there is consistency in recommending SSRI drug treatments for anxiety disorders, there is some contradictory information regarding which medications should be prescribed to children and adolescents. While all guidelines recommend SSRIs, the British Association of Psychopharmacology specifically notes several antidepressants are judged unsuitable for children and adolescents due to an unfavourable balance between harms and benefits [259, 268]. This includes the SSRIs sertraline, paroxetine, citalopram, and escitalopram, as well as the non-SSRIs mirtazapine and venlafaxine. All of these drugs are listed as first- or second-line medications by at least one guideline in Appendix 7. The British Association of Psychopharmacology also notes that risks associated with SSRIs are reduced when treating anxiety disorders in people under 18 years compared to treating depression in the same age group [259, p.24]. AACAP (2007) guidelines similarly suggest the February 2004 black box

warning on SSRIs for under 18-year-olds is directed primarily at children and adolescents with depressive disorders [256, p.276]. Therefore, there remains some ambiguity in guidelines about the safety, effectiveness, and suitability of certain drugs for treating paediatric anxiety disorders.

2.3.5.5 Treatment of anxiety disorders with comorbid conditions

Comorbidity is common with anxiety disorders [196, 255, 258, 260, 262]. According to the Canadian Psychiatric Association (CPA) 2006 clinical practice guidelines (CPGs) [264], up to 79% of children or adolescents diagnosed with anxiety will have at least one other psychiatric disorder, with comorbid ADHD occurring in 25% of cases. Advice on treatment of comorbidities in young people is limited, however. One Canadian guideline recommends antidepressants in preference to benzodiazepines for comorbid depression [265, p.10], and buspirone is the medication of choice if there are comorbid substance use problems in BMJ Best Practice guidelines [261, p.19].

2.3.5.6 Adverse events and monitoring

With the exception of a warning about the likelihood of increased suicidal thinking in young people taking SSRIs [196, 251, 254, 256, 258, 260, 262, 264, 265], there is minimal advice on monitoring and management of adverse events. Several guidelines (for either children or adults) recommend monitoring cardiac function when prescribing clomipramine and other tricyclic antidepressants [251, 256, 258]. Weight monitoring was also recommended for clomipramine [251, 254], FGAs [259], and SGAs [254], with additional recommendations to monitor lipid levels and blood glucose levels when administering SGAs in one guideline [254]. Only the 2006 CPA guidelines included a full baseline laboratory assessment for patients using SGAs, recommending monitoring of weight changes and adverse effects fortnightly, or weekly if children are aged under 11 years [264, p.12S].

2.3.5.7 Changes in treatment recommendations

There have been minor changes to anxiety guidelines for children and adolescents since the earliest publication by AACAP in 1993 [269]. In the 1993 and 1997 AACAP anxiety guidelines, tricyclic antidepressants were given more prominence as treatment options [269, 270], but occurred only for panic disorder and OCD in the later 2007 [255] and 2012 [254] guidelines. Similarly, UK BAP guidelines [259] remained substantially unchanged from the earlier 2005 version [268]. All guidelines (current and previous) highlight there are few controlled studies of psychotropic medications for treating anxiety in children and adolescents.

2.3.6 Psychotic disorders

The guidelines summarised in this section on managing psychotic disorders in children and adolescents are listed in Table 2.14.

Table 2.14 Australian and international guidelines for management of schizophrenia and other psychoses for children, adolescents and adults

Country	Organisation	Year	Title	Reference
Australia	eTG Complete (child)	2019	Childhood schizophrenia and other psychoses	eTG complete (2019) *Childhood schizophrenia and other psychoses*. (accessed 2 Jun 2019). [175]
Australia	eTG Complete (adult)	2019	Schizophrenia and related psychoses.	eTG complete (2019) *Schizophrenia and related psychoses*. (accessed 2 Jun 2019) [273]
Australia	Orygen (adult)	2016	Australian Clinical Guidelines for Early Psychosis: 2nd ed.	Orygen Youth Health (2016) *Australian Clinical Guidelines for Early Psychosis: 2nd ed*. (accessed 21 Oct 21). [271]
UK	NICE (child)	2013	Psychosis and schizophrenia in children and young people: recognition and management. – cg155	NICE (2013) *Psychosis and schizophrenia in children and young people: recognition and management*. (accessed 4 Jun 2018). [106]
]UK	BMJ Best Practice (adult)	2018	Schizophrenia.	BMJ Best Practice (2018) *Schizophrenia*. (accessed 18 Oct 2018).[275]
UK	BAP (adult)	2011	Evidence-based guidelines for the pharmacological treatment of schizophrenia	Barnes TR (2011) Evidence-based guidelines for the pharmacological treatment of schizophrenia: recommendations from the British Association for Psychopharmacology.[277]
Scotland	SIGN (adult)	2013	Management of schizophrenia: A national clinical guideline: SIGN131.	SIGN (2013) *Management of schizophrenia: A national clinical guideline: SIGN131.* (accessed 18 Oct 2018).[279]
US	AACAP (child)	2013	Practice parameter for the assessment and treatment of children and adolescents with schizophrenia.	McClellan J, Stock S, American Academy of C, et al. (2013) Practice parameter for the assessment and treatment of children and adolescents with schizophrenia. [276]
International	WFSBP (adult)	2017	World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia - a short version for primary care.	Hasan A, Falkai P, Wobrock T, et al. (2017) World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia - a short version for primary care. [278]

Abbreviations organisations/institutions: AACAP, American Academy of Child and Adolescent Psychiatry; APA, American Psychological Association; BAP, British Association of Psychopharmacology; eTG Complete, Electronic Therapeutic Guidelines Complete; NICE, National Institute for Health and Care Excellence; SIGN, Scottish Intercollegiate Guidelines Network; WFSBP, World Federation of Societies of Biological Psychiatry.
Abbreviations disorders: FEP, first episode psychosis; MDD, major depressive disorder; PD, personality disorder; PTSD, post-traumatic stress disorder.

2.3.6.1 Approved psychotropic drugs

Table 2.15 TGA-approved psychotropic drugs for treating schizophrenia/psychosis in children and adolescents

Medicine	Medicine Name	Age range	Indications
Lurasidone[a]	Latuda/Lupin	>12 years	Schizophrenia
Risperidone	Risperdal	>14 years	Schizophrenia
Quetiapine	Seroquel	13-17 years	Schizophrenia
Periciazine	Neulactil	>6 years	Schizophrenia maintenance
Chlorpromazine[b]	Largactil	<5 years (adjust dose by bodyweight) >5 years -1/3 to ½ adult dose	Schizophrenia, mania, psychotic depression[c]
Clozapine[d]	Clozaril	>16 years	Treatment resistant schizophrenia
Lithium	Lithicarb	<11 years	Schizoaffective illness and chronic schizophrenia

Notes:
a. Lurasidone was approved for schizophrenia in adolescents over 12 years in April 2018.
b. Chlorpromazine is available in tablet, liquid, and injectable formulations. The PI for chlorpromazine (last update 17 December 2019) only describes indications for children with psychosis, ASD and behaviour problems.
c. Use of chlorpromazine should be in conjunction with an appropriate non-pharmacological management program and long-term use should only be carried out under the supervision of a physician experienced in the management of psychotic disorders in children.
d. Clozapine can only be prescribed by authorised GPs who are registered on the clozapine patient monitoring system (see section 2.3.6.3.4).

2.3.6.2 Introduction

Psychotic disorders defined by the DSM-5 include schizophrenia, schizoaffective disorder, schizophreniform disorder, schizotypal personality disorder, delusional disorder, brief psychotic disorder, psychosis due to medication or medical conditions, catatonia, and other "unspecified schizophrenia spectrum disorders" [271]. Paediatric schizophrenia is rare, consisting of early-onset schizophrenia (onset before 18 years of age) and childhood-onset (before 13 years of age) [272]. Childhood-onset schizophrenia is estimated to affect 0.04% of children [272]. The disorder usually manifests in late adolescence or early adulthood. It is currently diagnosed with adult diagnostic criteria, but with caution, as many childhood behaviours can be misinterpreted as a form of psychosis or schizophrenia (e.g., imaginary friends) [272]. There were few paediatric guidelines, so adult guidelines have also been summarised.

Psychotic disorders encompass positive symptoms (e.g., hallucinations, delusions, disorganised thinking and speech), negative symptoms (e.g., lack of motivation, blunted affect, social withdrawal), cognitive symptoms (e.g., impaired memory, planning, social cognition), mood symptoms (in particular, depressive symptoms and anxiety), and aggression and hostility [273].

Psychotic disorders are also categorised by stage. The first stage is the prodromal phase, also termed ultra-high-risk (UHR) psychosis [271]. This stage is marked by mild non-specific symptoms with mild neurocognitive and functional impairments, which can be indistinguishable from depression and substance use disorders [271, p.27]. While some researchers have identified rates of transition from UHR to full-blown psychosis in 22% of patients within 12 months, other studies have shown rates under 10% [274, p.11], and there is some debate as to whether the benefits of any treatment for UHR psychosis can outweigh the harms from stigma and unnecessary treatments [271].

The second stage is classified as first-episode psychosis (FEP) [271]. Although some individuals may recover and never experience a subsequent episode, schizophrenia is more commonly considered a lifelong condition, with people experiencing multiple episodes and chronic functional impairment [275, 276]. Treatment recommendations for psychotic disorders are summarised in Appendix 8.

2.3.6.3 Australian guidelines

There are currently no guidelines specific to child and adolescent psychotic disorders in Australia. The RANZCP 2016 guidelines specifically state "childhood onset schizophrenia [is] a very rare condition requiring specialist management" [274, p.3], and no paediatric recommendations are included in the guideline. Australian eTG Complete guidelines provide a short document addressing childhood schizophrenia [175], noting that childhood and adult diagnostic criteria are the same and antipsychotic drugs have similar efficacy in adolescents and adults. The child guidelines [175] refer practitioners to adult guidelines [273], which have also been summarised in this chapter. Orygen, the Australian Centre of Excellence in Youth Mental Health, published guidelines that apply to ages 15-25 years in 2016 [271] that essentially summarise the RANZCP adult guidelines [274].

Australian guidelines for treating psychosis are similar to international ones and will be discussed in conjunction with international guidelines under each diagnostic category listed below: UHR psychosis, FEP and acute psychotic episodes, maintenance and relapse prevention, and treatment-resistant psychosis. Only two guidelines in Appendix 8 specifically focus on children and adolescents: the NICE 2013 "Psychosis and schizophrenia in children and young people: recognition and management" guidelines [106] and AACAP 2013 "Practice Parameter for the Assessment and Treatment of Children and Adolescents With Schizophrenia" guidelines [276]. All other guidelines for treating psychosis summarised in this chapter refer to the adult population, with minor references made to children.

2.3.6.3.1 UHR psychosis

Most guidelines recommend minimal treatment for individuals classified in the category of UHR psychosis. Close monitoring [273], "watchful waiting" [277], supportive counselling, and psychological therapies (e.g., CBT) [106, 271, 275] are recommended as first-line treatments for adults and children. AACAP [276] paediatric-specific guidelines gave no recommendations, stating that there were no interventions with conclusive evidence for treating prodromal psychosis [276, p.985]. Only adult guidelines mentioned the possibility of pharmacological treatment, but only at ultra-low doses [273, 277]. While restricting the use of antipsychotics, however, several guidelines did not restrict the use of other drugs for comorbid conditions at this stage of psychotic illness [106, 271, 273, 275].

2.3.6.3.2 FEP and acute psychotic episodes

All clinical practice guidelines (CPGs) for treatment of FEP and recurrent acute episodes of psychosis, including those specific to children and adolescents, recommend antipsychotic drugs, mostly concurrent with psychosocial treatments [106, 271, 273, 276, 278, 279]. Guidelines also state that all SGAs are equivalent in efficacy and that prescribing decisions for specific SGAs should depend on the tolerability and adverse effect profiles of individual patients [106, 271, 273, 275, 277, 278, 280, 281]. The SGA clozapine, however, is generally not recommended as treatment for FEP (see also Section 2.3.6.3.4). Although reported to be one of the most effective antipsychotics for positive symptoms [273, 278], negative symptoms [273], comorbid substance misuse [277], the management of suicidality [271, 275, 277, 278], and aggression or hostility [275, 277, 279], clozapine is not recommended as a first-line treatment due to its serious adverse effects (e.g., agranulocytosis, myocarditis, excessive weight gain) [271, 273, 275, 276, 278]. Olanzapine is also rarely recommended as first-line treatment for FEP [106, 271, 273, 275, 276], especially for children and adolescents [106, 276] due to problems with significant weight gain. Many guidelines also state that FGAs are equally efficacious to SGAs for treating psychosis [106, 271, 273, 275-281].

2.3.6.3.3 Maintenance and relapse prevention

Schizophrenia is considered a chronic condition, which is lifelong in many cases [273, 275, 276]. Therefore, guidelines generally recommend maintenance treatment continue for at least one to two years after remission from FEP (Appendix 8), and if relapses occur during this period, the maintenance period may be extended to five years [273] or indefinitely [273, 275, 276].

While olanzapine is considered superior to other SGAs for preventing relapse, this benefit is not considered sufficient to outweigh the higher risk of weight gain, metabolic syndrome, and coronary heart disease [275, p.26], especially in children and adolescents [271, p.62].

2.3.6.3.4 Treatment-resistant psychosis

Clozapine is recommended as the first-line option for treatment-resistant psychosis in most guidelines [271, 273, 274, 276-279]. If clozapine is ineffective, the addition of another antipsychotic [106, 271, 273, 277, 279] or lamotrigine [279] is recommended.

In Australia, clozapine is listed under the Highly Specialised Drug (HSD) program of the PBS [282], due to its severe life-threatening adverse effects [283]. Drugs listed on the HSD are generally only prescribed by medical practitioners affiliated with private or public hospitals [282]. Clozapine may also be prescribed as maintenance treatment for schizophrenia in primary care by GPs, provided they are authorised to prescribe it and the patient and GP are both registered on the "clozapine patient monitoring system" [283].

2.3.6.3.5 Managing comorbidities and prominent negative symptoms

Many guidelines address associated symptoms of schizophrenia, such as aggression, hostility, and depression. Psychosis, however, is considered the primary disorder for treatment unless other conditions are more disabling [271], with comorbidities addressed concurrently where necessary [106, 271, 276].

For associated symptoms of aggression or hostility, clozapine is recommended as monotherapy [275, 277, 279] or with adjunctive benzodiazepines or anticonvulsants [277]. For depressive symptoms, some guidelines recommend the addition of an antidepressant [276, 278, 284]. For bipolar disorder comorbidity, the addition of a mood stabiliser is recommended [275].

2.3.6.4 Adverse events and monitoring

Antipsychotic medications are associated with a range of adverse effects (in particular, extrapyramidal and cardiometabolic effects), and all guidelines recommend a monitoring regime. Recommendations for individual antipsychotics from three of the guidelines in this section have been summarised in Appendix 9. Monitoring for adverse effects is particularly important for children and adolescents, as they are more prone to developing antipsychotic-induced movement disorders, endocrine and metabolic changes, and weight gain [106, 175, 271, 276]. Orygen 2016 guidelines [271] recommend using an algorithm for monitoring cardiometabolic health for adolescents on psychotropic medications available from the New

South Wales Health, Education, and Training Institute website (www.heti.nsw.gov.au), which has been incorporated into the recommendations in Appendix 9 and is discussed in more detail in Chapter 6.

2.3.6.5 Changes in treatment recommendations

NICE guidelines published in 2013 [106] were the first guidelines from the organisation that were specific to the treatment of psychosis and schizophrenia in children and adolescents [285]. Recommendations were similar to their 2009 adult guidelines, with a few extra cautions related to the increased sensitivity to adverse effects in paediatric patients [106].

AACAP has provided guidelines specific to children and adolescents since the early 1990s [276, 286-288]. The range of available medications, however, was smaller in the early guidelines: in 2001, SGAs included risperidone, quetiapine, olanzapine, and clozapine [288]. By 2013, aripiprazole and paliperidone were added to AACAP recommendations, and, as occurred with the 2013 NICE guidelines, olanzapine was removed as a first-line option due to issues with weight gain in young patients [276].

2.3.7 Autism spectrum disorders

The guidelines summarised in this section on managing autism spectrum disorders (ASDs) in children and adolescents are listed in Table 2.16.

Table 2.16 Australian and international guidelines for management of autism spectrum disorders in children and adolescents

Country	Organisation	Year	Title	Reference
Australia	eTG Complete	2019	Autism spectrum disorder.	eTG Complete (2019) *Autism spectrum disorder*. (accessed 9 Apr 2020). [294]
New Zealand	Ministries of Health and Education	2016	New Zealand Autism Spectrum Guideline.	Ministries of Health and Education (2016) *New Zealand Autism Spectrum Guideline*. (accessed 14 Aug 2022). [295]
US	AACAP	2014	Practice parameter for the assessment and treatment of children and adolescents with autism spectrum disorder.	Volkmar F, Siegel M, Woodbury-Smith M, et al. (2014) Practice parameter for the assessment and treatment of children and adolescents with autism spectrum disorder. [291]
US	AAP	2007	Management of children with autism spectrum disorders.	Myers SM, Johnson CP. Management of children with autism spectrum disorders. [297]
US	AAP	2012	A practice pathway for the identification, evaluation, and management of insomnia in children and adolescents with autism spectrum disorders.	Malow BA, Byars K, Johnson K, et al. (2012) A practice pathway for the identification, evaluation, and management of insomnia in children and adolescents with autism spectrum disorders. [301]
US	AAP	2012	Clinical practice pathways for evaluation and medication choice for attention-deficit/hyperactivity disorder symptoms in autism spectrum disorders.	Mahajan R, Bernal MP, Panzer R, et al. (2012) Clinical practice pathways for evaluation and medication choice for attention-deficit/hyperactivity disorder symptoms in autism spectrum disorders. [298]
US	AAP	2016	Assessment and Treatment of Anxiety in Youth with Autism Spectrum Disorders.	Vasa RA, Mazurek MO, Mahajan R, et al. (2016) Assessment and Treatment of Anxiety in Youth with Autism Spectrum Disorders. [300]
US	AAP	2016	Irritability and Problem Behavior in Autism Spectrum Disorder: A Practice Pathway for Pediatric Primary Care.	McGuire K, Fung LK, Hagopian L, et al. (2016) Irritability and Problem Behavior in Autism Spectrum Disorder: A Practice Pathway for Pediatric Primary Care. [299]
UK	NICE	2013	Autism spectrum disorder in under 19s: recognition, referral and diagnosis – cg128	NICE (2013) *Autism spectrum disorder in under 19s: recognition, referral and diagnosis*. (accessed 3 Sep 2018). [292]
UK	NICE	2013	*Autism spectrum disorder in under 19s: support and management*. – cg170	NICE (2013) *Autism spectrum disorder in under 19s: support and management*. (accessed 3 Sep 2018). [293}
UK	BMJ Best Practice	2018	Autism spectrum disorder.	BMJ Best Practice (2018) *Autism spectrum disorder.* (accessed 11 Apr 2020). [289]

Country	Organisation	Year	Title	Reference
UK	BAP	2017	Autism spectrum disorder: Consensus guidelines on assessment, treatment and research.	Howes OD, Rogdaki M, Findon JL, et al. (2017) Autism spectrum disorder: Consensus guidelines on assessment, treatment and research from the British Association for Psychopharmacology. [290]
Scotland	SIGN	2016	Assessment, diagnosis and interventions for autism spectrum disorders: A national clinical guideline: SIGN145.	SIGN (2016) *Assessment, diagnosis and interventions for autism spectrum disorders: A national clinical guideline: SIGN145*. (accessed 18 Oct 2019). [296]

Abbreviations organisations/institutions: AACAP, American Academy of Child and Adolescent Psychiatry; AAP, American Academy of Pediatrics; BAP, British Association of Psychopharmacology; eTG Complete, Electronic Therapeutic Guidelines Complete; NICE, National Institute for Health and Care Excellence; SIGN, Scottish Intercollegiate Guidelines Network.

2.3.7.1 Approved psychotropic drugs

Table 2.17 TGA-approved psychotropic drugs for ASD in children, adolescents and adults

Medicine	Medicine Name	Age range	Indicated use
Chlorpromazine[a]	Largactil	<5 years (adjust dose by bodyweight) >5 years -⅓ to ½ adult dose	Severe behavioural disturbances in children with mental retardation or autism: treatment of self-injurious, aggressive behaviour or overactivity[b]
Haloperidol	Serenace	> 2 years	Severely aggressive or hostile children
Periciazine	Neulactil	> 6 years	Aggression
Risperidone	Risperdal	Children and adolescents	Behavioural disorders associated with autism in children and adolescents
Melatonin (PR)[c]	Slenyto	2-18 years	Insomnia in children and adolescents with Autism Spectrum Disorder and/or Smith-Magenis syndrome

Notes:
Any drugs approved for aggressive, self-injurious behaviour are included in this list, but only chlorpromazine, risperidone and melatonin are specific to autism spectrum disorder (ASD).
a. Chlorpromazine is available in tablet, liquid, and injectable formulations. The product information (PI) for chlorpromazine (last update 17 December 2019) only describes indications for children with psychosis, ASD and behaviour problems.
b. Use of chlorpromazine should be in conjunction with an appropriate non-pharmacological management program and long-term use should only be carried out under the supervision of a physician experienced in the management of disorders in children.
c. Melatonin (PR [prolonged release]) was approved for use in children and adolescents for the given conditions on 22 May 2020.

2.3.7.2 Introduction

Autism is a disturbance in social relatedness marked by core symptoms of impaired social interactions and emotional communication skills, poor peer relations, and the presence of restricted and repetitive behaviours (stereotypies) [289-292]. It is often associated with language delays [289, 292], cognitive deficits [289-291, 293], learning difficulties [289, 291,

293], and in extreme cases, aggression [289-291, 293-295], explosive temper tantrums [289-291, 294], and self-injurious behaviour [289-291, 295]. Autism spectrum disorders (ASDs) also include milder symptoms of autism that encompass diagnoses of Asperger's syndrome, pervasive developmental disorder (PDD), childhood disintegrative disorder (CDD), and Rett's syndrome [295, p.5].

2.3.7.3 Australasian guidelines

There are two Australasian guidelines for ASD, the eTG Complete Autism Spectrum Disorder guidelines [294] and the New Zealand (NZ) Autism Spectrum Disorder guidelines [295] (Appendix 10). Both emphasise that management of ASD should focus on family support and psychosocial interventions, including educational and behavioural programs and programs designed to enhance communication skills. No medications are recommended for the treatment of core symptoms of ASD in either guideline [294, 295]. Medications are considered useful, however, for reducing the severity of symptoms associated with ASD, such as temper tantrums, irritability, aggression, and self-injurious behaviours [294, 295]. In Australia, eTG Complete guidelines recommend risperidone as a first-line treatment for children aged over 4 years, with periciazine and trifluoperazine as second-line options used only for extreme behavioural disturbances [294]. All drugs are to be used in conjunction with non-pharmacological programs [294]. NZ guidelines recommend both risperidone and aripiprazole in conjunction with non-drug programs [295].

2.3.7.4 International guidelines

In concordance with Australasian guidelines, international guidelines on ASD unanimously recommend non-drug approaches to the treatment of core symptoms of ASD, reserving medications for extreme symptoms and behavioural problems, especially irritability and aggression [289-292, 294, 296, 297]. Most guidelines recommend risperidone and aripiprazole as the preferred medications for severe aggression or irritability symptoms [289-291, 296-299].

2.3.7.5 Comorbidity

Comorbid disorders are prevalent in young people with ASD. According to the BAP 2017 guidelines [290], 69-79% of young people with ASD have at least one lifetime comorbid psychiatric condition compared to lifetime psychiatric disorder rates of 40% in the general population. For children diagnosed with ASD, there is a 42-55% prevalence of comorbid anxiety disorder, 28-53% prevalence of ADHD, 7-37% prevalence of DBDs, and 50-80% prevalence of sleep difficulties [290, p.7]. Where there is a clear diagnosis for a comorbid

condition, it is recommended clinicians refer to appropriate guidelines for the comorbid condition [290, 292], but with caution due to the observed sensitivity to psychotropic medication side effects in ASD patients [299]. Methylphenidate is recommended for patients with ASD and attentional/hyperactive symptoms [289, 290, 295-298], but again with caution, as stimulants can worsen agitation, anxiety, and stereotypies in young people with ASD [295, 298-300]. Melatonin is recommended for patients with ASD and sleep problems [289, 290, 295-297, 299, 301], and SSRIs are recommended as potential options for mood and anxiety symptoms [289, 290, 295-297, 300].

2.3.7.6 Adverse events and monitoring

When antipsychotics are used to treat ASDs, monitoring for adverse effects is recommended [289, 290, 293-295, 297, 299, 302]. Only a few guidelines, however, mention the broad range of adverse effects associated with antipsychotics, including hyperprolactinaemia, extrapyramidal symptoms, and metabolic abnormalities [294, 297, 299]. Two of these guidelines, inclusive of the Australian eTG Complete guidelines, also provide advice on where to access information on antipsychotic monitoring algorithms [294, 299]. When using antidepressants, monitoring for increased agitation and suicidality is recommended by 2016 NZ [295] and 2007 AAP guidelines [297].

2.3.7.7 Changes in treatment recommendations

Recommendations for ASD treatment for autism have not changed substantially over the last 20 years. The first (1999) version of the AACAP guideline [303], as well as current guidelines [289, 293, 296, 297], mention that there are no effective medications for the treatment of core symptoms of autism. The 1999 AACAP guidelines included a variety of medication classes that the authors claimed had been used in autism with varying degrees of success, including SSRIs, tricyclic antidepressants, and anxiolytics [303, p.1615]. Recent guidelines still recommend these classes of drugs to varying degrees for cautiously treating "target symptoms" [291] or "associated" symptoms or behaviours [290, 295-297, 300] (see Appendix 10). More recent versions of guidelines also list specific drugs, such as risperidone and aripiprazole, whereas the earlier 1999 AACAP guideline refers to the drug class of neuroleptics as a whole [303]. In some cases, more recent guidelines also specify drugs that should be avoided [290, 295]. For example, NZ [295] and BAP [290] guidelines specifically exclude citalopram for the treatment of repetitive behaviours.

2.3.8 Eating disorders

The guidelines summarised in this section on managing eating disorders in children and adolescents are listed in Table 2.18.

Table 2.18 Australian and international guidelines for managing eating disorders in children, adolescents and adults

Country	Disorder	Organisation	Year	Title	Reference
Australia	AN, BN, BED, EDNOS	eTG Complete (all ages)	2019	Overview of eating disorders.	eTG Complete (2019) *Overview of eating disorders*. (accessed 2 Jun 2020). [305]
Australia	AN, BN, BED, ARFID	RANZCP (all ages)	2014	Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of eating disorders.	Hay P, Chinn D, Forbes D, et al. (2014) Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of eating disorders. [304]
UK	AN, BN, BED, OSFED	NICE (all ages)	2017	Eating disorders: recognition and treatment - ng69.	NICE (2017) *Eating disorders: recognition and treatment - ng69*. (accessed 3 Sep 2018). [306]
UK	AN, BN, BED, OSFED	NICE (all ages) (archived)	2004	Eating disorders: Core interventions in the treatment and management of anorexia nervosa, bulimia nervosa and related eating disorders - cg9.	NICE (2004) *Eating disorders: Core interventions in the treatment and management of anorexia nervosa, bulimia nervosa and related eating disorders - cg9*. (accessed 3 Sep 2018). [316]
UK	AN	BMJ Best Practice	2018	Anorexia nervosa.	BMJ Best Practice (2018) *Anorexia nervosa*. (accessed 13 Mar 2019). [311]
UK	BN	BMJ Best Practice (all ages)	2018	Bulimia nervosa	BMJ Best Practice (2018) *Bulimia nervosa*. (accessed 13 Sep 2018) [315]
US (child)	AN, BN, BED, ARFID	AACAP (child and adolescent)	2015	Practice parameter for the assessment and treatment of children and adolescents with eating disorders.	Lock J, La Via MC, American Academy of C, et al. (2015) Practice parameter for the assessment and treatment of children and adolescents with eating disorders. [309]
US	AN, BN, BED, EDNOS	APA (all ages)	2006	Treatment of patients with eating disorders, third edition.	Yager J, Devlin MJ, Halmi KA, et al. (2006) Treatment of patients with eating disorders, third edition. American Psychiatric Association. [314]
US	ARFID	JCAP article (adolescent and young adult)	2017	Adjunctive Use of Olanzapine in the Treatment of Avoidant Restrictive Food Intake Disorder in Children and Adolescents in an Eating Disorders Program.	Brewerton TD and D'Agostino M (2017) Adjunctive Use of Olanzapine in the Treatment of Avoidant Restrictive Food Intake Disorder in Children and Adolescents in an Eating Disorders Program. [310]

Country	Disorder	Organisation	Year	Title	Reference
US	ARFID	JAACAP article (child, adolescent and young adult)	2018	Mirtazapine and Weight Gain in Avoidant and Restrictive Food Intake Disorder.	Gray E, Chen T, Menzel J, et al. (2018) Mirtazapine and Weight Gain in Avoidant and Restrictive Food Intake Disorder. [317]
International	AN, BN, BED	WFSBP	2011	World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of eating disorders.	Aigner M, Treasure J, Kaye W, et al. (2011) World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of eating disorders. [312]

Abbreviations organisations/institutions: AACAP, American Academy of Child and Adolescent Psychiatry; APA, American Psychiatric Association; BAP, British Association of Psychopharmacology; eTG Complete, Electronic Therapeutic Guidelines Complete; JAACAP, Journal of the American Academy of Child and Adolescent Psychiatry ; JCAP, Journal of Child and Adolescent Psychopharmacology; NICE, National Institute for Health and Care Excellence; RANZCP, Royal Australian and New Zealand College of Psychiatrists; WFSBP, World Federation of Societies of Biological Psychiatry.
Abbreviations disorders: AN, anorexia nervosa; ARFID, avoidant restrictive food intake disorder; BED, binge eating disorder; BN, bulimia nervosa; EDNOS, eating disorder not otherwise specified; OSFED, other specified feeding and eating disorders.

2.3.8.1 Approved psychotropic drugs

No psychotropic drugs have been approved by the TGA for the treatment of eating disorders in children and adolescents.

2.3.8.2 Introduction

Eating disorders are characterised by persistent unhealthy disturbances in eating patterns commonly associated with body image concerns [304]. Eating disorders are associated with high morbidity due to increased risks of malnutrition and physical health problems, including cardiac issues, electrolyte abnormalities, and reductions in bone mineral density [305, 306].

In the DSM IV-TR [249], there were only two main eating disorders described: anorexia nervosa (AN) and bulimia nervosa (BN), with all residual categories falling into eating disorders not otherwise specified (EDNOS) [307]. In the updated DSM-5 edition in 2013 [187] the category “disorders usually first diagnosed in infancy, childhood, or adolescence” was removed from the DSM [307]. Binge eating disorder (BED) was included as a separate category, and feeding disorder of infancy and childhood was transferred to the new eating disorders chapter “Feeding and Eating Disorders” and renamed avoidant-restrictive food intake disorder (ARFID) [307]. The category “other specified feeding and eating disorder” (OSFED) now contains any residual categories of eating disorders [308].

Prevalence rates for eating disorders of AN, BN, and BED are low in the general population and extremely rare in young people aged under 15 years [305]. With the exception of the

AACAP guideline [309], all guidelines refer to all age groups, with small sections referring to children and adolescents. Of the two Australian-based guidelines, eTG Complete [305] and RANZCP [304] guidelines, only the latter mentions children and adolescents. They state there is insufficient evidence to recommend any psychotropic medications in this population and that antidepressants and anxiolytics can be used in exceptional situations to relieve symptoms but should be used with caution. Australian and international guidelines have been discussed together in this section and summarised in Appendix 11.

There were no guidelines for ARFID, newly defined in the most recent version of the DSM 5 [187]. Unlike other EDs, such as AN and BN, ARFID is not driven by body image issues [310]. Usually a child-onset disorder [310], ARFID is driven by extreme sensitivity to the characteristics of food, including taste, texture, smell, and temperature, or traumatic experiences with food consumption, such as fear of choking or vomiting [187, 310]. Although no guidelines were found for this disorder, the latest recommendations from the published literature have been summarised in Section 2.3.8.6.

2.3.8.3 Anorexia Nervosa (AN)

The key goal in the treatment of AN is to help the patient reach a healthy body weight for age, establish normal eating behaviours [305, 308, 311], and identify any underlying issues contributing to the disorder [305]. For primary symptoms of AN, guidelines unanimously agree that there are no medications that have been proven to be of benefit [304, 305, 309, 311-313]. Therefore, irrespective of age, non-pharmacological treatments are recommended as first-line, with family therapy preferred for adolescents [304, 308, 309, 311, 313, 314]. Medications should only be considered for extreme symptoms of agitation [305], insomnia [305], anxiety [304, 314], or OCD [304, 311, 313, 314] associated with the disorder, and even then, used with caution [304]. Anxiety, depression, and OCD can also occur secondary to starvation [304, 305, 309, 311]. Therefore, restoration of healthy weight is recommended before diagnosing and treating comorbid conditions with medication [313, 314].

2.3.8.4 Bulimia Nervosa (BN)

Non-pharmacological approaches are first line for BN, although a number of guidelines also recommend SSRIs as effective treatments, with preference for fluoxetine over other antidepressants [304, 305, 309, 312-315]. Other types of antidepressants [304, 305, 314, 315] and the anticonvulsant topiramate [304, 305, 312-314] are also recommended if there is no response to SSRIs. BMJ Best Practice [315] and APA guidelines [313, 314] mentioned specific medications that are contraindicated for BN patients. Both warn against the use of

bupropion in BN [313-315], and APA guidelines also warn against the use of lithium in those with comorbid bipolar disorder [313, 314].

2.3.8.5 Binge Eating Disorder (BED)

Treatment of BED, which includes patients who are overweight and obese [305, 309, 312, 316], recommends non-pharmacological treatments as first-line. A range of antidepressants [304, 312-314, 316], topiramate [304, 305, 312-314], and the anti-obesity drug orlistat [304, 305, 312] are recommended in some guidelines (Appendix 11).

2.3.8.6 Avoidant Restrictive Food Intake Disorder (ARFID)

Although there are no evidence-based guidelines recommending psychotropic medication treatments for ARFID [310, 317], two small studies of adolescents and young adults on low-dose olanzapine [310] and mirtazapine [317] have shown evidence of symptomatic improvement. Patients receiving olanzapine also experienced improvement in comorbid symptoms of anxiety, depression, and cognitive impairments [310]. However, both papers were published recently (2017 and 2018) and would have little impact on prescribing practices in Australian general practice during the study period.

2.3.8.7 Changes in treatment recommendations

Treatment for eating disorders has changed little over the years. Medications have shown little promise for treating core symptoms. BED and BN guidelines in the UK have become more conservative, indicating less support for pharmacological treatments. The 2004 NICE guidelines [316] reported good evidence for SSRIs for these conditions, but later 2017 NICE guidelines excluded all SSRI recommendations [308].

2.3.9 Sleep disorders

The guidelines summarised in this section for managing sleep disorders in children and adolescents are listed in Table 2.19.

Table 2.19 Australian and international guidelines for management of sleep disorders in children, adolescents and adults

Country	Disorder	Organisation	Year	Title	Reference
Australia	Insomnia, sleep terrors, sleepwalking	eTG Complete (child and adolescent)	2019	Sleep disorders in children and adolescents.	eTG complete (2019) *Sleep disorders in children and adolescents*. (accessed 11 Jul 2020). [320]
Australia	Insomnia, sleep terrors, sleepwalking	eTG Complete (adult)	2020	Insomnia, parasomnias and jet lag.	eTG complete (2020) *Insomnia, parasomnias, and jet lag*. (accessed 12 Jul 2020). [176]
UK	Dyssomnias	BMJ Best Practice (child and adolescent)	2018	Dyssomnias in children.	BMJ Best Practice (2018) *Dyssomnias in children*. (accessed 12 Jul 2020). [318]
UK	Parasomnias	BMJ Best Practice (child and adolescent)	2018	Parasomnias in children.	BMJ Best Practice (2018) *Parasomnias in children*. (accessed 12 Jul 2020). [319]
UK	Parasomnias, circadian rhythm disorders	BAP (all ages)	2010	Consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders.	Wilson SJ, Nutt DJ, Alford C, et al. (2010) British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders. [324]
US	ASWPD, DSWPD, N24SWD, ISWRD	AASM (all ages)	2015	Practice Guideline for the Treatment of Intrinsic Circadian Rhythm Sleep-Wake Disorders: ASWPD, DSWPD, N24SWD, and ISWRD.	Auger RR, Burgess HJ, Emens JS, et al. (2015) Clinical Practice Guideline for the Treatment of Intrinsic Circadian Rhythm Sleep-Wake Disorders: Advanced Sleep-Wake Phase Disorder (ASWPD), Delayed Sleep-Wake Phase Disorder (DSWPD), Non-24-Hour Sleep-Wake Rhythm Disorder (N24SWD), and Irregular Sleep-Wake Rhythm Disorder (ISWRD). An Update for 2015: An American Academy of Sleep Medicine Clinical Practice Guideline. [321]
US	Insomnia (ASD)	AAP (child and adolescent)	2012	A practice pathway for the identification, evaluation, and management of insomnia in children and adolescents with ASD.	Malow BA, Byars K, Johnson K, et al. (2012) A practice pathway for the identification, evaluation, and management of insomnia in children and adolescents with autism spectrum disorders. [301]
Canada	Sleep disorders	CPS (child and adolescent)	2012	Melatonin for the management of sleep disorders in children and adolescents.	Cummings C and Canadian Paediatric Society CPC (2012) Melatonin for the management of sleep disorders in children and adolescents. [322]

Abbreviations organisations/institutions: AAP, American Academy of Pediatrics; AASM, American Academy of Sleep Medicine; AFP, Australian Family Physician; eTG Complete, Electronic Therapeutic Guidelines Complete; BAP, British Association for Psychopharmacology; CPS, Canadian Paediatric Society.
Abbreviations disorders: ASD, autism spectrum disorder; ASWPD, advanced sleep-wake phase disorder; DSWPD; delayed sleep-wake phase disorder; ISWRD, irregular sleep-wake rhythm disorder; N24SWD, non-24-hour sleep-wake rhythm disorder.

2.3.9.1 Approved psychotropic drugs

Table 2.20 TGA-approved psychotropic drugs for sleep disorders in children and adolescents

Medication	Medication name	Age range	Indications
Methylphenidate	Ritalin 10	>5 years	Narcolepsy
Methylphenidate -LA[a]	Ritalin-LA[a]/Concerta	>5 years	Narcolepsy
Dexamphetamine	Aspen dexamphetamine	>2 years	Narcolepsy
Melatonin (PR)[b]	Slenyto	2-18 years	Insomnia in children and adolescents with Autism Spectrum Disorder and/or Smith-Magenis syndrome

Notes:
a. LA, long-acting
b. PR, prolonged release. Melatonin (PR) TGA approved 22 May 2020).

2.3.9.2 Introduction

Sleep disorders fall into two main categories: dyssomnias and parasomnias [176, 318-320]. Dyssomnias include insomnia, delayed sleep-phase disorders (DSPDs), and narcolepsy [318], while parasomnias include sleepwalking, night terrors, nightmares, rapid eye movement (REM) sleep behaviour disorders, as well as isolated recurrent sleep paralysis (IRSP) [176, 319].

2.3.9.3 Australian and international guidelines

eTG Complete guidelines [320] are the only Australian guidelines to address sleep disorders in children and adolescents but provide little guidance on managing them. Two short paragraphs suggest good sleep hygiene practices be adopted as first-line therapy (Appendix 12), with the recognition that nightmares and parasomnias will often resolve in children as they grow [320]. For more information on treatment of parasomnias, clinicians are referred to adult guidelines for managing sleep disorders [176]. However, pharmacological treatment is usually not needed in children and adolescents [176]. The eTG Complete and international guidelines are summarised in Appendix 12.

The limited number of international guidelines also recommend the adoption of non-pharmacological practices first-line for adults and children. This is followed by melatonin as second-line in almost all situations [176, 301, 318-324]. Benzodiazepines [176, 319] are listed among the other medication options, including for parasomnias in children [176, 319]. The antidepressant paroxetine is also listed as a third-line option for sleep terrors in children and adolescents in the BMJ Best Practice guidelines for parasomnias in children [319], after first-line environmental adjustment (see Figure 2.2) and second-line benzodiazepines have been trialled [319] (Appendix 12).

- Going to bed and getting up at the same time each day
- Avoiding excessive and late daytime naps
- Avoiding excessive light exposure before bedtime (any device with a screen, including TV, video games, cell phones, and computer use)
- Avoiding spending a lot of time awake in bed
- Getting regular exercise every day in the mid to late afternoon
- Limiting caffeine-containing drinks
- Avoidance of nicotine (relevant in adolescents)
- Avoidance of alcohol (relevant in adolescents)
- Avoidance of dealing with school-related or work-related issues before bedtime (work may be relevant in older adolescents)
- If sleep onset does not take place within 20 minutes of going to bed, it is suggested that the patient gets out of bed and engages in a relaxing activity, such as reading, for a while and then returns to bed when feeling sleepy.

Adequate sleep time for children is considered to be approximately:

- Infants: up to 16 hours daily
- Toddlers and preschool children: 11-14 hours (includes overnight and nap sleep times)
- Primary school children (1st-8th): 10 hours
- High school children (9th-12th): 9 hours
    - ensure a comfortable temperature for sleep and maximal darkness

Figure 2.2 A summary of recommended advice to parents to establish healthy sleep patterns in their children. **Source**: BMJ Best Practice (2018) *Parasomnias in children*. [319, p.21].

2.3.9.4 Changes in treatment recommendations

There have been no major changes to guidelines for sleep problems in children and adolescents over time. Non-pharmacological treatments are recommended first-line in all clinical practice guidelines (CPGs), and melatonin is mentioned as a treatment option in multiple CPGs [176, 301, 318-324].

2.3.10 Enuresis (bedwetting) disorders

The guidelines summarised in this section for managing enuresis (bedwetting) disorders in children and adolescents are listed in Table 2.21.

Table 2.21 Australian and international guidelines for management of bedwetting disorders in children and adolescents

Country	Organisation	Year	Title	Reference
Australia	RCHM	2019	Enuresis - Bedwetting and monosymptomatic enuresis. (child and adolescent)	The Royal Children's Hospital Melbourne (2019) *Enuresis - Bedwetting and monosymptomatic enuresis*. (accessed 26 Apr 2020). [329]
Australia	Article-Australian Prescriber	2014	Paediatric urinary incontinence. (child and adolescent)	Nankivell G and Caldwell P (2014) Paediatric urinary incontinence. [327]
UK	NICE	2010	Bedwetting in under 19s. (child and adolescent)	NICE (2010) *Bedwetting in under 19s*. (accessed 26 Apr 2020). [328]
UK	BMJ Best Practice	2020	Enuresis. (child and adolescent)	BMJ Best Practice (2020) *Enuresis*. (accessed 22 Jul 2022). [325]
US	AACAP	2004	Practice parameter for the assessment and treatment of children and adolescents with enuresis.	Fritz G, Rockney R, Bernet W, et al. (2004) Practice parameter for the assessment and treatment of children and adolescents with enuresis. [326]
International	Consensus based on ICCS guidelines	2012	Practical consensus guidelines for the management of enuresis. (child and adolescent)	Vande Walle J, Rittig S, Bauer S, et al. (2012) Practical consensus guidelines for the management of enuresis. [330]
International	Consensus based on ICCS guidelines	2017	Enuresis: practical guidelines for primary care. (child and adolescent)	Vande Walle J, Rittig S, Tekgul S, et al. (2017) Enuresis: practical guidelines for primary care. [331]

Abbreviations organisations/institutions: AACAP, American Academy of Child and Adolescent Psychiatry; NICE, National Institute for Health and Care Excellence; ICCS, International Children's Continence Society; RCHM, Royal Children's Hospital of Melbourne.

2.3.10.1 Approved psychotropic drugs

Table 2.22 TGA-approved psychotropic drugs for bedwetting disorders in children and adolescents

Medicine	Medicine Name	Age range	Indications
Amitriptyline	Endep	No age limits specified	Nocturnal enuresis
Imipramine	Tofranil	>4 years	Nocturnal enuresis

2.3.10.2 Introduction

Enuresis, or bedwetting, is a common condition of childhood [325-330]. Primary enuresis occurs when a child has never been dry, and secondary enuresis occurs when a child has previously been dry for at least 6 months but has had a recurrence of the problem [325-327].

As children are generally expected to be dry by the age of 5 years, treatment is not recommended before this age [325, 327-331].

2.3.10.3 Treatment guidelines – Australian and international

First-line options are always non-pharmacological, with an emphasis on education and behavioural approaches. (see Appendix 13). Parents are educated on the normality of the condition in children [326, 330], as well as providing advice on fluid intake [325-331], avoiding constipation [327, 329-331], bedtime routines, and toilet training [325, 327, 328, 330]. If education and behavioural approaches fail, guidelines recommend alarm therapy as second-line treatment [325-331].

Drug options are only used where alarms are unacceptable to the patient or ineffective [325-330]. While the tricyclic antidepressant imipramine has been the primary pharmacological treatment for several decades, the synthetic anti-diuretic hormone desmopressin has become a more commonly used drug [326] and is now universally recommended as first-line pharmacological treatment when drugs are indicated for enuresis [325-331]. Three guidelines also recommend anticholinergic drugs if desmopressin is ineffective, relegating imipramine to the last option due to its association with adverse cardiovascular effects [325, 327, 328]. In Australia, imipramine is still approved for treatment of enuresis in children from 5 years of age [327, 332], although now specifically contraindicated in the Royal Children's Hospital Melbourne (RCHM) guidelines [329]. Non-psychotropics oxybutynin [333] and desmopressin [334] are also TGA-approved for children 6 years and over.

2.3.10.4 Changes in treatment recommendations

There have been no changes to guidelines for treatment of enuresis over the study period.

2.3.11 Other mental health conditions

The following section includes other diagnostic conditions, including substance use disorder (SUD), learning disorder (LD), and personality disorder (PD). Although recognised as mental health disorders, they have not been considered major topics of interest for this thesis for the reasons outlined below but have been included to determine if psychotropics are being prescribed off-label for these conditions.

Treatments for SUD do not include psychotropic medications in the ATC categories of N05 (antipsychotics, anxiolytics, hypnotics/sedatives) and N06 (antidepressants, stimulants), which are the focus of this thesis. Learning disorders resources located by literature searches did not recommend any medications for treating children and adolescents. PD, although

having no recognised medications suitable for the primary diagnosis, does have psychotropic drugs recommended for symptoms or comorbidities (see Table 2.23). However, until the publication of the latest manual of mental disorders, the DSM-5 [187], children aged under 18 years could not be diagnosed with PD [335]. A diagnosis of PD requires a pervasive, longstanding pattern of maladaptive behaviour, and a young person's personality was considered to be evolving and changing during adolescence, precluding a PD diagnosis [336]. The recommendations for SUD, LD, and PD are listed in Sections 2.3.11.1 to 2.3.11.3.

2.3.11.1 Substance Use Disorders (SUD)

2.3.11.1.1 TGA-approved psychotropic drugs for treatment of SUD in children and adolescents

No psychotropic drugs have been approved by the TGA for the treatment of substance abuse disorders in children and adolescents.

2.3.11.1.2 Treatment recommendations

Substance use disorders include unhealthy consumption of addictive substances, including tobacco, alcohol, opioids, and illicit drugs such as cocaine, cannabis, and ecstasy [337, 338]. Australian resources for adolescents recommend treatment with a range of psychological interventions [339, 340] and family therapies [339], as do several international guidelines [337, 341-344].

A US review of pharmacotherapies for substance use disorders in adolescents found little quality research about adolescents and limited generalisability from adult studies [345]. Some international guidelines provide the option for prescribing naltrexone or acamprosate for alcohol use disorder with caution in older adolescents (16-17-year-olds) [344] and methadone for opioid use disorder in 16-18-year-olds [346].

Although medications used in SUDs can be used with caution in adolescents if indicated, they are rarely used [339].

2.3.11.2 Learning disorders

There was little literature on treatment for learning disorders. Guidelines included only non-pharmacological options such as counselling, psychoeducation, classroom modifications, and special education programs [347-349].

2.3.11.3 Personality disorders

The guidelines summarised in this section on managing personality disorders are listed in Table 2.23.

Table 2.23 Australian and international guidelines for management of personality disorders for children, adolescents and adults

Country	Organisation	Year	Title	Reference
Australia	NHMRC	2012	Clinical Practice Guideline for the Management of Borderline Personality Disorder.	NHMRC (2012) *Clinical Practice Guideline for the Management of Borderline Personality Disorder*. (accessed 13 Sep 2019). [182]
Australia	Illawarra Health and Medical Research Institute.	2015	Treatment Guidelines for Personality Disorders.	Project Air Strategy for Personality Disorders (2015) Treatment Guidelines for Personality Disorders 2nd Ed. Wollongong: University of Wollongong, Illawarra Health and Medical Research Institute. (accessed 25 Mar 2020) [350]
UK	NICE	2009	Borderline personality disorder: recognition and management: cg78.	NICE (2009) *Borderline personality disorder: recognition and management: cg78*. (accessed 3 Sep 2018). [183]
UK	NICE	2009	Antisocial personality disorder: prevention and management: cg77.	NICE (2009) *Antisocial personality disorder: prevention and management: cg77*. (accessed 3 Sep 2018). [352]
International	WFSBP	2007	World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of personality disorders.	Herpertz SC, Zanarini M, Schulz CS, et al. (2007) World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of personality disorders. [179]
US	APA	2005	Practice Guideline for the Treatment of Patients with Borderline Personality Disorder.	Oldham JM (2005) Guideline Watch: American Psychiatric Association (APA) Practice Guideline for the Treatment of Patients with Borderline Personality Disorder. [351]

Abbreviations organisations/institutions: APA, American Psychiatric Association; NHMRC, National Health and Medical Research Council; NICE, National Institute for Health and Care Excellence; WFSBP, World Federation of Societies of Biological Psychiatry.

2.3.11.4 Approved psychotropic drugs

Table 2.24 TGA-approved psychotropic drugs for the treatment of personality disorders

Medicine	Medicine Name	Age range	Indications
Lithium	Lithicarb	>11 years	Personality disorders in young people with cyclothymia

2.3.11.4.1 Introduction

PD is defined as enduring patterns of behaviour and inner experience that cause distress and maladaptive cognitions, emotional reactions, poor impulse control, and unstable interpersonal relationships [179]. The age of onset for PD is usually during late adolescence to early adulthood [350]. PD was not listed as a diagnosis applicable to children or adolescents until the DSM-5 was released in 2013 [187].

2.3.11.4.2 Australian and international guidelines

Australian [182, 350] and international [179, 183, 351, 352] guidelines (see Table 2.23) consider psychological therapies first-line treatments for patients of all ages. Medications are not considered useful for treating the primary disorder but can be used to treat target symptoms or comorbidities [182, 183, 350-352]. The World Federation of Societies of Biological Psychiatry also recognises the poor outcomes of biological treatments for PD, but based on limited evidence, it still recommends SSRIs for emotional reactivity, impulsivity, and comorbid anxiety [179]. Antipsychotics (specifically, risperidone in adolescents) are recommended for anger, impulsivity, and psychotic-like cognitive and perceptual distortions in patients with PDs [179]. Clinicians are recommended to follow adult treatment guidelines for treating adolescent PD, given the absence of studies in adolescents [179, 182, 183]. Of note, the only TGA-approved medication for children with PD is for comorbid cyclothymia [353] (see Table 2.24).

2.4 Guideline recommendations for antipsychotic prescribing in children and adolescents

This thesis examines prescribing practices for all psychotropic agents (Chapters 4 and 8), with Chapters 5 and 6 examining one class of psychotropics, antipsychotics, in greater depth. An additional table was created to identify which clinical practice guidelines mentioned use of antipsychotics for management of child and adolescent mental disorders (see Appendix 14). The table distinguishes between paediatric and adolescent recommendations and Australian and international guideline recommendations.

3 Chapter 3. Methodology

3.1 Preface

This chapter includes an overview of methodology used in the three papers included in this thesis. It includes a description of the general practice database (MedicineInsight) that was used in all analyses, data cleaning and data extraction processes, and statistical methods used to address the research questions.

The first paper examined trends in prescribing of all psychotropics from 2011 to 2018. Included medication classes were antipsychotics, antidepressants, medications for ADHD (including stimulants and non-stimulant alpha2-agonist or antihypertensive drugs), anxiolytics, and sedatives/hypnotics, with melatonin examined separately. The second and third papers examine only one class, antipsychotics, in more detail. The second paper analysed diagnostic patterns associated with antipsychotic prescribing, and the third examined monitoring for key antipsychotic-related adverse events in children and adolescents prescribed antipsychotics.

3.2 Study population

Children and adolescents aged 18 years and under who attended a general practice included in the MedicineInsight database from 2011 to 2018.

3.3 Data source - MedicineInsight database

MedicineInsight is a large primary care database of electronic health records [354]. It was established in 2011, with core funding from the Australian government to improve primary care practices, improve the quality use of medicines, and monitor post-market surveillance of medicines [355]. Recruitment of general practices into the MedicineInsight program requires the provision of general information about the program to both GPs and patients attending the practice and a poster informing patients that their de-identified data will be collected by MedicineInsight prominently displayed at the practice [354]. Patients can negotiate with their GP to opt out of the program [354].

The database was managed by NPS MedicineWise until December 2022 and is now managed by the Australian Commission on Safety and Quality in Health Care (ACSQHC).

In the 2018/2019 financial year, MedicineInsight included data from 569 general practices, 2.89 million patients, and 13.8 million clinical encounters, representing approximately 8.6% of GPs and 13.2% of patients attending general practices [356]. This included 620,000

patients aged 0-19 years. Some states and territories are over- or under-represented in MedicineInsight when compared to census data, and GPs in cities and remote/very remote areas are somewhat over-represented in the MedicineInsight database [355]. However, the coverage of the database is considered broadly representative of the Australian population in terms of age, gender, socio-economic level, and proportion of Indigenous patients [357].

In participating practices, all data recorded in the clinical information system (CIS) are transferred to a data warehouse monthly using a secure third-party extraction tool (Figure 3.1). To enhance data quality, only general practices established for at least two years with no interruptions of more than six weeks and a consistent volume of transactions are used in analyses. MedicineInsight uses a range of controls to ensure patient confidentiality, including the use of unique encrypted identifiers generated at the time of data extraction and restricting the release of some data fields to limit any possibility of re-identification of patients [354].

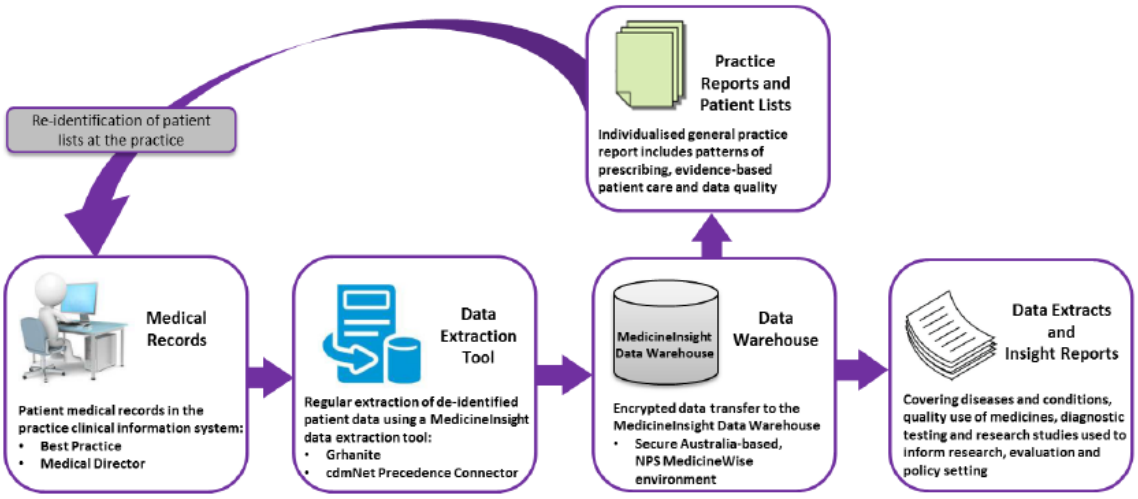


Figure 3.1 Illustration of MedicineInsight data collection processes.
Source: MedicineInsight Data Book version 3.0. Sydney: NPS MedicineWise, June 2020. [355]

As a CIS, MedicineInsight is not specifically designed for research purposes but can provide important insights into treatment practices, medication use, and health outcomes [356]. The use of well-designed data extraction algorithms, described in Section 3.3.3, can generate robust analyses [356].

3.3.1 Data fields

There are 15 data fields available in the MedicineInsight database, including prescriptions issued, pathology requests and results, and clinical observations. Data fields are populated using drop-down menus with pre-defined codes in GP software ("Best Practice" or "Medical Director"). Alternatively, GPs can record information in free-text fields. The data fields used in this thesis are listed in Table 3.1.

Table 3.1 Data sources within MedicineInsight

Data table	Variables used in analysis
Patient details	Patient identifier number (ID), gender, year of birth, Indigenous status, IRSAD decile, current smoking status
Provider	Site ID, remoteness indicator, IRSAD decile
Script item	Date of issue, medicine name, medicine active ingredient
Encounters	Date of encounter, encounter reason
Diagnosis reason	Date of visit when diagnosis recorded, diagnosis reason
Prescription reason	Date of visit when prescription recorded, prescription reason
Pathology	Result date, blood glucose, blood lipids, liver function, prolactin
Observations	Observation date, weight, height, waist circumference, blood pressure, blood glucose, lipids
Allergy Reaction	Date recorded, allergy substance, reaction type

Source: MedicineInsight Data Book version 3.0. Sydney: NPS MedicineWise, June 2020. [355]

3.3.2 Data cleaning

Entries in the "Encounters" dataset may include various administrative items such as "forms", "recall", "update file", and phone calls, emails or reminders. An encounter is defined as all but administrative actions. Therefore, all such entries were removed from the dataset.

3.3.3 Derived data

Some data fields, such as patient and provider details, are available for use in the downloaded format. Variables such as diagnosis, medicines prescribed, and allergy status needed to be derived from data fields using appropriate algorithms.

3.3.3.1 Medications

A list of all psychotropic medications approved by the TGA for use in any age group in Australia was generated, including all generic formulations and brand names (see Table S1, Chapter 4). Entries on this list were then used to create an algorithm to extract prescription information from entries in two MedicineInsight fields: the "medicine active ingredient" (generic) field and the "medicine name" field, listing brand or trade names. A final prescriptions file was created and matched to a database that included all GP visits for all children and adolescents from 2011 to 2018, merging the two files by linking visit date and prescription date. Medications were then grouped into class and sub-class according to the Anatomical Therapeutic Chemical (ATC) classification system [358] (Table 3.2; Supplementary Table S1 Chapter 4). Although melatonin is classified as a sedative/hypnotic under the ATC system, it is not a traditional psychotropic and is sometimes classified as a

neurohormonal or chronobiotic drug [359]. There has been little research examining trends in melatonin prescribing. Therefore, it was separately examined.

Table 3.2 Medication classes and sub-classes used in analyses

Class	ATC code	Sub-class
Antipsychotics	NO5A	FGA (first-generation antipsychotic)
		SGA (second generation antipsychotic)
Antidepressants	NO6A	SSRI (selective serotonin reuptake inhibitor)
		SNRI (serotonin and noradrenaline reuptake inhibitor)
		TCA (tricyclic antidepressant)
		MAOI (monoamine oxidase inhibitor)
		NaSSA (noradrenaline and specific serotonergic antidepressant)
		Other antidepressant
ADHD drugs	NO6B	Stimulant
	CO2A	Alpha-2 agonist
Anxiolytics	NO5B	Benzodiazepine
		Azaspirodecanedione
Hypnotics/sedatives	NO5C	Benzodiazepine
		Z-drug
Melatonin	NO5C	Melatonin receptor agonist

Abbreviation: ATC, Anatomical Therapeutic Chemical.

3.3.3.2 Diagnoses

The procedure used for extracting diagnoses from the MedicineInsight database has been recently validated using MedicineInsight data by Havard et al. (2021) [360].

Diagnostic information was derived from three fields: encounter reason, diagnosis reason, and prescription reason, with a dichotomised "yes/no" variable created for analyses. The three reason data fields were populated either automatically using codes from GP software or manually in free-text fields [360]. Algorithms to extract diagnoses used keywords selected by reference to terms used to classify disorders in the Diagnostic and Statistical Manual of Mental Disorders version 5 (DSM-5) [187], in consultation with a child psychiatrist (refer Chapter 5, Supplementary Table S2). Results were then manually checked for misclassifications. For example, attention deficit hyperactivity disorder could be written in full, or as ADHD, or as acronyms such as ADD, which would pick up additional terms such as addiction or Addison's disease. These misclassified items were corrected by recoding the diagnosis variable from "yes" to "no". Similarly, comments such as "mum thinks child has…" in the field that mentioned a diagnostic term were not classified as diagnoses. Any obvious misspellings such as "austism", "asbergers", "dyslexia", or "biopolar" were included in the relevant algorithm.

As psychotropic drugs can be used for multiple conditions (e.g., antidepressants can be used to treat OCD, depression, enuresis, or chronic pain), all psychiatric diagnoses were extracted using only the three reasons data fields. In the third paper of this thesis, physical health conditions were also used in analyses. For non-psychiatric conditions, a modified algorithm was sometimes required to capture condition-specific medications as evidence of a diagnosed condition where appropriate [361]. For example, asthma diagnoses were recorded if Ventolin, albuterol, budesonide, or other asthma-related medications were prescribed.

The final algorithm was then run on the three data fields, and a final diagnosis dataset was created. Patients were deemed to have a diagnosis if the diagnostic term was present in at least one of the three fields (diagnosis, encounter, reason) for the date of visit. If there was more than one diagnosis recorded on a given visit, all were included as diagnoses for that date. For example, if the reason field mentioned ADHD with comorbid anxiety and depression, three diagnoses were generated for that patient on that day.

3.3.3.3 Pathology dataset

Data was extracted from the pathology dataset for the third paper that examined health monitoring in children and adolescents prescribed antipsychotics. Most pathology results are received electronically but may also be recorded manually. Pathology tests examined in this thesis include blood glucose, glycated haemoglobin (HbA1c), lipids (total cholesterol, HDL, triglycerides), prolactin, and liver function (specifically, alkaline phosphatase levels [ALP]). Variables were derived from the result-name field in the pathology dataset, which records the test in full text or acronym formats. The purpose of the analysis was to determine if monitoring had taken place, so a monitoring event was registered even if values were missing or invalid for a given test.

For several parameters (e.g., glucose, lipids), testing was occasionally recorded in the observations dataset, discussed in the next section. Therefore, records from both datasets were merged and one variable created to represent testing “yes” or “no” for each parameter reported in Chapter 6. This increased the likelihood that all incidences of monitoring were captured from the database.

3.3.3.4 Observations dataset

Clinical observations included in cardiometabolic monitoring included height, weight, BMI, and blood pressure. Extraction processes were the same as for the pathology dataset. A monitoring event was registered even if values for the measure were missing or implausible.

3.3.3.5 Sociodemographic information

Where adjusted analyses were undertaken, patient and general practice characteristics were included. Patient sociodemographic variables used in analyses included age, gender, socio-economic level, and Indigenous status. Practice characteristics included the socio-economic level associated with the practice's geographical location, its state, and geographical remoteness. Several analyses were also stratified by age, patient gender, and socio-economic position (refer to Table 3.4).

3.3.3.5.1 Socio-economic status

Studies examining the impact of social disadvantage often use measures of socio-economic position, commonly defined by individual factors of income, education, and occupation [362]. Other broader measures of deprivation or disadvantage include additional information on housing, access to resources, and neighbourhood characteristics [362], which would more comprehensively capture the social determinants of health (SDH) identified in Figure 1.2 (Chapter 1).

The Australian Bureau of Statistics (ABS) calculates four Socio-Economic Indexes for Areas (SEIFA) [363]. These include the Index of Education and Occupation (IEO), the Index of Economic Resources (IER), the Index of Relative Socio-economic Disadvantage (IRSD), and the Index of relative Socio-economic Advantage and Disadvantage (IRSAD) [363]. The indexes summarise the collective characteristics of people living in defined areas (suburbs and localities [SALs]), with information collected from the Australian population census [132]. The ABS broadly defines relative socio-economic advantage and disadvantage as a person's ability to participate in society via access to economic, material, and social resources [364]. The IEO focuses on the proportion of skilled residents in an area, and the IER focuses on financial aspects related to socio-economic advantage and disadvantage. The IRSD and IRSAD include a range of social factors such as family and housing structure, in addition to income, education, and occupational factors [132].

Socio-economic status in this thesis was analysed using the IRSAD [132], as it includes the broadest range of factors and most closely corresponds to an index representative of SDH as

described in Section 1.8 (see Chapter 1). Table 3.3 lists the factors included in the IRSAD area-level index. MedicineInsight provides information on IRSAD deciles. Due to low numbers in some levels, a new variable was created, dividing into quintiles. If patient IRSAD was missing, practice IRSAD was used as a proxy. The first quintile includes patients living in the most advantaged areas, and the fifth quintile includes those in the most disadvantaged areas.

Table 3.3 Variables related to SDH included in the Index of relative Socio-economic Advantage and Disadvantage (IRSAD)

SDH	Variable description	Level of advantage/ disadvantage
Education	Per cent of people aged 15 years and over at university or other tertiary institution	Advantage
Education	Per cent of people aged 15 years and over whose highest level of educational attainment is a certificate III or IV qualification	Disadvantage
Education	Per cent of people aged 15 years and over whose highest level of education attainment is a diploma qualification	Advantage
Education	Per cent of people aged 15 years and over who have no educational attainment	Disadvantage
Education	Per cent of people aged 15 years and over whose highest level of education is Year 11 or lower. Includes Certificate I and II	Disadvantage
Employment	Per cent of people (in the labour force) unemployed	Disadvantage
Housing	Per cent of occupied private dwellings with four or more bedrooms	Advantage
Housing	Per cent of occupied private dwellings paying mortgage greater than $2,800 per month	Advantage
Housing	Per cent of occupied private dwellings paying rent greater than $470 per week	Advantage
Housing	Per cent of occupied private dwellings paying rent less than $250 per week (excluding $0 per week)	Disadvantage
Housing	Per cent of occupied private dwellings requiring one or more extra bedrooms (based on Canadian National Occupancy Standard)	Disadvantage
Income	Per cent of people living in households with stated annual household equivalised income greater than $91,000 (approx 9th and 10th deciles)	Advantage
Income	Per cent of people living in households with stated annual household equivalised income between $1 and $25,999 (approx. 1st and 2nd deciles)	Disadvantage
Miscellaneous	Per cent of families with children under 15 years of age who live with jobless parents	Disadvantage
Miscellaneous	Per cent of people aged under 70 who need assistance with core activities due to a long–term health condition, disability or old age	Disadvantage
Miscellaneous	Per cent of one parent families with dependent offspring only	Disadvantage

SDH	Variable description	Level of advantage/ disadvantage
Miscellaneous	Per cent of people aged 15 and over who are separated or divorced	Disadvantage
Occupation	Per cent of employed people classified as Machinery Operators and Drivers	Disadvantage
Occupation	Per cent of employed people classified as 'labourers'	Disadvantage
Occupation	Per cent of employed people classified as Managers	Advantage
Occupation	Per cent of employed people classified as Professionals	Advantage
Occupation	Per cent of employed people classified as Low Skill Sales	Disadvantage
Occupation	Per cent of employed people classified as Low Skill Community and Personal Service Workers	Disadvantage

Source: Australian Bureau of Statistics (2021) *Socio-Economic Indexes for Areas (SEIFA): Technical Paper*.[363]
Abbreviation: SDH, social determinants of health.

3.3.3.5.2 Geographical remoteness

Rurality of the GP practice was determined using statistical areas defined by the Australian Statistical Geography Standard (ASGS) [365]. The ASGS uses census data and defines geographical boundaries to meet the needs of researchers in a manner that helps to ensure confidentiality of participant information and maximise usefulness as a research tool. The areas, which roughly align with distance from major cities/urban centres, are defined as: major city, inner regional, outer regional, remote, or very remote areas. As numbers were low in the study sample in some of the more remote regions, a new three-level variable was created: major cities, inner regional, or outer regional/remote/very/remote.

3.3.3.5.3 Age, gender and ethnicity

For confidentiality reasons, actual birthdates are not available in MedicineInsight [355]. Age is represented by the year in which the date of birth occurs. For the first paper on trends in psychotropic prescribing, age was grouped into four categories: 0-4 years, 5-9 years, 10-14 years, 15-18 years. For the second paper examining antipsychotic prescribing, numbers were sparse for children aged under 10 years, so age was defined into three categories: 0-9 years, 10-14 years, 15-18 years.

Gender was divided into two categories: male and female, and Indigenous status was divided into three categories: neither Aboriginal nor Torres Strait Islander, Aboriginal or Torres Strait Islander, or not recorded/not stated. Indigenous status was only used as a covariate in the third paper (Chapter 6).

3.3.3.5.4 Other covariates

Other variables included in the analyses for the third paper were patient allergies, smoking status, and weight status at baseline (overweight, obese, or normal weight).

Allergies are recorded in MedicineInsight by the drug, reagent, or other substance/factor suspected of causing the reaction, and a dichotomous variable representing allergies "yes/no" generated. The allergies variable included allergic reactions and adverse drug events. The smoking variable is categorised into four groups: smoker, non-smoker, ex-smoker, and not recorded. Initial explorations of the dataset noted some rare and implausible entries, such as a child less than 1 year of age with a record of a smoking-related prescription such as nicotine patches or the smoking-cessation drug, varenicline. For the purposes of the current analysis, children aged under 10 years were deemed to be non-smokers.

For the sensitivity analysis in paper 3 (Chapter 6), a dichotomous variable for overweight or obesity was calculated. Child growth standards developed by the World Health Organization (WHO) [366] were used to calculate this variable using gender-specific weight-for-age, height-for-age, and BMI-for-age percentile charts (e.g., https://www.who.int/tools/child-growth-standards/). Detailed instructions downloaded from the WHO website [367] were used to calculate the percentile for each child for each visit where weight was recorded. The MedicineInsight database lacks a precise date of birth, so percentiles were calculated for mid-year. For example, a child aged 5 years in MedicineInsight may have been born any time from the 1st January to the 31st December of the given year, so percentiles were calculated for 5 years 6 months. For children aged 0-9 years, percentiles for weight-for-age were used, and for those aged 10-18 years, BMI-for-age percentiles were used [368]. The dataset was initially cleaned to remove any implausible weights, heights, and BMI values by excluding weights with z-scores greater than +/-5 or +/-6, depending on the measure and age, as recommended by Blossner et al. (2009) [368].

Given evidence that children and adolescents can gain weight rapidly while taking antipsychotics [9, 90], a narrow baseline was chosen for this analysis and included any weight recorded on the day of the incident event or up to 14 days after.

3.4 Statistical analyses

All statistical analyses in this thesis used Stata version 16 (StataCorp, Texas, USA). Some descriptive tables were constructed using Microsoft Excel (2016) using data generated from

Stata analyses. Table 3.4 summarises the research questions for each paper and the statistical approaches used for each analysis.

Table 3.4 Summary of analytical methods used for analysis in Chapters 4 through 6

Chapter	Main analysis	Study period	Research questions	Study sample	Statistical methods
Chapter 4	Prevalence of all psychotropic prescribing.	2011-2018	1). What is the rate of prescribing for the five main classes of psychotropic drugs (antidepressants, antipsychotics, ADHD drugs, anxiolytics, sedatives/hypnotics) and melatonin in a cohort of children and adolescents in Australian primary care from 2011 to 2018? 2). Is there an increasing trend in prescribing across the study period from 2011 to 2018? 3). How do psychotropic prescribing trends differ by age, gender and socio-economic level? 4). Which drugs are most commonly prescribed, by age group, in a selected year: 2018?	537,371 "regular" (at least 3 visits in 2 consecutive years, with at least one visit in each year) patients aged 0-18 years.	1). Robust Poisson regression reporting incident rate ratios (IRRs) 2).Descriptive tables
Chapter 5	Off-label prescribing of antipsychotics.	Compare 2017 to 2011	1). Is there a change in the prescribing rate of antipsychotics to children and adolescents with mental health diagnoses in 2017, compared to 2011? 1a). Which diagnoses exhibit increases, decreases or no change? 2). Does the proportion of patients with mental health diagnoses who are prescribed antipsychotics vary by sociodemographic characteristics from 2011 to 2017? 3). Has the rate of off-label prescribing of antipsychotics changed from 2011 to 2017? 4). What sociodemographic characteristics are associated with antipsychotic prescribing? 5). Which antipsychotics were most commonly prescribed for each diagnostic category in each year? 6. What is the extent of co-prescribing of other classes of psychotropics with antipsychotics in each year?	2011: 8,418 "regular" patients with record of mental health diagnosis and antipsychotic in 2011. 2017: 27,412 "regular" patients with record of mental health diagnosis and antipsychotic in 2017. "Regular" patients for this analysis were patients included in the 2011 or 2018 cohort and "regular patients" (as defined in Chapter 4) at any time during 2011 to 2018.	1).Logistic regression, reporting marginal predicted percentages 2).Descriptive tables reporting frequencies
Chapter 6	Monitoring of health status within 12 months of incident antipsychotic prescriptions.	2011-2017	1). How frequently are children and adolescents monitored for antipsychotic-related adverse effects within 12 months following their first antipsychotic prescription? 2). Are children and adolescents receiving antipsychotic prescriptions monitored more often than patients not receiving antipsychotics?	3,840 patients aged 0-18 years receiving antipsychotic prescriptions during 2011-2017. 551,611 non-users of antipsychotics during 2011-2017.	1).Descriptive table reporting frequencies 2).AIPW analysis

3.4.1 Chapter 4 (paper 1): Trends in prescriptions of psychotropic medications to children and adolescents

The first study (Chapter 4) examined psychotropic prescribing trends for very young children, previously not explored in the Australian context. Therefore, the four-category age-group variable was used in this paper to examine preschool children (aged 0-4 years) as a separate category.

3.4.1.1 Statistical model -Poisson analysis

This paper examined trends in prescribing of all psychotropic classes to children and adolescents. Poisson regression was used to estimate the number of children and adolescents prescribed psychotropics annually from 2011 to 2018, reporting the incidence rate ratio (IRR) or prevalence ratio.

With binary outcomes, Poisson regression is becoming an increasingly popular alternative to logistic regression [369]. Poisson provides prevalence ratios that are easier to interpret than odds ratios [370] and is less prone to problems with non-convergence [369]. Therefore, reporting incidence rates from Poisson that directly estimates the prevalence ratio, was considered a more suitable option. Poisson regression can, however, generate large standard errors [371], which were adjusted in this analysis by calculating robust standard errors [369, 371].

A Poisson analysis was performed for all psychotropics combined and for each level of the age group, gender, and IRSAD variables. A similar set of analyses was performed for each psychotropic class and melatonin and included in a supplementary document (see Supplementary Tables S3 to S8, Chapter 4).

3.4.1.2 Descriptive analyses

There are very few psychotropics TGA-approved for children and adolescents in Australia, and only a few specific drugs from each class can be prescribed “on-label”. Therefore, tables illustrating the pattern of prescribing of the different psychotropic classes and individual drugs were generated. Descriptive tables were produced detailing prescribing in 2018, the year with the largest number of patients.

3.4.2 Chapter 5 (paper 2): Reasons for prescribing antipsychotics

The second paper examined prescribing patterns for one class of psychotropics, antipsychotics. The aim was to examine how many children with mental health diagnoses

were prescribed off-label antipsychotics and whether there had been a change in off-label prescribing from 2011 to 2017. Prescribing patterns were also examined by sociodemographic characteristics of age, gender, patient IRSAD, and remoteness. Due to low numbers of children in the 0-4 age group receiving antipsychotic prescriptions, age was collapsed into three categories for these analyses. A ten-level mutually exclusive hierarchy of diagnoses was created, with higher levels representing categories that had TGA antipsychotic approval for children and adolescents (e.g., psychosis) and lower levels representing off-label prescribing. As age, diagnosis, and specific antipsychotic are important in determining off-label prescribing, an algorithm was generated considering all these factors. Details of the hierarchy and algorithm are described in Chapter 5.

3.4.2.1 Linking diagnoses with prescriptions

Diagnoses may be recorded in the database on a different date from the antipsychotic prescription date. GPs might not have recorded a diagnosis at every visit or may have recorded the diagnosis but initially treated the child or adolescent using "watchful waiting" or psychosocial therapies [165] as recommended by treatment guidelines (Chapter 2 discussed guidelines in detail). Therefore, in this study, prescriptions were linked to diagnoses if they occurred on the same day or within the same calendar year. For prescriptions issued at the beginning or end of each year, mental health diagnoses recorded within a period of 180 days before or 90 days after the prescription were also linked. For example, if a prescription was issued on 1 January 2011 and a diagnosis was recorded in the last 6 months of 2010, the prescription was linked to the diagnosis. Similarly, if a prescription was written on 31 December 2011, any mental health diagnosis recorded between January and March 2012 was linked to the prescription. This reduced the possibility of missed diagnoses and, therefore, reduced the likelihood of incorrectly inflating rates of off-label prescribing. The MedicineInsight dataset included years 2010 to 2018. To ensure adequate observations for 6 months prior to and 3 months post-prescription were available, the comparison years selected were 2011 and 2017.

3.4.2.2 Statistical model -Logistic analysis

Logistic regression was performed to compare proportions of children prescribed antipsychotics in 2011 and 2017. For comparability of studies within this thesis, wherever possible, it was decided to use the same baseline predictors in our models. Inclusion of all important covariates also reduces residual confounding bias, or the likelihood that the model is missing key predictors [369]. (See Section 3.4.3.1 for further discussion of

confounding.) All logistic results were adjusted for patient age, gender, and IRSAD, and practice characteristics of state, rurality (geographical remoteness), and IRSAD. As numbers were low in some diagnostic categories, the state variable was recategorised into fewer groups in some analyses to reduce problems with convergence. For ease of interpretation of results, predicted probabilities were derived from odds ratios and presented in this paper (Chapter 5).

Logistic regression has four basic assumptions: independence of errors (outcome group samples are independent), linearity in the logit for continuous variables (not relevant in our model), no or low multicollinearity (correlation between predictor variables), and absence of extreme outliers [372]. These assumptions were checked for each analysis. The hierarchical structure of our analysis and use of a dichotomous "yes/no" outcome variable for each patient ensured group samples were independent. The data did not contain any extreme outliers, and multicollinearity was assessed and reported in Table 3.5. Consideration was also given to the power of the analyses and the possibility of finite sample bias [372-374]. Using an existing observational dataset precludes the ability to pre-emptively determine adequate group sample sizes for the proposed analyses. Therefore, to assess how representative the logistic results were in this study, post-hoc tests and calculations were performed to determine the reliability of findings, including events per variable (EPV), power, and desired sample size estimates (Table 3.5).

3.4.2.2.1 Multicollinearity

Multicollinearity occurs when there is high correlation between predictors in regression models, which can result in unstable estimation coefficients and inflated standard errors [375]. Multicollinearity was assessed using the Stata "vif" command (variance inflation factor) and is reported in Table 3.5. All analyses recorded a vif less than 5, indicative of unproblematic levels of multicollinearity [375].

3.4.2.2.2 Finite sample bias

The issue of finite or small sample bias is a well-known problem in logistic regression [373, 376-378]. The bias has historically been handled using a common rule of thumb: establishing a minimum number of 10 events per variable (EPV) for determining adequate sample size [373, 376]. However, this rule of thumb has been extensively critiqued, tested, and modified over the last three decades [377]. EPV is calculated as the number of outcome events (e.g., number of children prescribed antipsychotics in the current study) divided by the number of

covariates (excluding the intercept) in the logistic model (7 in the current study) [376]. Strictly speaking, it is the number of degrees of freedom for each multilevel predictor [373]. Under this second definition, a 5-category predictor such as IRSAD would count as 4 predictors, summing to 21 predictors for the logistic model used in these analyses.

Studies examining the effect of various sample sizes and EPVs on the accuracy of the coefficients, standard errors, and odds ratios have reported varying findings, from EPVs of 5 being adequate [378] to recommendations of 50 [379], with one research team suggesting an EPV of 150 would be needed to completely eliminate any small sample bias [377]. van Smeden and colleagues [380] carried out over 4,000 simulations to test out-of-sample predictive performance of logistic models and determined that total sample size, the events fraction (proportion of "yes" events), and the number of predictors were critical in determining adequate sample size. Using the equation suggested by van Smeden (see Figure 3.2), an approximate adequate sample size was also calculated (Table 3.5).

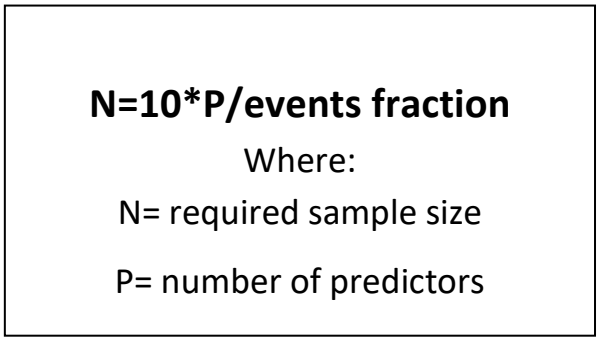


Figure 3.2 Formula for calculation of adequate sample size for logistic regression. Event fraction = number of "yes" events.
Reference: van Smeden et al. (2019), [380, p.2470].

Table 3.5 Post-hoc calculations assessing adequacy of sample size for logistic analyses

Level		Sample size -total[a]	Sample size smaller group[b]	EPV- Peduzzi[c]	EPV- van Smeden[d]	Events fraction[e]	Required sample size[f]	VIF[g]	Power[h]	p-value[i]
1	Psychosis	276	67	9.57	3.19	0.243	865	3.34	0.410	0.105
2	ASD+DBD	307	63	9.00	3.00	0.205	1023	3.21	0.090	0.616
3	Bipolar disorder	238	82	11.71	3.90	0.345	610	3.48	0.883	<0.001
4	DBD/CD	3650	852	121.71	40.57	0.233	900	2.81	0.812	0.014
5	ASD	4186	1100	157.14	52.38	0.263	799	2.57	0.871	0.032
6	ADHD	4410	893	127.57	42.52	0.202	1037	2.76	0.475	0.062
7	ED	705	182	26.00	8.67	0.258	813	2.85	0.949	0.006
8	DEP/ANX	13055	2872	410.29	136.76	0.220	955	2.82	0.892	0.001
	DEP	6333	1623	231.86	77.29	0.256	819	2.74	0.987	<0.001
	ANX	9524	1748	249.71	83.24	0.184	1144	2.75	0.542	0.063
	DEP & ANX	2802	499	71.29	23.76	0.178	1179	2.77	0.724	0.009
9	Sleep disorder	3359	729	104.14	34.71	0.217	968	2.46	0.353	0.134
10	Other	5644	1578	225.43	75.14	0.280	751	2.27	0.250	0.127

Abbreviations: ADHD, attention deficit hyperactivity disorder; ANX, anxiety disorder; ASD, autism spectrum disorder; CD, conduct disorder; DBD, disruptive behaviour disorder; DEP, depression; ED, eating disorder; EPV, events per variable; VIF, variance inflation factor.

Notes:

a. Total sample size for MedicineInsight, 2011 and 2017 combined.

b. Sample size for the smaller outcome group. In this analysis all numbers were smaller in 2011.

c. Calculation of EPV using 7 predictor variables, as outlined by Peduzzi P, et al (1996) [376].

d. Calculation of EPV using 21 predictors, using suggested rule outlined by Austin and Steyerberg (2017) [373].

e. For determining events fraction, the events in 2011 were classified as fraction of "yes" events (see van Smeden M, et al. (2019) [380].

f. Calculation using 21 predictors and events fraction calculated in column 7.

g. Variance inflation factor calculated using Stata 16 "vif" command.

h. Power calculated using Stata 16 "power twoprop" command.

i. p value as reported in analyses in Chapter 5, Table 2.

The information presented in Table 3.5 highlights possible issues with four diagnostic categories (levels 1, 2, 3 and 7). Two of these categories (psychosis and ASD+DBD) had inadequate sample sizes and low power, resulting in non-significant findings. Given the small sample sizes, caution was advised when interpreting all results (refer to Chapter 5).

Reporting marginal effects instead of odds ratios (ORs) has been shown to reduce small sample bias, even for very small samples, and high multicollinearity [381]. To reduce bias and increase the likelihood that logistic models would adequately represent the data, marginal effects were reported in these analyses.

3.4.2.3 Descriptive analyses

Similar to paper 1 (Chapter 4), to better understand prescribing patterns, an unadjusted analysis of individual drugs prescribed for each level of the diagnostic hierarchy was included.

3.4.3 Chapter 6 (paper 3): Monitoring health status of children and adolescents receiving antipsychotics

The third paper examined the number of times a patient was checked for cardiometabolic, endocrine, and other adverse effects associated with antipsychotic use. The date of incident antipsychotic prescribing was determined using the first visit during the study period on which an antipsychotic was prescribed. The number of monitoring events from the date of first prescription to 12 months post-prescription was counted for weight, BMI, waist circumference, blood pressure, cholesterol (total, HDL), triglycerides, prolactin, and liver function (using measures of alkaline phosphatase [ALP]).

Descriptive statistics were reported first. A second analysis using a technique for estimating causal effects from observational datasets (Augmented Inverse Probability Weighting [AIPW]) sought to determine if the extent of monitoring was increased in patients receiving antipsychotics compared to patients attending general practice when no antipsychotic was prescribed.

3.4.3.1 Confounding in observational studies

Critical to obtaining reliable estimates of causality in observational studies is adequate control for confounding [382, 383]. A confounder is a common cause of the exposure and outcome, which obscures the true effect of the treatment on the outcome [383, 384]. By definition, a confounder is associated with the outcome and also with the exposure but is

not an effect of the outcome nor on the causal pathway between the exposure and the outcome (mediator) [383, 384]. In this study, the exposure was receipt of an antipsychotic prescription, and the outcome was the number of occasions patients were monitored on cardiometabolic parameters within 12 months of the first prescription.

Potential confounders in the present study were selected by reference to the literature and expert opinion and included, as a minimum, the baseline adjustment variables used in the analyses for paper 1 (Chapter 4) and paper 2 (Chapter 5) in this thesis. Variables for Indigenous status, smoking levels, health conditions, and allergies were also included.

To assist in visualising the relationships between variables in the model, a directed acyclic graph (DAG) was constructed using resources available online from daggity.net [385, 386]. A DAG is a helpful tool for visualising the covariate connections [386, 387] and provides a minimal sufficient adjustment set of confounders to identify causal effects. The simplified structure of a typical DAG is presented in Figure 3.2. Confounders need to be included in the adjustment set, but colliders must not, or bias will be introduced into the analysis [385]. Including a mediator in the adjustment set will reduce the estimate of the effect and introduce overadjustment bias [388]. The DAG used in this paper is included in Chapter 6 (Supplementary Figure 1).

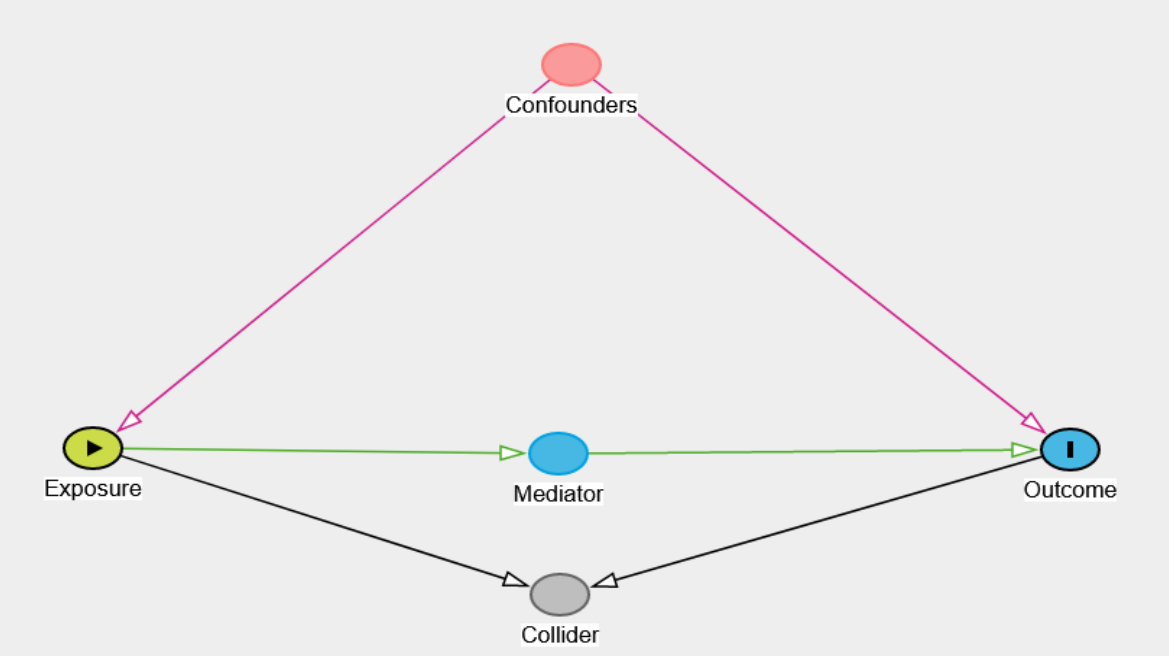


Figure 3.3 Simplified representation of a Directed Acyclic Graph used to visualise the set of adjustment variables used in analyses to identify causal effects.
Diagram created using the online resource DAGitty, available at daggity.net.

3.4.3.2 Preliminary analyses

In this study (Chapter 6), age was used as a continuous variable. Initial explorations of the dataset indicated very few antipsychotics prescribed to toddlers (11 patients) and none to babies in their first year of life. Age also demonstrated a non-linear relationship with antipsychotic prescribing rates. Therefore, the analysis was restricted to patients aged 3 to 18 years, and a quadratic function for age was included in the models.

The outcome variables were counts of visits where monitoring was undertaken by health care providers at the practice. Therefore, Poisson was used for the outcome regression in the AIPW analysis (see Section 3.4.3.3). Initial investigations indicated that all outcomes were overdispersed with a predominance of zeros, raising concerns about the reliability of the effect estimates. However, using the Poisson option in AIPW analyses has been shown to be robust for overdispersed and zero-inflated outcome distributions [389].

3.4.3.3 Augmented Inverse Probability Weighting (AIPW)

RCTs are considered the gold standard for assessing treatment effects [390-392]. However, some questions cannot be ethically or effectively addressed through an RCT. It would be unethical to randomise children to receive or not receive antipsychotics to determine the level of monitoring occurring in general practice, so the research question for the third paper in this thesis was answered using observational data and a technique called Augmented Inverse Probability Weighting (AIPW) [391]. Electronic health records (EHRs) were used to determine if the treatment group (antipsychotics prescribed) "caused" GPs to monitor patients for cardiometabolic problems when compared with a "control" group that did not receive antipsychotics.

Augmented Inverse Probability Weighting (AIPW) is a "doubly robust" estimator of regression coefficients that can be used to estimate causal effects using observational data [382]. The AIPW analysis involves the specification of two models: one for the outcome and one for a binary exposure (treatment). The exposure model calculates a propensity score (PS) that estimates the conditional probability of assignment to treatment or control based on observed baseline characteristics. The inverse probability of the PS is then used to produce a weighted average for two regression analyses that estimate the outcome model (one for treatment/exposed, one for control/unexposed) [382, 392]. It is considered doubly robust because only one of the two models needs to be correctly specified to generate unbiased effect estimates [382, 393]. The augmentation term is a product of bias terms

generated from the two models, which, if zero for either regression, reduces the bias to zero [382]. Estimates are generated for average treatment effects (ATEs), and potential outcome means (POMs) for the treatment and control groups.

Using AIPW to estimate effects as "causal", three assumptions must be fulfilled: 1). exchangeability, 2). positivity, and 3). consistency.

3.4.3.3.1 Exchangeability

Exchangeability is upheld in RCTs because if treated individuals remained untreated, they would have the same outcome as untreated individuals. Exchangeability is achieved through randomisation, whereby all unmeasured predictors are distributed equally between groups. In AIPW analysis, this is achieved through conditional exchangeability or conditioning on baseline measured confounders [390]. However, at best, only approximate conditional exchangeability is achieved in observational studies, and expert knowledge is used to enhance the plausibility of the causal model [383, 394].

3.4.3.3.2 Positivity

The positivity assumption requires that there is a positive (non-zero) probability of being assigned to each treatment arm. A high overlap in PS distribution can create problems with the positivity assumption, and patients with extreme probabilities close to 0 or 1 can create bias in estimates [395]. The overlap function in Stata was used in the present analysis to ensure patients had a non-zero probability of receiving treatment, and those with extreme values were excluded. In the rare cases where this was required, the number of patients excluded was small.

3.4.3.3.3 Consistency

The assumption of consistency requires the same version of treatment exists across all participants. While this may be an issue when addressing varied treatment options or procedures for a specific disease, in this study consistency would be achieved because the one treatment was "prescription of an antipsychotic (yes/no)".

3.4.4 Benefits of AIPW in estimation of causal effects from epidemiological data

AIPW has several advantages over other methods used to estimate causal effects, such as ordinary least squares regression, propensity score matching, and inverse probability weighting [382, 383], which are discussed below.

3.4.4.1 Ordinary regression

A simple regression that is correctly specified and includes all confounders in the model could produce reliable results if the above three conditions (exchangeability, positivity, and consistency) held true. In most situations, however, this is unlikely in ordinary regression due to the unlikely situation that all confounders have been identified and measured. Unmeasured confounding violates the exchangeability assumption [382, 383].

3.4.4.2 Propensity score matching

Propensity scores can also be used in a number of ways to adjust for confounding [396]. The PS is a patient's probability of receiving treatment or no treatment (control) based on measured baseline characteristics. The PS can be used for matching between treatment and control groups on a 1:1 or many-to-1 basis. However, this method discards multiple observations and can result in paradoxical increases in covariate imbalances between groups [397]. Further, this method can be used to generate an average treatment effect for the treated (ATET), but not an average treatment effect (ATE). Propensity scores can also be used to stratify the data [396]. However, both methods (matching and stratification) can lead to biased estimates [396].

3.4.4.3 Inverse probability weighting (IPW)

As an alternative to PS matching, control for confounding may use the PS to weight the data [393, 396]. Inverse probability weighting (IPW) balances the baseline characteristics of exposed and unexposed groups by weighting each individual patient by the inverse probability of receiving their actual treatment [382, 390]. Weights are calculated as 1/PS for those in the treatment group and 1/(1-PS) for those in the reference control group. This creates a pseudo-population in which the distribution of confounders is the same amongst the treatment and control groups and the same as the distribution in the original population [382]. In this pseudopopulation the assumption of exchangeability is satisfied. This also has the advantage of keeping most observations in the analysis [395].

3.4.4.4 Advantages of AIPW

The AIPW analysis incorporates the IPW in a way that can correct the estimator (using the augmentation term) when either the treatment model or the outcome model is misspecified [382]. A further benefit of the AIPW technique is the incorporation of two regressions for the outcome model: one for each level of the exposure (one for treated and one for untreated). This can be advantageous if a confounder differentially affects the exposed and unexposed

groups [382]. AIPW estimators have been demonstrated to be superior to other methods for handling confounding, including IPW [382, 392, 398].

3.4.5 Limitations

MedicineInsight is a useful resource for researchers analysing a range of health outcomes in the Australian population [354], but does come with limitations. The database records prescriptions written, and this may not reflect usage by patients. It cannot be determined if the prescriptions were dispensed or consumed as recommended by the GP. Also, important diagnostic and treatment outcome information may be in progress notes and inaccessible to researchers [399].

Children and adolescents are also likely to be receiving treatment from paediatricians and other child specialists (e.g., child psychiatrists), resulting in a disjointed history of treatment and outcomes as information transfer between hospitals, specialists, and primary care may not always occur [399]. MedicineInsight is an open cohort, so patients may also attend other practices. Any health services received from non-participating practices are absent from the dataset. If patients attend multiple MedicineInsight practices, multiple patient records will be generated and are not cross-referenced, resulting in some duplication of patients, though this is estimated to be less than 4% [355].

To address some of these issues in papers 1 (Chapter 4) and 2 (Chapter 5), the dataset was restricted to patients who were “regular” visitors to the practice using a modified version of the Royal Australian College of General Practitioners (RACGP) definition of “active” patient [400]. Active patients are classified by the RACGP as patients who attended a GP at least three times within two years. The “regular” definition for this research project was more stringent, including the caveat that there should also be at least one visit in each of those two years. Use of a “regular patient” definition results in a more accurate understanding of the GP’s role in the treatment of health conditions of interest.

In the third paper (Chapter 6), inclusion criteria were the presence of an incident antipsychotic prescription. The comparison group consisted of antipsychotic-naive patients. To assess how accurately this analysis represented the GP’s role in the patient’s treatment, a sensitivity analysis was performed on patients attending the practice with at least one follow-up visit in the year following the initial visit (at least 2 visits in 12 months).

3.4.5.1 Confounding bias

As discussed earlier, another important issue when using EHR data is confounding bias. If all required covariates are not available in the dataset, the results may not accurately reflect the true estimates of treatment effects [383]. Although a powerful analytic method [398], the AIPW results will only generate true estimates if the model is correctly specified and all confounding variables are accurately recorded and available [383].

3.4.5.2 Selection bias

Selection bias occurs when patients selected for the analysis differ in some way from those excluded from the analysis [401]. Although MedicineInsight is considered largely representative of the total Australian population attending GPs, practices were recruited through non-random sampling [356] that could result in selection bias. Certain states were over- or under-represented, and one Primary Health Network in one state (Queensland) was not included.

Selection bias in studies using EHRs can be particularly problematic [402]. Haneuse and Daniels (2016) highlight the importance of the interplay between patient and health care provider decisions and the role of differing health care systems in addressing the issue of missing data and selection bias [402]. Reasons for missing baseline data may include, for example, patient refusal to have weight measured or GP decisions to not measure a parameter on a given visit because a patient had not fasted [402]. The problem of missing weight at baseline was evident in the AIPW analysis in this thesis (89.5% missing). Consequently, the analysis including weight at baseline as a covariate was analysed as a sensitivity analysis.

Although it is impossible to ensure no selection bias occurs in observational studies, it can be minimised through careful selection of covariates [383, 402]. A further measure to limit the effect of selection bias in the AIPW analysis is the use of DAGs, which help to identify colliders (see Figure 3.3). If used as covariates, colliders can introduce selection bias [385, 403]. Therefore, any colliders identified in the DAG were excluded from analyses. As recommended by Hernan and Robins, covariates were selected based on expert knowledge to generate a priori assumptions about the causal structure included in the DAG for this paper (Chapter 6) [383].

4 Chapter 4. Trends in prescription of psychotropic medications to children and adolescents in Australian primary care from 2011 to 2018.

4.1 Publication reference

This paper has been published in the Australian and New Zealand Journal of Psychiatry (ANZJP).

> Klau J, Bernardo CO, Gonzalez-Chica DA, Raven M, Jureidini J. (2022) Trends in prescription of psychotropic medications to children and adolescents in Australian primary care from 2011 to 2018. *Australian and New Zealand Journal of Psychiatry* 56(11): 1477-1490. https://doi.org/ 10.1177/00048674211067720.

A copy of the article and supplementary tables, as published in the ANZJP, are included in this chapter.

4.2 Preface

Chapter 4 addresses the following research questions of this thesis:

> 1). What is the rate of prescribing for the five main classes of psychotropic drugs (antidepressants, antipsychotics, ADHD drugs, anxiolytics, sedatives/hypnotics) and melatonin in a cohort of children and adolescents in Australian primary care from 2011 to 2018?
>
> 2). Is there an increasing trend in prescribing across the study period from 2011 to 2018?
>
> 3). How do psychotropic prescribing trends differ by age, gender, and socio-economic level?
>
> 4). Which drugs are most commonly prescribed, by age group, in a selected year: 2018?

This study examined psychotropic prescribing patterns by general practitioners (GPs), previously unexplored in an Australian context. The dataset used, MedicineInsight, was established in 2011 and became available to researchers in 2017. The resource is a rich electronic health record dataset providing real-world data. The few previous studies addressing paediatric psychotropic prescribing used PBS datasets.

A second focus of this study was to explore social determinants of prescribing. Only two Australian studies have addressed this topic in paediatric patients: one using a longitudinal survey dataset and another using a sample of 10% of PBS prescriptions. The results from this paper expand on this small knowledge base.

4.3 Key findings

1. There was a marked increase in prescribing to children and adolescents across the study period for the three main classes of antidepressants, antipsychotics, and ADHD drugs.
2. Melatonin prescribing increased the most rapidly over the study period.
3. Patients residing in lower socio-economic areas (the most socially disadvantaged areas) were the most likely to be prescribed psychotropic medications.

4.4 Statement of Authorship

Title of Paper	Trends in prescription of psychotropic medications to children and adolescents in Australian primary care from 2011 to 2018
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Klau J, Bernardo CO, Gonzalez-Chica DA, et al. (2022) Trends in prescription of psychotropic medications to children and adolescents in Australian primary care from 2011 to 2018. *Australian and New Zealand Journal of Psychiatry* 56(11): 1477-1490. https://doi.org/ 10.1177/00048674211067720

Principal Author

Name of Principal Author (Candidate)	Julie Klau		
Contribution to the Paper	JK contributed to the conceptualisation and design of the study, analyses and interpretation of results, and wrote the original manuscript. JK also assisted with the preparation of variables in the database, engaged in ongoing editing and refinements, and submitted the article to the journal as primary and corresponding author.		
Overall percentage (%)	80%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature	80%	Date	29 April 2024

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Associate Professor David Gonzalez-Chica		
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Contribution to the Paper	MR assisted with major critical revisions of the manuscript, contributing to intellectual content.		
Signature	5%	Date	11 April 2024

Name of Co-Author	Professor Jon Jureidini		
Contribution to the Paper	JJ assisted with conceptualisation and design of the study, and provided critical revisions of the manuscript, contributing to intellectual content.		
Signature	5%	Date	11 April 2024

4.5 Main paper

Research

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Trends in prescription of psychotropic medications to children and adolescents in Australian primary care from 2011 to 2018

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Abstract

Objective: To examine trends in prescribing psychotropic medications to children and adolescents in Australian primary care from 2011 to 2018.

Method: A retrospective cohort study examined prescriptions written by general practitioners using MedicineInsight, a large Australian primary care database, covering approximately 9% of all general practitioner practices. Numbers of patients receiving prescriptions for five main classes of psychotropics (antipsychotics, antidepressants, attention deficit hyperactivity disorder medications, anxiolytics, and hypnotics/sedatives [including benzodiazepines and Z-drugs, but excluding melatonin]) were examined annually by age-group (0–4, 5–9, 10–14, 15–18 years). Melatonin was analysed separately.

Results: The number of patients prescribed any psychotropic increased from 25.6 to 36.2 per 1000 individuals from 2011 to 2018 (average annual increase +4.5%, 95% confidence interval [4.1%, 4.9%]; overall +41.4%). Among the five main classes, the largest annual increase was for attention deficit hyperactivity disorder medications (+9.6%, 95% confidence interval [8.8%, 10.5%]; overall +95.8%), followed by antipsychotics (+6.2%, 95% confidence interval [5.0%, 7.3%]; overall +62.8%) and antidepressants (+4.5%, 95% confidence interval [4.0%, 5.0%]; overall +42.8%). Hypnotic/sedative prescribing decreased on average 6.5% per year (95% confidence interval [–8.0%, –5.0%]; overall −40.2%). Anxiolytic prescribing remained steady. Melatonin prescriptions showed the highest increase of all (+24.7%, 95% confidence interval [23.7%, 25.8%]; overall +606.7%). The largest annual increase in antipsychotic, antidepressant or attention deficit hyperactivity disorder medication prescribing occurred in 10- to 14-year-olds (+7.5%, +6.5% and +10.4%, respectively). The largest point prevalence occurred in 2018 among 15- to 18-year-olds, with 98.5 per 1000 prescribed antidepressants. Antidepressants were more frequently prescribed to females; antipsychotics, attention deficit hyperactivity disorder medications and melatonin more often to males. The most prescribed antipsychotics were risperidone (<15 years) and quetiapine (15- to 18-year-olds). Fluoxetine was the most prescribed antidepressant in those aged 5+ years and amitriptyline in 0- to 4-year-olds.

Conclusion: General practitioner prescribing of melatonin, antipsychotics, antidepressants and attention deficit hyperactivity disorder medications to under-19-year-olds increased markedly from 2011 to 2018. Although benzodiazepine and Z-drug prescriptions declined, this was offset by a substantial increase in melatonin prescribing.

Keywords

Psychotropic prescribing, children, adolescents, antidepressants, antipsychotics, melatonin

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Introduction

Globally, prescriptions of most classes of psychotropic medications to children and adolescents have been on the rise in recent decades (Bachmann et al., 2016, 2017; Barczyk et al., 2020; Hálfdánarson et al., 2017; Hartz et al., 2016; John et al., 2016; Lagerberg et al., 2019; Pringsheim et al., 2019; Raman et al., 2018; Sarginson et al., 2017). This is despite ongoing debate about the efficacy and safety of psychotropics in young people (Hetrick et al., 2012, 2021; Vitiello et al., 2009), concerns about antidepressant-induced suicidality (Whitely et al., 2020) and evidence of increased risk of adverse events in children compared with adults (Correll et al., 2015).

A recent study found an increase in antipsychotic prescriptions from 2005 to 2014 in 0- to 19-year-olds in 10 of 16 countries, with Australia having the third highest increase (+159%) (Hálfdánarson et al., 2017). Several international studies have also found increases in antidepressant prescribing, ranging from +26% in the United States from 2005 to 2012 (Bachmann et al., 2016), to +78% in New Zealand (NZ) from 2008 to 2016 (Barczyk et al., 2020). In the United Kingdom, general practice antidepressant prescribing to 3- to 17-year-olds from 2006 to 2015 almost doubled, with the most rapid increase evident in 15- to 17-year-olds (Sarginson et al., 2017).

For attention deficit hyperactivity disorder (ADHD) medications, findings are similar. A multi-country analysis of ADHD medication prescriptions from 2005 to 2012 identified increases ranging from 10.7% (United States) to 302.7% (Denmark) (Bachmann et al., 2017). A more recent NZ study found a rise of 41.3% from 2011 to 2016 (Barczyk et al., 2020). In all countries, ADHD prescription rates were highest in 10- to 14-year-olds.

Few studies, however, have examined prescribing of anxiolytics and hypnotics/sedatives, with varying results. Anxiolytic prescribing was stable in Norway (2004–2014) (Hartz et al., 2016), increased 50% in NZ (2008–2016) (Barczyk et al., 2020) and showed an increase only in 15- to 18-year-olds in Wales (2003 to 2011) (John et al., 2015). Hypnotic/sedative prescribing was reported in the same studies. Rates of hypnotic/sedative prescribing were stable in the Welsh study, but increased by 37.5% in the NZ study. The Norwegian study reported substantial increases in prescribing in adolescents only (girls, +238%; boys, +157%), which the authors attributed to increasing use of melatonin (Hartz et al., 2016).

In Australia, the Pharmaceutical Benefits Scheme (PBS) provides government subsidies for approved medications for all Australian citizens and eligible residents. Studies using dispensing data from the PBS have also shown psychotropic medications have been increasingly prescribed to children and adolescents (Drug Utilisation Sub-Committee [DUSC], 2018; Karanges et al., 2014; Morrison et al., 2014). Examining dispensing of antidepressants, antipsychotics and ADHD medications from 2009 to 2012, Karanges et al. (2014) found increases for all ages (>2 years), but the most rapid increase was observed in 10- to 14-year-olds for antidepressants (+35.5%) and antipsychotics (+49.1%). DUSC reports have analysed subsidised antipsychotics for children and adolescents from 2010 to 2012 (Morrison et al., 2014), and stimulant use for all age-groups from 2013 to 2017 (DUSC, 2018). However, PBS datasets only provide information on prescriptions dispensed. They do not provide data on private prescriptions or approved medications not listed on the PBS schedule. PBS data also do not allow an estimation of the number of patients receiving medications.

To our knowledge, no study has explored recent trends for all classes of psychotropics for Australian children and adolescents nor analysed data from general practice, which is the main source of psychotropic prescribing. In 2018–2019, 86.3% of all psychotropics (90.6% of antidepressants, 73.9% of antipsychotics, 91.2% of anxiolytics, 93.0% of hypnotics/sedatives and 18.6% of psychostimulants) were prescribed by general practitioners (GPs) in Australia, with percentages remaining consistent from 2012 to the present (Australian Institute of Health and Welfare [AIHW], 2020: Table PBS.5). An examination of GP prescribing trends is, therefore, essential for a deeper understanding of psychotropic drug use in Australia. Importantly, no recent studies have examined psychotropics prescribing in Australia in 0- to 4-year-olds specifically.

This study examines (1) prescribing trends from 2011 to 2018 for all classes of psychotropic medications for Australian children and adolescents under 19 using a national primary care database of electronic health records, which includes private and PBS-subsidised prescriptions written by GPs; and (2) sociodemographic factors associated with these prescriptions. This study also includes an analysis of prescribing trends for melatonin.

Methods

Study design and data source

A retrospective cohort study was conducted using MedicineInsight (Busingye et al., 2019), a large longitudinal Australian primary care database of electronic health records. MedicineInsight was established in 2011, with core funding from the Australian Government, to improve the quality use of medicines and monitor medication safety. As of June 2020, the database consisted of data from 732 general practices (9.0% of all Australian general practices) and 5199 GPs (NPS MedicineWise, 2020). In participating practices, all data recorded into the clinical information system is automatically transferred to the MedicineInsight data warehouse monthly using a secure third-party extraction tool. To ensure data quality, only general practice sites established for at least 2 years with no interruptions of more than 6 weeks, and a consistent volume of data transactions,

are included in analyses. MedicineInsight data are de-identified. Each patient is assigned a unique patient identifier, which allows linking of all the records held in the database, enabling longitudinal analyses.

The database includes both subsidised (PBS) and private prescriptions written by GPs, regardless of whether they are dispensed. It also includes detailed individual-level data on all patient encounters, including diagnoses, medical tests, prescribed drugs and patient sociodemographics. The dataset has been successfully used in recent years to estimate trends in the use of insomnia medications in Australia (Begum et al., 2021).

Study population

This study includes all children and adolescents under 19 who attended a MedicineInsight practice from 2011 to 2018. Only 'regular patients' (defined as patients with at least three visits within the current and previous year, and at least one visit in each of those 2 years) were included in the analysis. The final sample included 537,371 unique patients (ranging from 112,997 in 2011 to 336,432 in 2018) attending 539 Australian practices.

Outcomes and covariates

The main outcome was recorded prescriptions of psychotropic medications, analysed in total, separately in five main classes and in subclasses. Melatonin was analysed separately. Numbers of original prescriptions recorded per patient were extracted from the MedicineInsight prescriptions table, using information on medication name and/or active ingredient. The five classes were antipsychotics, antidepressants, ADHD medications, anxiolytics and hypnotics/sedatives, excluding melatonin (Supplementary eTable S1). Supplementary eTable S2 lists current Therapeutic Goods Administration (TGA) drug approvals for psychotropic use in children and adolescents in Australia.

With the exception of the hypnotics/sedatives and ADHD drug classes, the groupings of medications were classified according to the Anatomical Therapeutic Chemical (ATC) classification system (World Health Organization [WHO] Collaborating Centre for Drug Statistics Methodology, 2021). The ADHD medications class included stimulants and non-stimulants (atomoxetine, guanfacine, clonidine, modafinil, armodafinil) used to treat ADHD. The hypnotics/sedatives class excluded melatonin. Although classified as a hypnotic/sedative in the ATC system, melatonin is not a traditional psychotropic and has been classified in some studies as a non-psychotropic (Efron et al., 2017) or neurohormonal drug or chronobiotic (Boafo et al., 2019). International studies have recorded substantial increases in paediatric hypnotic/sedative prescribing when including melatonin in the hypnotics/sedatives class (Barczyk et al., 2020; Hartz et al., 2016). Because of this, and because there are no studies addressing paediatric hypnotic/sedative prescribing in Australian primary care, we chose to analyse it separately. Mood stabilisers were excluded, because they are used extensively for epilepsy and seizures, and it was not possible to distinguish which prescriptions were for psychiatric conditions.

The main drug classes were further divided into subclasses. Antipsychotics were divided into first- and second-generation (atypical); antidepressants were divided into selective serotonin reuptake inhibitors (SSRIs), selective noradrenaline reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), noradrenaline and specific serotonergic antidepressants (NaSSAs), and other antidepressants. Hypnotics/sedatives included benzodiazepines and Z-drugs (zopiclone and zolpidem).

Patient sociodemographic data were also obtained. Gender was divided into male or female, and age stratified into four groups (0–4, 5–9, 10–14 or 15–18 years), roughly corresponding to infancy/toddler years, childhood, puberty and older adolescence. We used the 0- to 4-year age-group as a proxy for the pre-school period. In most states and territories, children start their preparatory year of school during the year they turn 5 and start formal schooling by age 6 (Australian Curriculum Assessment and Reporting Authority [ACARA], 2019). Socioeconomic position, derived from residential and practice postcodes, was analysed using the Index of Relative Socio-economic Advantage and Disadvantage (IRSAD) divided into quintiles. IRSAD is an indicator that summarises information obtained from census data about the economic and social conditions (i.e. income, education, employment, occupation and housing variables) of people and households within specified geographic areas, with higher scores indicating more advantaged areas (Australian Bureau of Statistics [ABS], 2018a, 2018b). State, rurality (major cities, inner regional, outer regional/remote/very remote) and practice IRSAD quintiles were also included as covariates for adjustment.

Statistical analysis

Prescriptions by age-group for each main drug class, melatonin and the five main psychotropic classes combined were calculated as adjusted annual rates of prescriptions per 1000 patients. Trends in psychotropic prescriptions between 2011 and 2018 were analysed using Poisson regression and reported as average annual changes (percentages) with 95% confidence intervals (CIs), using the practice as cluster, and robust standard errors (Tables 1 and 2).

To explore prescribing in greater detail, tables of prescriptions were created for the year 2018 only, including class and subclass of medications (Table 3) and the most frequently prescribed medications within each class (Table 4).

Table 1. Trends in prescribing of all psychotropic medications (excluding melatonin) to children and adolescents, according to patient sociodemographics, from 2011 to 2018.[a]

	Year							Change 2011–2018				
	2011	2012	2013	2014	2015	2016	2017	2018	Annual average change		Total change	
	n = 112,997	*n* = 126,302	*n* = 144,248	*n* = 168,821	*n* = 200,921	*n* = 231,326	*n* = 269,903	*n* = 336,432	%	95% CI	Absolute	%	95% CI
Overall (crude)	25.6	28.7	31.1	32.9	33.9	35.8	37.8	36.2	+4.5	[4.1, 4.9]	+10.6	41.4	[35.9, 47.2]
Age													
0–4 years	**0.9**	**0.9**	**0.8**	**0.8**	**0.6**	**0.7**	**0.8**	**0.7**	–3.4	[–7.9, 1.3]	–0.2	–22.5	[–47.6, 14.5]
5–9 years	**11.4**	**12.0**	**13.0**	**14.2**	**14.2**	**15.0**	**16.1**	**16.6**	+5.3	[1.2, 9.6]	+5.1	+45.4	[18.3, 78.7]
10–14 years	**31.9**	**35.7**	**39.9**	**40.8**	**43.5**	**45.9**	**49.5**	**54.1**	+7.1	[5.2, 9.0]	+22.3	+69.9	[46.6, 96.9]
15–18 years	**93.4**	**102.6**	**103.4**	**103.9**	**104.3**	**109.8**	**114.2**	**120.4**	+3.2	[2.1, 4.2]	+27.0	+28.9	[19.8, 38.7]
Gender													
Male	**31.6**	**33.0**	**33.9**	**34.9**	**36.0**	**38.5**	**40.7**	**43.1**	+4.7	[3.2, 6.3]	+11.5	+36.6	[23.3, 51.4]
Female	**24.9**	**28.4**	**29.8**	**30.1**	**30.2**	**31.6**	**33.1**	**35.2**	+4.0	[3.0, 5.0]	+10.3	+41.4	[30.9, 52.7]
IRSAD quintile													
1. Least disadvantaged	**19.5**	**20.8**	**21.2**	**21.7**	**22.9**	**25.5**	**26.3**	**27.3**	+5.3	[3.6, 7.0]	+7.8	+40.1	[25.0, 57.0]
2.	**24.2**	**26.0**	**27.5**	**26.2**	**27.3**	**27.4**	**29.3**	**31.3**	+3.2	[1.2, 5.2]	+7.1	+29.4	[12.3, 49.2]
3.	**31.6**	**34.4**	**35.5**	**36.5**	**35.9**	**38.8**	**41.3**	**43.4**	+4.3	[2.5, 6.1]	+11.9	+37.6	[21.6, 55.6]
4.	**31.3**	**35.5**	**38.1**	**39.4**	**39.1**	**40.0**	**42.2**	**46.3**	+4.4	[2.6, 6.3]	+15.0	+47.9	[30.6, 67.5]
5. Most disadvantaged	**37.3**	**42.7**	**43.5**	**45.2**	**45.9**	**47.9**	**50.3**	**53.0**	+4.2	[2.6, 5.9]	+15.6	+41.8	[24.2, 61.9]

Rates are reported as the number of patients receiving a prescription for any psychotropic medication, per 1000 patients. IRSAD: Index of Relative Socio-economic Advantage and Disadvantage.
[a]Adjusted for age, gender, patient IRSAD and practice characteristics (state, rurality, practice IRSAD). Numbers marked in bold type indicate $p < 0.05$ for the difference between each category and the reference for the given year. Reference categories were: 15–18 years, male and IRSAD quintile 1 (least disadvantaged).

Table 2. Trends in prescribing of psychotropic medications to children and adolescents by drug class, from 2011 to 2018.

Drug class	Year							Change 2011–2018			
	2011	2012	2013	2014	2015	2016	2017	2018	Annual average change		Total change	
	n = 112,997	n = 126,302	n = 144,248	n = 168,821	n = 200,921	n = 231,326	n = 269,903	n = 336,432	%	95% CI	Absolute	%	95% CI
Antipsychotics	2.8	3.3	3.5	4.1	4.3	4.6	4.9	4.5	+6.2	[5.0, 7.3]	1.7	+62.8	[44.1, 83.8]
Antidepressants	16.9	19.4	20.9	22.3	22.7	24.4	25.5	24.2	+4.5	[4.0, 5.0]	7.3	+42.8	[35.9, 50.0]
ADHD drugs	5.3	5.8	6.8	7.7	8.1	8.6	9.8	10.4	+9.6	[8.8, 10.5]	5.1	+95.8	[79.6, 113.5]
Anxiolytics	2.5	2.8	3.0	2.9	3.0	3.0	3.3	2.5	+0.2	[−1.1, 1.4]	0.0	+0.2	[−12.4, 14.6]
Hypnotics/sedatives	2.0	2.1	1.9	1.9	1.7	1.7	1.6	1.2	−6.5	[−8.0, −5.0]	−0.8	−40.2	[−49.2, −29.6]
Melatonin	1.7	2.9	4.2	5.9	7.4	9.0	11.1	11.8	+24.7	[23.7, 25.8]	10.1	+606.7	[510.9, 717.6]

Rates are reported as the number of patients receiving a prescription, per 1000 patients. ADHD: attention deficit hyperactivity disorder.

All results were adjusted by age, gender, patient IRSAD quintiles and practice characteristics (state, rurality, practice IRSAD). All analyses were carried out using Stata version 16 (StataCorp, Texas, USA).

Ethics approval

The independent MedicineInsight Data Governance Committee approved the present study (protocol 2019-029), and the Human Research Ethics Committee of the University of Adelaide exempted it from a full ethical review due to the use of non-identifiable data.

Results

The sample included 537,371 patients under 19 years (51.1% females), ranging between 112,997 in 2011 and 336,432 in 2018. These individuals mainly attended practices located in major cities (66.4%), 22.4% in inner regional and 11.3% in outer regional/remote/very remote areas. Participants in higher IRSAD areas were over-represented (30.1% very high [least disadvantaged], 19.0% high, 22.4% middle, 13.4% low and 15.2% very low [most disadvantaged] IRSAD quintiles).

Change over time

The prescription of all psychotropics, excluding melatonin, increased from 25.6 per 1000 patients in 2011 to 36.2 per 1000 in 2018 (average annual increase +4.5%, 95% CI [4.1, 4.9]; overall +41.4%) (Table 1). The prescription rate remained steady at less than 1 per 1000 patients in 0- to 4-year-olds. The highest rate was for those 15–18 years. Except for the 0- to 4-year-olds, prescriptions increased over time, especially among 10- to 14-year-olds (+7.1%, 95% CI [5.2, 9.0]; overall +69.9%). Prescription rates were higher in males, but a similar annual increase was found in both genders. The highest rate in any year was among those in more disadvantaged areas, but the annual increase was similar in all IRSAD quintiles.

The annual trends for each class of drug are reported in Table 2. The highest prescription rate in any year was for antidepressants (ranging from 16.9 per 1000 patients in 2011 to 25.5 per 1000 in 2017). There was an increase in prescriptions for all classes, except anxiolytics, which showed no change, and hypnotics/sedatives, which had a 40.2% decrease between 2011 and 2018. The rate of melatonin prescriptions increased just over 600% between 2011 and 2018 (annual change +24.7%, 95% CI [23.7, 25.8]; overall +606.7%).

Figure 1 and Supplementary eTables S3–S8 illustrate the adjusted trends by sociodemographic characteristics. Antipsychotic and antidepressant prescription rates (Figure 1(a) and (b)) increased only among those 10 years or over; for younger children, these prescriptions remained low. ADHD medication prescriptions (Figure 1(c)) showed a

Table 3. Number of regular patients prescribed medications by class and subclass in 2018, according to age-groups.

	All	0–4 years	5–9 years	10–14 years	15–18 years
Total[a] – all psychotropics including melatonin	14,075	329	1974	4130	8272
Antipsychotics – *n* (%)[b]	1507 (10.7)	13 (4.0)	174 (8.8)	456 (11.0)	864 (10.4)
FGA	2.9%	7.7%	1.7%	2.4%	3.4%
SGA	**97.7%**	**92.3%**	**99.4%**	**98.0%**	**97.2%**
Antidepressants – *n* (%)[b]	8126 (57.7)	16 (4.9)	249 (12.6)	1499 (36.3)	6362 (76.9)
SSRI	**87.0%**	**50.0%**	**88.0%**	**89.5%**	**86.5%**
SNRI	6.6%	12.5%	0.8%	0.8%	8.2%
TCA	7.2%	31.3%	11.2%	9.7%	6.4%
MAOI	0.1%	0.0%	0.0%	0.0%	0.1%
NaSSA	4.1%	6.3%	1.2%	1.2%	4.9%
Other	1.1%	0.0%	0.0%	0.4%	1.3%
ADHD medications – *n* (%)[b]	3487 (24.8)	22 (6.7)	935 (47.4)	1731 (41.9)	800 (9.7)
STIM	**75.8%**	13.6%	**74.9%**	**77.5%**	**74.9%**
ADREN	36.9%	**86.4%**	36.7%	36.9%	35.9%
Anxiolytics – *n* (%)[b]	847 (7.0)	23 (7.0)	72 (3.6)	149 (3.6)	603 (7.3)
Hypnotic/sedative – *n* (%)[b]	397 (2.8)	13 (4.0)	35 (1.8)	60 (1.5)	289 (3.5)
BZ	**84.9%**	**92.3%**	**100.0%**	**95.0%**	**80.6%**
Z-drugs	17.6%	7.7%	0.0%	5.0%	22.8%
Melatonin – *n* (%)	3977 (28.3)	255 (77.5)	880 (44.6)	1254 (30.4)	1588 (19.2)

The subclass with the highest percentage within class for each age-group is marked in bold. FGA: first-generation antipsychotic; SGA: second-generation antipsychotic; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin and noradrenaline reuptake inhibitor; TCA: tricyclic antidepressant; MAOI: monoamine oxidase inhibitor; NaSSA: noradrenaline and specific serotoninergic antidepressant; Other, includes agomelatine, bupropion, reboxetine, vortioxetine; STIM: stimulants and atomoxetine; ADREN: antiadrenergic medication; BZ: benzodiazepine; Z-drug: benzodiazepine-related drug.

[a]Number of patients prescribed each category or subcategory of psychotropics do not add to totals of all psychotropics including melatonin, because some patients were prescribed more than one category of medication.

[b]Number and proportion of regular patients prescribed the corresponding class of medication. Percentages do not round up to 100%, because some patients were prescribed drugs from more than one class. Percentage of regular patients prescribed a subclass of psychotropics within the corresponding class (antipsychotics, antidepressants, ADHD medications, hypnotics/sedatives) do not round up to 100%, because some patients were prescribed more than one subclass.

similar annual increase in the three older age-groups, ranging from 8.7% to 10.4% per year, but no change was found in 0- to 4-year-olds. Annual average anxiolytic prescribing declined in 10- to 14-year-olds (–3.7%, 95% CI [–6.8, –0.4]), while overall change was non-significant (–16.0%, 95% CI [–37.7, 13.1]); prescribing remained steady in all other age-groups (Figure 1(d)). Hypnotics/sedatives (Figure 1(e)) were the only medications showing a decrease from 2011 to 2018 (annual change –6.5%, 95% CI [–8.0, –5.0]; overall –40.2%), but the reduction was only evident among those 0–4 years and especially 15–18 years. The decrease in hypnotics/sedatives was driven largely by an annual reduction in prescriptions for nitrazepam (–13.1%, 95% CI [–20.0, –5.5]), temazepam (–8.7%, 95% CI [–10.5, –6.8]) and zolpidem (–14.6%, 95% CI [–19.7, –9.2]; Supplementary eTable S9). Melatonin (Figure 1(f)) was the only medication with an increase in prescription rates across all age-groups (Supplementary eTable S8).

Females were more likely than males to be prescribed antidepressants in any year; but antipsychotics, ADHD medications and melatonin prescriptions were more frequent among males (Supplementary eTables S3–S8). Both genders showed similar increases in annual antipsychotic and antidepressant prescription rates, and similar decreases in hypnotic/

Table 4. Most frequently prescribed drugs in 2018 by age-group,[a] reported as percentage of total patients on each class of drug in each age-group.

	Age-group			
	0–4 years	5–9 years	10–14 years	15–18 years
Antipsychotics (*N*=1507)[b]	*n*=13	*n*=174	*n*=456	*n*=864
Risperidone (SGA)	**84.6%**	**93.7%**	**69.5%**	22.8%
Quetiapine (SGA)	7.7%	3.4%	19.3%	**59.5%**
Chlorpromazine (FGA)	7.7%	0.6%	0.4%	1.0%
Aripiprazole (SGA)	0.0%	4.0%	6.4%	5.6%
Olanzapine (SGA)	0.0%	1.1%	5.0%	11.5%
Periciazine (FGA)	0.0%	0.0%	1.5%	1.3%
Lurasidone (SGA)[c]	0.0%	0.0%	0.0%	1.6%
Antidepressants (*N*=8126)[b]	*n*=16	*n*=249	*n*=1499	*n*=6362
Amitriptyline (TCA)	**25.0%**	8.4%	7.7%	5.8%
Sertraline (SSRI)	6.3%	14.1%	19.5%	21.9%
Fluoxetine (SSRI)	12.5%	**67.1%**	**56.0%**	**43.0%**
Venlafaxine (SNRI)	12.5%	0.4%	0.3%	2.8%
Paroxetine (SSRI)	12.5%	0.0%	0.3%	1.5%
Fluvoxamine (SSRI)	0.0%	4.8%	9.3%	5.8%
Escitalopram (SSRI)	12.5%	3.2%	6.5%	17.4%
Nortriptyline (TCA)	6.3%	1.6%	0.4%	0.2%
Mirtazepine (NaSSA)	6.3%	1.2%	1.2%	4.9%
Imipramine (TCA)	0.0%	1.2%	1.1%	0.1%
Citalopram (SSRI)	6.3%	0.8%	1.8%	3.3%
ADHD medications (*N*=3487)[b]	*n*=22	*n*=935	*n*=1731	*n*=800
Methylphenidate[d] (STIM)	9.1%	**55.4%**	**52.8%**	**48.8%**
Clonidine (ADREN)	**86.4%**	30.6%	27.4%	29.5%
Lisdexamphetamine (STIM)	4.5%	12.3%	17.0%	13.6%
Atomoxetine (NRI)	0.0%	5.6%	6.6%	7.6%
Dexamphetamine (STIM)	0.0%	6.0%	4.7%	6.6%
Guanfacine[e] (ADREN)	0.0%	2.9%	3.5%	1.6%
Anxiolytics (*N*=847)[b]	*n*=23	*n*=72	*n*=149	*n*=603
Diazepam (BZ)	43.5%	45.8%	**67.8%**	**76.6%**
Clobazam[f] (BZ)	**47.8%**	**52.8%**	23.5%	6.8%
Oxazepam (BZ)	4.3%	0.0%	2.7%	7.6%
Alprazolam (BZ)	4.3%	1.4%	2.7%	4.0%
Lorazepam (BZ)	0.0%	1.4%	4.0%	7.8%

(Continued)

Table 4. (Continued)

	Age-group			
	0–4 years	5–9 years	10–14 years	15–18 years
Hypnotics/sedatives (*N* = 397)[b]	*n* = 13	*n* = 35	*n* = 60	*n* = 289
Midazolam[g] (BZ)	**84.6%**	**82.9%**	**61.7%**	9.3%
Nitrazepam[f] (BZ)	7.7%	14.3%	3.3%	2.8%
Temazepam (BZ)	7.7%	2.9%	30.0%	**69.2%**
Zolpidem (Z-drug)	0.0%	0.0%	3.3%	7.3%
Zopiclone (Z-drug)	7.7%	0.0%	1.7%	15.6%
Melatonin (*N* = 3977)	*n* = 255	*n* = 880	*n* = 1254	*n* = 1588

The most prescribed drug from each age-group is marked in bold. FGA: first-generation antipsychotic; SGA: second-generation antipsychotic; TCA: tricyclic antidepressant; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin and noradrenaline reuptake inhibitor; STIM: stimulant drug; NRI: noradrenaline reuptake inhibitor; ADREN, centrally acting antiadrenergic agent; BZ: benzodiazepine; Z-drug: benzodiazepine-related drug.
[a]The top five drugs are listed in each category for each age-group. Because the top five varied in different age-groups, more than five drugs are listed in some classes. For completeness, all percentages are calculated for all drugs listed for all age-groups.
[b]Numbers for age-groups do not add to total, because some patients had more than one type of drug prescribed during 2018.
[c]Lurasidone was approved for schizophrenia in adolescents 13–17 years in April 2018.
[d]The percentage of children prescribed methylphenidate differed substantially from that reported by Karanges et al. (2014) from 2009 to 2012 (on average 85%). This would be partly due to the approval of new drugs for treatment of ADHD over the last decade and the inclusion of non-stimulant antiadrenergic medications in our drug category.
[e]Guanfacine was approved on 22 August 2017.
[f]Clobazam and nitrazepam are also used as anti-epileptics.
[g]Midazolam is primarily used for sedation before and after medical procedures.

sedative prescriptions. ADHD drug prescriptions increased more rapidly in females than males. This reduced the differential in prescribing rates in males versus females from 4.7 times in 2011 to 3.4 in 2018. Anxiolytic prescriptions remained steady over time among males and females.

Rates of antipsychotic and ADHD prescriptions in the lowest IRSAD quintile (most disadvantaged) were around three times those recorded in the highest quintile (least disadvantaged) (Supplementary eTables S3, S5). For antidepressant prescriptions, the rate in the lowest quintile was around 1.7 times the rate in the highest quintile (eTable S4). However, there were no substantial differences in the annual increases across quintiles for antipsychotics, antidepressants and ADHD drugs.

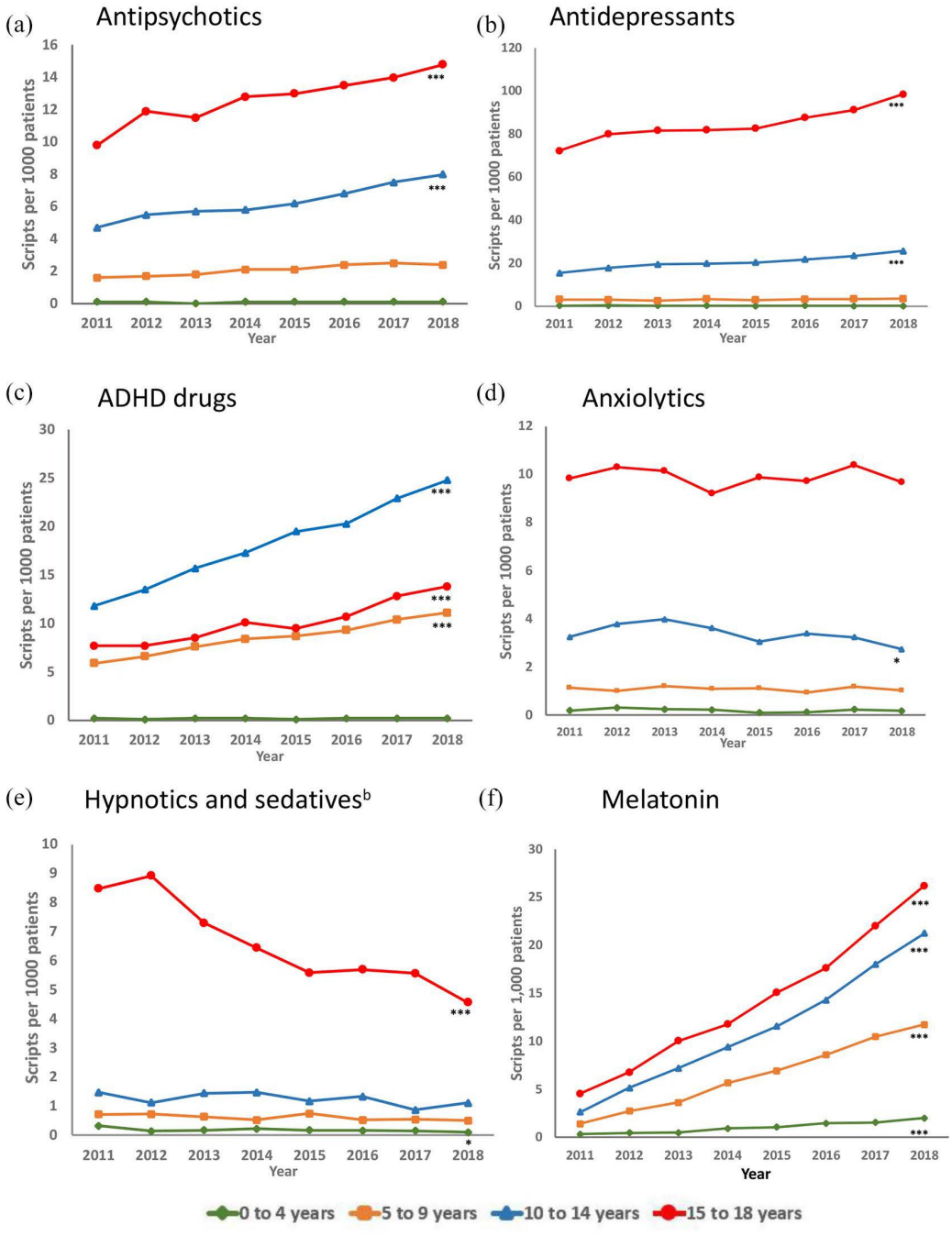
For hypnotics/sedatives (Supplementary eTable S7) and melatonin (Supplementary eTable S8) prescribing, there were no substantial differences in trends across time for IRSAD quintiles; hypnotic/sedative prescribing decreased around 8% and melatonin increased around 26%. There appeared to be no consistent change in rates from high to low IRSAD quintiles for anxiolytics, hypnotics/sedatives or melatonin.

Prescribing patterns in 2018

Of all 14,075 children and adolescents who were prescribed one of the main psychotropic classes or melatonin in 2018, 57.7% were prescribed antidepressants (*n* = 8126), 24.8% ADHD medications (*n* = 3487), 10.7% antipsychotics (*n* = 1507), 7.0% anxiolytics (*n* = 847), 2.8% hypnotics/sedatives (*n* = 397) and 28.3% melatonin (*n* = 3977; some individuals were prescribed more than one group of drugs). Figure 2 shows that the most frequently prescribed class of psychotropics and melatonin varied with age. Among 0- to 4-year-olds (*n* = 329) melatonin was prescribed more than any other psychotropic. For those 5–9 (*n* = 1974) or 10–14 years (*n* = 4130), ADHD medications were the most common psychotropics prescribed. Among 15- to 18-year-olds (*n* = 8272), antidepressants were the most frequent psychotropics prescribed (76.9%), with a point prevalence of 98.5/1000 patients. This was more than twice the prevalence in 10- to 14-year-olds (36.3%) and at least six times the prevalence among those under 10 years (Table 3).

The most frequently prescribed subclasses of medications in 2018 were also examined (Table 3). In all age-groups, second-generation antipsychotics (SGAs) were far more often prescribed than first-generation antipsychotics, with well over 90% of prescriptions being for SGAs. SSRIs were the most frequently prescribed class of antidepressants in all age-groups (50.0% among 0- to 4-year-olds and more than 85% in other age-groups). With ADHD medications, the non-stimulant antiadrenergic medications predominated

Figure 1. Trends in prescribing by age-group for the five major classes of psychotropic medications and melatonin from 2011 to 2018, reported as prescriptions per 1000 patients.[a] (A) Antipsychotics, (B) Antidepressants, (C) ADHD drugs, (D) Anxiolytics, (E) Hypnotics and sedatives[b] and (F) Melatonin.



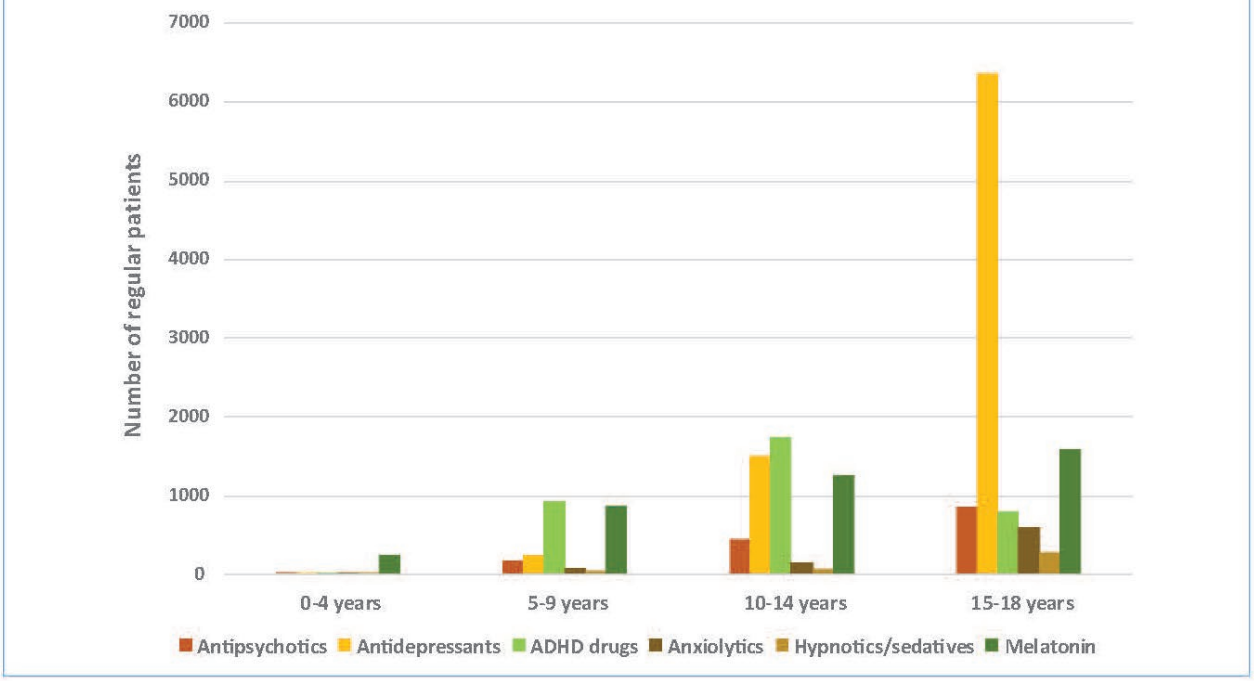
Full data available in Supplementary eTables S3–S8.

[a]Adjusted for age, sex, patient IRSAD (Index of Relative Socio-economic Advantage and Disadvantage) quintiles and practice characteristics (state, rurality and practice IRSAD).

[b]The hypnotics and sedatives category in this analysis did not include melatonin.

Significance of trend for annual average change: $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ are noted below the trend line.

Figure 2. Number of regular patients receiving prescriptions for psychotropics by drug class and age-group in 2018.



ADHD: attention deficit hyperactivity disorder.

in 0- to 4-year-olds, but the stimulant class was prescribed more often in other age-groups.

Table 4 lists the most frequently prescribed medications from each psychotropic class by age-group for the year 2018. Risperidone was the most prescribed antipsychotic for children under 15, but quetiapine was the most prescribed in 15- to 18-year-olds. Amitriptyline was the most prescribed antidepressant in 0- to 4-year-olds, but fluoxetine was the most prescribed in the other three age-groups. Clonidine was the most prescribed ADHD medication in 0- to 4-year-olds, with methylphenidate predominating in older children.

Among patients prescribed a psychotropic in 2018, 17.5% (n=2134) were prescribed more than one type of medication concurrently, with almost 10% of these patients (n=206) prescribed three or more (data not shown). Psychotropic polypharmacy in children and adolescents will be examined in a future study using the same database.

Discussion

To our knowledge, this is the first study to explore psychotropic prescribing to children and adolescents using a large Australian general practice database. Four main findings can be highlighted. First, the prescribing rate for psychotropics, excluding melatonin, has increased at an annual average of 4.5%, with 3.6 out of 100 children and adolescents being prescribed at least one psychotropic in 2018. The most rapid increase was among 10- to 14-year-olds. Second, trends differed according to the class of psychotropic medication. The highest increase was for ADHD medications, followed by antipsychotics and antidepressants. Third, patients in more disadvantaged areas were more likely to be prescribed antipsychotics, antidepressants and ADHD medications than those in the least disadvantaged areas. Finally, melatonin showed the most pronounced rise, increasing just over 600% between 2011 and 2018.

Our trends are consistent with those reported in studies using Australian PBS data (DUSC, 2018; Hálfdánarson et al., 2017; Karanges et al., 2014; Raman et al., 2018) and data from other countries (Barczyk et al., 2020; Hartz et al., 2016). However, although these studies showed similar increases for antidepressants, antipsychotics and ADHD medications, rates differed from our findings, partly due to differing timespans and data sources. Individual drug classes are examined in more detail below.

Antipsychotics

From 2011 to 2018, there was a 62.8% increase in the prescribing of antipsychotics to under-19-year-olds. It was higher than the increase observed in most European

countries and the United States from 2005 to 2014, but lower than the 159% increase observed from 2006 to 2014, using Australian PBS data (Hálfdánarson et al., 2017). This difference may be related to the fact that our dataset does not include prescriptions issued by specialists or drugs dispensed through hospital pharmacies. Our study also found the highest increase in 10- to 14-year-olds (+72.2%), continuing the trend observed by Karanges et al.'s (2014) study using PBS data (+49.1%, 2009–2012).

The most frequently prescribed antipsychotics by age-group were also similar to those reported by Karanges et al. (2014), who found risperidone the most prescribed antipsychotic in 3- to 9-year-olds and 10- to 14-year-olds, and quetiapine in 15- to 19-year-olds. Although impossible to determine from the current analysis, these results appear to be mostly consistent with current TGA drug approvals for psychotropic use in children and adolescents. Antipsychotics are approved for children with severe behavioural problems associated with autism and conduct disorders. Therefore, the increasing trend for antipsychotic prescribing is likely due partly to the increased prevalence of diagnosed/reported autistic disorders in 0- to 19-year-olds from 2009 to 2015 (AIHW, 2017). Other conditions for which antipsychotics are approved have had decreased diagnosis rates (e.g. conduct disorders; Sawyer et al., 2018), or are conditions rarely diagnosed in children and adolescents (e.g. schizophrenia; Galletly et al., 2016).

However, antipsychotics are increasingly being used as 'broad spectrum psychotropic drugs' for a diverse range of non-psychotic disorders in paediatric populations, including anxiety, ADHD, depression and insomnia (Carton et al., 2015; Penfold et al., 2013). There is some evidence suggesting that anxiety diagnoses have increased over the last decade (ABS, 2009/2018; Spence et al., 2018), and a 2014 PBS report has suggested antipsychotics are being used in children and adolescents with anxiety and stress in Australia (Morrison et al., 2014). Therefore, the increasing antipsychotic prescription rates may also reflect increasing off-label use.

Antidepressants

The overall increase in antidepressant prescriptions to children and adolescents (+42.8%) was consistent with international findings using both dispensing (Barczyk et al., 2020; Lagerberg et al., 2019) and general practice datasets (Bachmann et al., 2016; John et al., 2016; Pringsheim et al., 2019). Similar to antipsychotics, and again demonstrating a continuation of the trend previously observed in Australia (Karanges et al., 2014), our study recorded the highest increase in 10- to 14-year-olds. Although 15- to 18-year-olds were prescribed more antidepressants than any other age-group, the increase has been more rapid in 10- to 14-year-olds.

In Australia, no antidepressants are approved for managing depression in children and adolescents (Supplementary eTable S2). Despite this, and consistent with previous studies in Australia (Karanges et al., 2014) and NZ (Barczyk et al., 2020), most prescriptions in 5- to 18-year-olds were for fluoxetine. This is likely due to the inclusion of fluoxetine as a treatment option for depression in Australian (McDermott et al., 2011) and international guidelines (Cheung et al., 2018; National Institute for Health and Care Excellence [NICE], 2019). However, given that two meta-analyses have concluded that no SSRIs are beneficial in treating childhood or adolescent depression (Hetrick et al., 2012, 2021) and fluoxetine is not approved for any childhood conditions in Australia, the high rates of prescriptions for fluoxetine need to be investigated.

Consistent with international studies, TCAs were prescribed less often than SSRIs, most likely for nocturnal enuresis (Nankivell and Caldwell, 2014). In our study, although numbers were low, limiting the reliability of the finding, 31.3% of 0- to 4-year-olds who had been prescribed an antidepressant were prescribed a TCA – a higher percentage than any other age-group. However, no other study has explored TCA prescribing in this age-group to allow a comparison. Given that only non-pharmacological treatments for enuresis are recommended for children under 7 (BMJ Best Practice, 2020), the prescribing of TCAs in this age-group warrants further investigation.

ADHD medications

Corroborating findings of two large multi-country studies (Bachmann et al., 2017; Raman et al., 2018) and Australasian studies (Barczyk et al., 2020; Karanges et al., 2014), prescribing of ADHD medications increased in our study. Indeed, the overall and average annual increase was the highest of any psychotropic class and increased the most in 10- to 14-year-olds (+111.2%). This is in contrast to the findings of Karanges et al. (2014), and all countries examined in Bachmann et al. (2017), where 15- to 19-year-olds showed the highest increase in ADHD drug prescriptions.

However, comparing prescribing trends for ADHD medications across studies is difficult. Most studies have used dispensing datasets, and countries differ in their prescribing regulations for ADHD medications. In Australia, stimulants have strict prescribing guidelines, and the primary responsibility for treatment resides with specialists, although GPs can be nominated as co-prescribers in some circumstances (Australian ADHD Professionals Association, 2021). Consequently, the rate of prescribing of ADHD medications by GPs is low and has remained stable at around 19% of prescriptions dispensed from 2012–2013 to 2018–2019 (AIHW, 2020: Table PBS.7). Nonetheless, some evidence suggests that the prevalence of diagnosed ADHD in 6- to 17-year-olds may have decreased over the study period (9.9% to 7.8% from 1998 to 2013–2014) (Sawyer et al., 2018). If this trend has continued until 2018, the increasing rate of stimulant prescriptions in our study may indicate a

growing tendency to treat ADHD with medications in preference to non-pharmacological approaches.

A notable finding is the high percentage of 0- to 4-year-olds prescribed clonidine, which is not approved for children and adolescents in Australia (and is primarily prescribed for hypertension in adults). When combined with methylphenidate in children with ADHD, it has been associated with serious adverse events (Boehringer Ingelheim Pty Ltd, 2019).

Anxiolytics, hypnotics/sedatives and melatonin

Prescribing of anxiolytics in general practice showed no changes overall, declining only slightly in 10- to 14-year-olds. Hypnotic/sedative (benzodiazepines and Z-drugs) prescribing declined in the youngest and oldest age-groups. Australasian and international studies are scarce, and comparison was difficult due to differing drug groupings.

For anxiolytics, a Welsh study found a significant overall increase (+62%) only in the 15- to 18-year-olds (2003–2011) (John et al., 2015). A NZ investigation found a 50% increase in under-18 year-olds across 9 years (2008–2016) (Barczyk et al., 2020). However, in consonance with our findings, a Norwegian study from 2004 to 2014 found no meaningful change in prescribing (Hartz et al., 2016).

No other studies reported a decline in hypnotic/sedative prescribing. Studies from NZ (Barczyk et al., 2020) and Norway reported increases (Hartz et al., 2016), but these studies included melatonin in the hypnotic/sedative class. We found a substantial increase in prescriptions for melatonin in all age-groups, and our results would likely be more consistent with international studies if we had also analysed melatonin within the hypnotic/sedative class.

Given ongoing concerns about paediatric benzodiazepine use (O'Sullivan et al., 2015), prescribing melatonin may well be perceived as a safer and effective alternative. Indeed, studies reporting beneficial effects of melatonin for children with insomnia, with minimal reported adverse effects after years of daily use (Janjua and Goldman, 2016), may encourage off-label use of melatonin. However, until 2020, melatonin was not approved for any childhood conditions, and there are concerns with prescribing neurohormonal medications to pre-pubertal children (Boafo et al., 2019).

Demographics

Gender differences in our study were largely consistent with international studies. Females were prescribed antidepressants more often than males, although the female–male ratio was lower than that observed in several other countries (Bachmann et al., 2016; Barczyk et al., 2020; John et al., 2016). An inverse trend was found with antipsychotics, with males being prescribed the medications twice as often as females, similar to several European countries and the United States (Hálfdánarson et al., 2017), but differing from findings in NZ, where antipsychotic prescriptions were similar among boys and girls (Barczyk et al., 2020). ADHD medication prescription rates in males were on average 3.8 times those in females (Supplementary eTable S5), corroborating the NZ study findings (Barczyk et al., 2020). Although ADHD drugs were more frequently prescribed in males, our results showed that the increase was more rapid in females, similar to findings in Norway (Hartz et al., 2016).

Patterns of prescribing with age were similar to those in the NZ study (Barczyk et al., 2020). In both studies, there was an increase in prescriptions with increasing age observed for antidepressants, antipsychotics, anxiolytics and hypnotics/sedatives. The exception was ADHD medication prescribing, which was higher in 10- to 14-year-olds.

Regarding socioeconomic position, for antipsychotics, antidepressants and ADHD drugs, there was a tendency for those in the most disadvantaged areas to have higher prescription rates than those in the least disadvantaged areas. We only found one study that included socioeconomic factors – a Welsh primary care study analysing antidepressant prescribing (John et al., 2016). Findings were similar to our study. In Australia, there are higher rates of mental disorders in lower socioeconomic areas (Enticott et al., 2016; Lawrence et al., 2015), which could explain the higher rates of drug use in our study. However, it is also possible that children and adolescents in more disadvantaged areas are more likely to receive drug treatments rather than non-pharmaceutical options (Nunn et al., 2020). This may be due to different prescribing practices in lower socioeconomic areas, differing availability of alternative treatments and/or differing treatment preferences of those living in poorer areas. Analysis of social determinants of mental health is a limited but growing area of research, and future studies are needed to investigate sociodemographic correlates of mental disorders and psychotropic prescribing practices.

Strengths and limitations

MedicineInsight is a large, longitudinal database, covering 9% of GPs and over three million patients attending Australian general practices. Although some states, regions and participants in higher IRSAD areas were over-represented compared to census data, the patients in the database are considered representative of those attending Australian general practice (NPS MedicineWise, 2020). MedicineInsight records all prescriptions written by GPs, but does not indicate if they were dispensed, which could overestimate psychotropic use. Nonetheless, our findings were consistent with other national and international studies using dispensing data. Although most psychotropic prescribing occurs in

general practice, there may be situations where trends differ (e.g. specialist prescribing), so the results cannot be generalised beyond general practice. As with all real-world health care databases, MedicineInsight is reliant on staff consistently and accurately completing data fields, resulting in potential problems with missing or misclassified data.

Conclusion

This study shows increasing trends in psychotropic prescribing to children and adolescents in Australia, consistent with observed increases in other Australian and international data sources. From 2011 to 2018, prescriptions for antipsychotics, antidepressants and ADHD medications rose substantially, with the greatest increase in 10- to 14-year-olds. Although benzodiazepine and Z-drug prescriptions have decreased, this has been more than offset by a marked rise in melatonin prescribing. Future research is needed to explore and understand the reasons why psychotropic prescribing is increasing, and its impact on child and adolescent health and well-being.

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Supplemental Material

Supplemental material for this article is available online.

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4.6 Chapter 4 supplementary files

Supplementary Online Tables

Article

'Trends in prescription of psychotropic medications to children and adolescents in Australian primary care from 2011 to 2018'

Julie Klau, Carla Bernardo, David Gonzalez-Chica, Melissa Raven, Jon Jureidini

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ADHD drugs				
	Stimulants	N06B		
			Armodafinil	N06BA
			Atomoxetine[b]	N06BA
			Dexamphetamine	N06BA
			Lisdexamphetamine	N06BA
			Methylphenidate	N06BA
			Modafinil	N06BA
	Alpha2 Agonists	C02A		
			Clonidine	C02AC
			Guanfacine	C02AC
Anxiolytics				
	Benzodiazepines	N05B		
			Alprazolam	N05BA
			Bromazepam	N05BA
			Diazepam	N05BA
			Oxazepam	N05BA
			Lorazepam	N05BA
			Clobazam	N05BA
	Azaspirodecanediones	N05B	Buspirone	N05BE
Hypnotics/sedatives				
	Benzodiazepines	N05C		
			Flunitrazepam	N05CD
			Midazolam	N05CD
			Nitrazepam	N05CD
			Temazepam	N05CD
	Z-drugs	N05C		
			Zopiclone	N05CF
			Zolpidem	N05CF
Melatonin				
	Melatonin receptor agonist	N05C	Melatonin	N05CH01

Abbreviations: ATC, Anatomical Therapeutic Chemical; ADHD, attention deficit hyperactivity disorder; SSRI, selective serotonin re-uptake inhibitor; SNRI, serotonin and noradrenaline re-uptake inhibitor; TCA, tricyclic antidepressant; MAOI, monoamine oxidase inhibitor; NaSSA, noradrenaline and specific serotonergic antidepressant.

a. ATC codes were developed by the World Health Organization (WHO) for the classification of drugs and other medicinal products. N is the primary anatomical group for the nervous system. C is the primary anatomical group for the cardiovascular system.

b. Atomoxetine is a selective noradrenaline re-uptake inhibitor (NRI), but is classified under N06B with stimulants in the ATC classification system.

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eTable S2. Indications for use of psychotropics in children and adolescents in Australia. Indications approved by the Australian Therapeutic Goods Administration (TGA).

Medication	Medicine Name	Age range	Indicated use
Antipsychotics			
Chlorpromazine	Largactil	No age limits specified	Schizophrenia, mania, psychotic depression Severe behavioural disturbances in children with mental retardation or autism: treatment of self-injurious, aggressive behaviour or overactivity Nausea, vomiting
Clozapine	Clopine	> 16 years	Treatment resistant schizophrenia
Haloperidol	Serenace	> 2 years	Severely aggressive or hostile children, Tourettes
Lurasidone[a]	Latuda/Lupin	> 12 years	Schizophrenia
Periciazine	Neulactil	1-3 years	Not recommended – contraindicated < 1 year
Periciazine	Neulactil	3-6 years	Use reserved for exceptional situations in specialist units
Periciazine	Neulactil	> 6 years	Severe anxiety, impulsiveness, aggression, schizophrenia maintenance
Quetiapine	Seroquel	10-17 years	Monotherapy for treatment of acute mania associated with bipolar 1 disorder
Quetiapine	Seroquel	13-17 years	Schizophrenia
Risperidone	Risperdal	> 14 years	Schizophrenia
Risperidone	Risperdal	> 5 years	Treatment of conduct disorders or other disruptive behaviour disorders
Risperidone	Risperdal	Adolescents	Adolescents and adults with sub-average intellectual function or mental retardation and prominent destructive behaviours (e.g., aggression, impulsivity, self-injurious behaviours)
Risperidone	Risperdal	Children and adolescents	Behavioural disorders associated with autism in children and adolescents
Antidepressants			
Fluvoxamine	Luvox	> 7 years	Obsessive compulsive disorder; not recommended for depression
Sertraline	Zoloft	> 5 years	Obsessive compulsive disorder; not recommended for depression
Amitriptyline	Endep	No age limits specified	Nocturnal enuresis; not recommended for depression
Imipramine	Tofranil	> 4 years	Nocturnal enuresis; not recommended for depression

Lithium	Lithicarb	> 11 years	Acute treatment and prophylaxis of mania Schizoaffective illness and chronic schizophrenia Personality disorders in young people with cyclothymia
Lithium	Quilonium SR	> 11 years	Treatment of acute episodes of mania and hypomania, and for prophylaxis of recurrent manic-depressive illness
ADHD drugs			
Methylphenidate	Ritalin 10	> 5 years	ADHD, narcolepsy
Methylphenidate LA	Ritalin LA/Concerta	> 5 years	ADHD, narcolepsy
Lisdexamphetamine[b]	Vyvanse	> 5 years	ADHD
Dexamphetamine	Aspen Dexamphetamine	> 2 years	ADHD, narcolepsy
Guanfacine[c]	Intuniv	> 5 years	ADHD
Atomoxetine	Strattera	> 5 years	ADHD
Anxiolytics			
Diazepam	Antenex (tabs) Orion (Oral liquid)	> 6 months	Anxiety disorders or for the short-term relief of anxiety symptoms Acute alcohol withdrawal for relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis Muscle spasm due to local trauma, spasticity due to cerebral palsy, paraplegia
Oxazepam	Serepax	> 15 years	Anxiety disorders, anxiety associated with depression. Short term relief of anxiety symptoms. Relief of tremor, confusional states or anxiety associated with alcohol withdrawal
Lorazepam	Atvian	> 15 years	Anxiety disorders, anxiety associated with depression. Short term relief of anxiety symptoms. Pre-surgical medication taken night before or 1-2 hours prior to surgery
Clobazam	Frisium	> 3 years	Lennox-Gastaut epilepsy, seizures Not recommended for anxiety or sleep disorders
Hypnotics/sedatives			
Midazolam	Hypnovel	> 7 years	Anaesthesia, peri-operative sedation, relief of pre-operative apprehension
Melatonin (PR)[d]	Slenyto	2-18 years	Insomnia in children and adolescents with Autism Spectrum Disorder and/or Smith-Magenis syndrome

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Abbreviations: ADHD, attention deficit hyperactivity disorder; Methylphenidate LA, methylphenidate long-acting; Melatonin PR, melatonin prolonged release.

a. Lurasidone was approved for schizophrenia in adolescents 13 to 17 years in April 2018.

b. Lisdexamphetamine was approved for treating ADHD in children and adolescents on 23 October 2013.

c. Guanfacine was approved for treatment of ADHD on 22 August 2017.

d. Melatonin was approved for use in children and adolescents for the given conditions on 22 May 2020.

eTable S3. Trends in prescribing of antipsychotics to children and adolescents, according to patient sociodemographics, from 2011 to 2018[a]. Rates are reported as the number of patients receiving a prescription for any antipsychotic medication, per 1,000 patients.

	Year								Change 2011-2018				
	2011	2012	2013	2014	2015	2016	2017	2018	Annual average change		Total change		
	n=112,997	n=126,302	n=144,248	n=168,821	n=200,921	n=231,326	n=269,903	n=336,432	%	95% CI	Absolute	%	95% CI
Overall (crude)	2.8	3.3	3.5	4.1	4.3	4.6	4.9	4.5	+6.2	5.0;7.3	1.7	62.8	44.1;83.8
Age													
0-4 years	**0.1**	**0.1**	**0.0**	**0.1**	**0.1**	**0.1**	**0.1**	**0.1**	+5.5	-9.2;22.7	0.0	0.0	§
5-9 years	**1.6**	**1.7**	**1.8**	**2.1**	**2.1**	**2.4**	**2.5**	**2.4**	+6.3	-0.2;13.3	+0.8	+49.5	-6.0;137.8
10-14 years	**4.7**	**5.5**	**5.7**	**5.8**	**6.2**	**6.8**	**7.5**	**8.0**	+7.5	3.6;11.6	+3.3	+72.2	30.5;127.3
15-18 years	9.8	11.9	11.5	12.8	13.0	13.5	14.0	14.8	+4.8	2.6;7.0	+5.0	+51.2	26.5;80.6
Gender													
Male	4.7	5.4	5.0	5.4	5.7	6.5	6.6	6.6	+5.0	2.2;7.9	+1.9	+39.4	13.6;71.1
Female	**2.0**	**2.5**	**2.7**	**3.0**	**3.0**	**2.9**	**3.3**	**3.7**	+6.7	4.1;9.4	+1.7	+83.1	48.4;125.7
IRSAD quintile[b]													
1. Least disadvantaged	2.0	1.9	1.6	1.7	2.0	2.3	2.8	2.5	+6.9	2.0;12.0	+0.5	+24.1	-12.2;75.5
2.	2.5	**3.2**	**3.6**	**3.5**	3.0	3.2	**3.3**	3.8	+2.9	-1.6;7.6	+1.3	+51.6	5.9;117.2
3.	3.7	**4.2**	**3.9**	**4.4**	**4.6**	**5.1**	**5.5**	**6.1**	+7.5	3.5;11.7	+2.4	+64.1	23.0;118.9
4.	3.5	**4.5**	**5.2**	**5.8**	**5.6**	**5.4**	**6.1**	**6.1**	+5.2	1.2;9.3	+2.6	+74.2	25.3;142.0
5. Most disadvantaged	4.5	**6.0**	**5.5**	**6.5**	**7.0**	**7.5**	**6.9**	**7.5**	+5.5	2.5;8.7	+3.0	+65.7	32.9;106.7

§ Due to small numbers in this group, percentage calculations were not useful.

a. Adjusted for age, gender, patient IRSAD, and practice characteristics (state, rurality, practice IRSAD). Numbers marked in bold type indicate p<0.05 for the difference between each category and the reference for the given year. Reference categories were: 15-18 years, male, and IRSAD quintile 1 (Least disadvantaged).

b. IRSAD, Index of Relative Socio-economic Advantage and Disadvantage.

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eTable S4. Trends in prescribing of antidepressants to children and adolescents according to patient sociodemographics from 2011 to 2018[a]. Rates are reported as the number of patients receiving a prescription for any antidepressant medication per 1,000 patients.

	Year								Change 2011-2018				
	2011	2012	2013	2014	2015	2016	2017	2018	Annual average change		Total change		
	n=112,997	n=126,302	n=144,248	n=168,821	n=200,921	n=231,326	n=269,903	n=336,432	%	95% CI	Absolute	%	95% CI
Overall (crude)	16.9	19.4	20.9	22.3	22.7	24.4	25.5	24.2	+4.5	4.0;5.0	+7.3	42.8	35.9;50.0
Age													
0-4 years	**0.2**	**0.3**	**0.2**	**0.2**	**0.1**	**0.2**	**0.1**	**0.1**	-7.5	-16.8;2.8	-0.1	-19.6	-67.9;101.5
5-9 years	**3.1**	**3.0**	**2.5**	**3.3**	**2.8**	**3.3**	**3.3**	**3.4**	+2.5	-3.0;8.3	+0.3	+7.5	-24.6;53.4
10-14 years	**15.4**	**17.8**	**19.4**	**19.8**	**20.3**	**21.7**	**23.4**	**25.6**	+6.5	4.4;8.7	+10.3	+66.5	41.1;96.3
15-18 years	72.2	79.8	81.7	81.8	82.5	87.7	91.2	98.5	+3.9	2.9;4.9	+26.3	+36.4	27.1;46.5
Gender													
Male	17.2	18.3	18.4	19.0	19.2	20.8	21.9	23.3	+4.4	2.9;6.0	+6.1	+35.2	21.4;50.6
Female	19.5	**22.0**	**22.9**	**23.0**	**23.1**	**24.4**	**25.5**	**27.7**	+4.2	3.2;5.2	+8.2	+42.2	31.8;53.4
IRSAD quintile[b]													
1. Least disadvantaged	14.0	14.4	15.2	15.9	16.3	18.2	18.8	19.8	+5.5	3.7;7.3	+5.8	+41.9	25.4;60.6
2.	**18.7**	**18.7**	**20.5**	**18.7**	**19.9**	20.8	**21.4**	**23.8**	+3.6	1.7;5.5	+5.1	+27.7	9.2;49.3
3.	**20.2**	**23.7**	**23.7**	**24.3**	**23.6**	**25.8**	**27.6**	**28.6**	+4.2	2.5;6.0	+8.4	+41.5	25.5;59.5
4.	19.4	**22.9**	**24.5**	**24.7**	**24.4**	**25.3**	**25.8**	**29.3**	+4.2	2.3;6.1	+9.9	+50.6	30.6;73.6
5. Most disadvantaged	**23.8**	**27.4**	**26.0**	**27.4**	**27.4**	**28.2**	**29.9**	**32.7**	+3.8	2.0;5.5	+8.9	+37.7	19.9;58.1

a. Adjusted for age, gender, patient IRSAD, and practice characteristics (state, rurality, practice IRSAD). Numbers marked in bold type indicate p<0.05 for the difference between each category and the reference for the given year. Reference categories were: 15-18 years, male, and IRSAD quintile 1 (Least disadvantaged).

b. IRSAD, Index of Relative Socio-economic Advantage and Disadvantage.

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eTable S5. Trends in prescribing of ADHD medications to children and adolescents according to patient sociodemographics from 2011 to 2018[a]. Rates are reported as the number of patients receiving a prescription for any ADHD medication per 1,000 patients.

	Year								Change 2011-2018				
	2011	2012	2013	2014	2015	2016	2017	2018	Annual average change		Total change		
	n=112,997	n=126,302	n=144,248	n=168,821	n=200,921	n=231,326	n=269,903	n=336,432	%	95% CI	Absolute	%	95% CI
Overall (crude)	5.3	5.8	6.8	7.7	8.1	8.6	9.8	10.4	+9.6	8.8;10.5	+5.1	95.8	79.6;113.5
Age													
0-4 years	**0.2**	**0.1**	**0.2**	**0.2**	**0.1**	**0.2**	**0.2**	**0.2**	+1.5	-9.0;13.1	0.0	-12.3	-60.1;93.0
5-9 years	5.9	6.6	7.6	8.4	8.7	9.3	**10.4**	**11.1**	+8.7	3.6;14.1	+5.2	+87.5	46.3;140.2
10-14 years	**11.8**	**13.5**	**15.7**	**17.3**	**19.5**	**20.3**	**22.9**	**24.8**	+10.4	7.7;13.2	+13.0	+111.2	72.0;159.3
15-18 years	7.7	7.7	8.5	10.1	9.5	10.7	12.8	13.8	+9.6	4.7;14.7	+6.1	+78.7	32.2;141.7
Gender													
Male	9.3	10.1	11.1	12.2	13.1	14.0	15.6	16.8	+8.7	6.0;11.6	+7.5	+80.6	53.5;112.5
Female	**2.0**	**2.2**	**3.0**	**3.6**	**3.5**	**3.7**	**4.6**	**5.0**	+12.7	9.6;16.0	+3.0	+150.0	92.7;224.4
IRSAD quintile[b]													
1. Least disadvantaged	3.1	3.0	3.6	3.9	4.1	4.8	5.4	6.0	+11.0	5.9;16.4	+2.9	+90.8	38.1;163.6
2.	3.5	3.9	4.2	4.8	5.3	5.3	5.8	6.2	+7.8	3.3;12.5	+2.7	+76.9	27.7;145.1
3.	**7.2**	**7.5**	**8.3**	**9.8**	**9.9**	**10.7**	**11.9**	**13.4**	+9.5	5.4;13.7	+6.2	+85.8	43.1;141.4
4.	**7.1**	**8.1**	**8.8**	**10.7**	**10.9**	**11.1**	**13.5**	**14.7**	+10.4	6.4;14.5	+7.6	+107.5	58.6;171.5
5. Most disadvantaged	**9.2**	**10.8**	**13.6**	**14.1**	**15.0**	**16.4**	**19.0**	**19.4**	+10.0	6.2;14.0	+10.2	+110.5	66.2;166.5

a. Adjusted for age, gender, patient IRSAD, and practice characteristics (state, rurality, practice IRSAD). Numbers marked in bold type indicate p<0.05 for the difference between each category and the reference for the given year. Reference categories were: 15-18 years, male, and IRSAD quintile 1 (Least disadvantaged).

b. IRSAD, Index of Relative Socio-economic Advantage and Disadvantage.

eTable S6. Trends in prescribing of anxiolytics to children and adolescents according to patient sociodemographics from 2011 to 2018[a]. Rates are reported as the number of patients receiving a prescription for any anxiolytic medication per 1,000 patients.

	Year								Change 2011-2018				
	2011	2012	2013	2014	2015	2016	2017	2018	Annual average change		Total change		
	n=112,997	n=126,302	n=144,248	n=168,821	n=200,921	n=231,326	n=269,903	n=336,432	%	95% CI	Absolute	%	95% CI
Overall (crude)	2.5	2.8	3.0	2.9	3.0	3.0	3.3	2.5	+0.2	-1.1;1.4	0.0	+0.2	-12.4;14.6
Age													
0-4 years	**0.2**	**0.3**	**0.2**	**0.2**	**0.1**	**0.1**	**0.2**	**0.2**	-3.9	-12.7;5.8	0.0	-4.2	-58.6;121.8
5-9 years	**1.1**	**1.0**	**1.2**	**1.1**	**1.1**	**0.9**	**1.2**	**1.0**	-0.6	-5.9;4.9	-0.1	-9.6	-42.0;40.8
10-14 years	**3.3**	**3.8**	**4.0**	**3.6**	**3.0**	**3.4**	**3.2**	**2.7**	-3.7	-6.8;-0.4	-0.1	-16.0	-37.7;13.1
15-18 years	9.8	10.3	10.1	9.2	9.9	9.7	10.4	9.7	+0.0	-2.1;2.1	-0.1	-1.7	-17.7;17.5
Gender													
Male	2.9	3.3	3.3	2.7	2.8	2.9	3.1	2.7	-1.3	-3.9;1.5	-0.2	-6.7	-26.3;18.2
Female	2.8	3.0	3.0	2.9	2.8	2.8	3.0	2.7	-0.7	-2.9;1.5	-0.1	-4.4	-20.4;14.8
IRSAD quintile[b]													
1. Least disadvantaged	2.2	2.4	2.4	2.2	2.4	2.6	2.6	2.3	+1.3	-1.7;4.4	+0.1	+7.3	-19.2;42.4
2.	3.0	3.3	3.3	2.8	2.6	2.4	2.9	2.6	-2.9	-6.4;0.7	-0.4	-14.7	-37.3;16.0
3.	2.9	3.4	**3.6**	2.9	**3.0**	3.0	3.3	3.0	-0.8	-4.0;2.6	+0.1	+2.0	-21.7;33.0
4.	3.7	3.0	3.5	**3.3**	**3.2**	3.3	**3.6**	3.3	+0.0	-4.4;4.6	-0.4	-11.8	-40.6;31.0
5. Most disadvantaged	3.4	3.7	3.3	**3.5**	**3.4**	3.1	3.0	2.9	-3.0	-6.3;0.4	-0.5	-14.5	-37.9;17.8

a. Adjusted for age, gender, patient IRSAD, and practice characteristics (state, rurality, practice IRSAD). Numbers marked in bold type indicate p<0.05 for the difference between each category and the reference for the given year. Reference categories were: 15-18 years, male, and IRSAD quintile 1 (Least disadvantaged).

b. IRSAD, Index of Relative Socio-economic Advantage and Disadvantage.

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eTable S7. Trends in prescribing of hypnotics/sedatives[a] to children and adolescents according to patient sociodemographics from 2011 to 2018[b]. Rates are reported as the number of patients receiving a prescription for any hypnotic/sedative medication per 1,000 patients.

	Year								Change 2011-2018				
									Annual average change		Total change		
	2011	2012	2013	2014	2015	2016	2017	2018					
	n=112,997	n=126,302	n=144,248	n=168,821	n=200,921	n=231,326	n=269,903	n=336,432	%	95% CI	Absolute	%	95% CI
Overall (3crude)	2.0	2.1	1.9	1.9	1.7	1.7	1.6	1.2	-6.5	-8.0;-5.0	-0.8	-40.2	-49.2;-29.6
Age													
0-4 years	**0.3**	**0.1**	**0.2**	**0.2**	**0.2**	**0.2**	**0.2**	**0.1**	-10.0	-17.6;-1.6	-0.2	-68.3	-85.4;-31.1
5-9 years	**0.7**	**0.7**	**0.6**	**0.5**	**0.8**	**0.5**	**0.6**	**0.5**	-4.7	-11.5;2.7	-0.2	-28.9	-60.9;29.2
10-14 years	**1.5**	**1.1**	**1.4**	**1.5**	**1.2**	**1.3**	**0.9**	**1.1**	-4.7	-9.9;0.7	-0.4	-24.8	-53.3;21.1
15-18 years	8.5	8.9	7.3	6.4	5.6	5.7	5.6	4.6	-8.5	-10.6;-6.3	-3.9	-46.2	-55.9;-34.3
Gender													
Male	2.7	2.2	2.1	1.5	1.4	1.6	1.5	1.2	-9.1	-12.0;-6.1	-1.4	-53.5	-64.0;-40.0
Female	**2.1**	2.3	1.9	1.9	1.7	1.6	1.5	1.3	-7.0	-9.4;-4.6	-0.8	-36.3	-48.7;-20.8
IRSAD quintile[c]													
1. Least disadvantaged	2.1	2.2	1.7	1.4	1.6	1.6	1.5	1.2	-6.2	-9.7;-2.6	-0.9	-42.7	-58.3;-21.3
2.	1.9	2.6	1.9	1.7	1.6	1.3	1.4	1.0	-10.6	-14.3;-6.7	-0.9	-48.0	-65.6;-21.4
3.	2.5	2.1	2.1	**2.2**	1.4	1.4	1.7	1.4	-7.6	-11.4;-3.7	-1.1	-44.3	-60.2;-22.0
4.	2.7	2.3	2.1	1.8	1.5	1.9	1.4	1.5	-7.4	-12.5;-2.0	-1.2	-43.5	-65.4;-7.9
5. Most disadvantaged	2.5	2.2	2.2	**2.0**	1.9	1.8	1.3	1.5	-7.7	-11.4;-3.7	-1.0	-39.3	-59.7;-8.6

a. The hypnotic/sedative category did not include melatonin

b. Adjusted for age, gender, patient IRSAD, and practice characteristics (state, rurality, practice IRSAD). Numbers marked in bold type indicate p<0.05 for the difference between each category and the reference for the given year. Reference categories were: 15-18 years, male, and IRSAD quintile 1 (Least disadvantaged).

c. IRSAD, Index of Relative Socio-economic Advantage and Disadvantage.

eTable S8. Trends in prescribing of melatonin to children and adolescents according to patient sociodemographics from 2011 to 2018[a]. Rates are reported as the number of patients receiving a prescription for melatonin per 1,000 patients.

	Year								Change 2011-2018				
	2011	2012	2013	2014	2015	2016	2017	2018	Annual average change		Total change		
	n=112,997	n=126,302	n=144,248	n=168,821	n=200,921	n=231,326	n=269,903	n=336,432	%	95% CI	Absolute	%	95% CI
Overall (crude)	1.7	2.9	4.2	5.9	7.4	9.0	11.1	11.8	+24.7	23.7;25.8	+10.1	+606.7	510.9;717.6
Age													
0-4 years	**0.3**	**0.5**	**0.5**	**0.9**	**1.0**	**1.5**	**1.6**	**2.0**	+26.7	20.2;33.6	+1.7	+534.3	233.0;1108.1
5-9 years	**1.4**	**2.7**	**3.6**	**5.7**	**6.9**	**8.6**	**10.5**	**11.7**	+26.5	22.1;31.1	+10.3	+732.8	466.0;1125.2
10-14 years	**2.6**	**5.1**	**7.2**	**9.4**	**11.6**	**14.3**	**18.0**	**21.3**	+26.6	23.0;30.2	+18.6	+711.1	494.7;1060.3
15-18 years	4.5	6.8	10.0	11.8	15.1	17.6	22.0	26.2	+23.9	21.3;26.6	+21.7	+477.3	356.5;630.1
Gender													
Male	2.3	4.0	5.4	7.2	8.0	10.1	11.6	13.8	+22.2	19.3;25.3	+11.5	+504.8	375.7;668.9
Female	**1.4**	**2.4**	**3.4**	**4.6**	**6.4**	**7.5**	**9.9**	**11.6**	+29.0	26.3;31.7	+10.2	+707.3	530.1;934.2
IRSAD quintile[b]													
1. Least disadvantaged	1.4	2.7	3.8	5.3	6.1	7.1	9.1	10.5	+24.7	20.8;28.7	+9.1	+655.1	431.2;973.5
2.	1.8	3.0	4.4	4.6	5.7	7.1	9.2	11.2	+24.9	20.7;29.2	+9.4	+534.1	331.9;830.8
3.	1.9	3.0	4.5	5.8	**8.1**	**9.8**	**11.8**	14.1	+27.1	23.3;31.1	+12.2	+633.4	437.6;900.4
4.	**2.7**	**4.4**	**5.1**	**8.2**	**8.4**	10.9	**12.5**	14.2	+21.6	17.2;26.2	+11.5	+418.6	267.5;631.6
5. Most disadvantaged	1.7	3.0	4.2	5.7	**8.6**	10.4	**12.9**	15.1	+30.0	23.5;36.8	+13.4	+791.9	394.0;1510.3

a. Adjusted for age, gender, patient IRSAD, and practice characteristics (state, rurality, practice IRSAD). Numbers marked in bold type indicate p<0.05 for the difference between each category and the reference for the given year. Reference categories were: 15-18 years, male, and IRSAD quintile 1 (Least disadvantaged).

b. IRSAD, Index of Relative Socio-economic Advantage and Disadvantage.

eTable S9. Trends in hypnotic/sedative prescriptions by individual medication (rate per 1,000 regular patients).

	Year								Change 2011-2018				
	2011	2012	2013	2014	2015	2016	2017	2018	Annual average change		Total change		
	n=112,997	n=126,302	n=144,248	n=168,821	n=200,921	n=231,326	n=269,903	n=336,432	%	95% CI	Absolute	%	95% CI
Midazolam	0.3	0.3	0.4	0.3	0.4	0.3	0.4	0.3	+1.3	-2.3;5.1	0.0	-16.4	-22.4;74.8
Temazepam	1.4	1.4	1.2	1.2	1.1	1.1	1.0	0.7	-8.7	-10.5;-6.8	-0.7	-51.9	-60.9;-40.9
Nitrazepam	0.1	0.1	0.1	0.1	0.1	0.0	0.0	0.0	-13.1	-20.0;-5.5	-0.1	-46.3	-75.6;18.4
Zopiclone	0.1	0.1	0.1	0.2	0.1	0.2	0.2	0.1	+4.4	-1.2;10.2	0.0	+75.4	-14.0;257.9
Zolpidem	0.2	0.2	0.1	0.2	0.1	0.1	0.1	0.1	-14.6	-19.7;-9.2	-0.1	-66.4	-80.7;-41.5
Flunitrazepam	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-45.5	-72.7;8.9	0.0	0.0	§

§ Due to very low numbers in this category, and a zero prescription rate in 2018, percentages could not be calculated.

5 Chapter 5. Antipsychotic prescribing patterns in children and adolescents attending Australian general practice in 2011 and 2017.

5.1 Publication reference

This paper has been published in JCPP Advances.

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5.2 Preface

The prevalence study (Chapter 4) found an annual increase of 6.2% and an overall increase from 2011 to 2018 of 62.8% for antipsychotic prescribing. Antipsychotics are often prescribed off-label in children and adolescents [48], and the conditions for which antipsychotics are prescribed are expanding [60, 404], which is a concerning international trend. This chapter examines comparable trends in Australia using the primary care database, MedicineInsight.

To examine the extent of off-label antipsychotic prescribing, diagnostic information was extracted for all years from 2011 to 2018, although reported only for two comparison years (2011 and 2017) in this paper (Supporting Information Table S5).

The present chapter addresses the following research questions:

1). Was there a change in the prescribing rate of antipsychotics to children and adolescents with mental health diagnoses in 2017, compared to 2011?

- 1a). Which diagnoses exhibited increases, decreases, or no change?

2). Did the proportion of patients with mental health diagnoses prescribed antipsychotics change from 2011 to 2017?

- 2a). Did changes vary by sociodemographic characteristics?

3). Has the rate of off-label prescribing of antipsychotics changed from 2011 to 2017?

- 3a). Did changes vary by sociodemographic characteristics?

4). Which antipsychotics were most commonly prescribed for each diagnostic category in each year?

5). What was the extent of co-prescribing of other classes of psychotropics with antipsychotics in each year?

5.3 Key findings

1. Children and adolescents with a mental disorder were more likely to be prescribed an antipsychotic for any mental disorder in 2017 compared to 2011.
2. Off-label prescribing was 10% higher in 2017 than in 2011.
3. The most common diagnosis associated with an antipsychotic prescription in both years was comorbid depression and anxiety, followed by autism, without associated behavioural issues recorded.
4. Females were less likely than males to receive an off-label antipsychotic in 2011 but more likely to receive an off-label antipsychotic in 2017.
5. Children and adolescents living in the most socio-economically disadvantaged areas recorded the largest change in off-label antipsychotic prescribing (increasing 20%) from 2011 to 2017.

5.4 Supplementary data

Crude prevalences of diagnoses for all years were not used in this paper but are reported in Table 5.2 at the end of this chapter. This data will be used to briefly examine off-label prescribing for other psychotropic classes in Chapter 8.

5.5 Statement of Authorship

Title of Paper	Trends in prescription of psychotropic medications to children and adolescents in Australian primary care from 2011 to 2018
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Klau J, Bernardo CO, Gonzalez-Chica DA, et al. (2022) Trends in prescription of psychotropic medications to children and adolescents in Australian primary care from 2011 to 2018. *Australian and New Zealand Journal of Psychiatry* 56(11): 1477-1490. https://doi.org/ 10.1177/00048674211067720

Principal Author

Name of Principal Author (Candidate)	Julie Klau		
Contribution to the Paper	JK contributed to the conceptualisation and design of the study, analyses and interpretation of results, and wrote the original manuscript. JK also assisted with the preparation of variables in the database, engaged in ongoing editing and refinements, and submitted the article to the journal as primary and corresponding author.		
Overall percentage (%)	80%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature	80%	Date	29 April 2024

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

iv. the candidate's stated contribution to the publication is accurate (as detailed above);

v. permission is granted for the candidate in include the publication in the thesis; and

vi. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Associate Professor David Gonzalez-Chica		
Contribution to the Paper	DG assisted with database preparation and advice on statistical analyses. DG also provided critical revisions of the manuscript, contributing to intellectual content.		
Signature	10%	Date	12 April 2024

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Contribution to the Paper	MR assisted with major critical revisions of the manuscript, contributing to intellectual content.		
Signature	5%	Date	11 April 2024

Name of Co-Author	Professor Jon Jureidini		
Contribution to the Paper	JJ assisted with conceptualisation and design of the study, and provided critical revisions of the manuscript, contributing to intellectual content.		
Signature	5%	Date	11 April 2024

5.6 Main paper

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ORIGINAL ARTICLE

JCPP Advances

Antipsychotic prescribing patterns in children and adolescents attending Australian general practice in 2011 and 2017

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Abstract

Background: Antipsychotics are increasingly prescribed to children and adolescents worldwide, but little is known about reasons for prescribing. We aimed to examine patterns of paediatric antipsychotic prescribing in Australian primary care services in 2011 and 2017, including diagnoses, sociodemographic characteristics, off-label prescribing, and psychotropic co-prescribing.

Methods: Retrospective analysis of electronic health records (EHRs) using a large Australian general practice database (MedicineInsight). Diagnoses of mental disorders were extracted from EHRs and associated with antipsychotic prescriptions within the same calendar year for three age-groups: 0–9, 10–14, and 15–18-year-olds.

Results: In 2017, children/adolescents with mental health diagnoses were more likely to be prescribed antipsychotics (2.9% of 27,412 patients) than in 2011 (2.0% of 8418 patients; absolute difference +0.9, 95% CI + 0.5, +1.4). The likelihood was greater for patients with bipolar disorders (21.6% vs. 41.5%), eating disorders (1.1% vs. 7.2%), and autism without behavioural problems (3.7% vs. 6.1%). Depression/anxiety (adjusted 26.8% of patients 2011; 30.8% 2017) was the most common diagnosis associated with antipsychotics in both years. Most antipsychotics were prescribed off-label (69.8% 2011; 79.7% 2017; absolute difference +9.8, 95% CI + 1.54, +18.4). Off-label prescribing increased most among those aged 15–18-years, females, and patients living in outer regional/remote/very remote communities and the most disadvantaged areas. The three most frequently prescribed antipsychotics in both years were risperidone, quetiapine, and olanzapine. Psychotropic co-prescribing among patients receiving antipsychotic prescriptions was approximately 69% in both years.

Conclusions: Prescribing antipsychotics for mental health diagnoses to children/adolescents attending Australian general practices was more frequent in 2017 than 2011, and most commonly associated with depression/anxiety diagnoses. In both years, most prescribing was off-label. The majority of patients were co-prescribed other classes of psychotropics along with antipsychotics.

KEYWORDS
adolescents, antipsychotic prescribing, children, off-label, polypharmacy

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INTRODUCTION

Antipsychotics are increasingly being prescribed to children and adolescents worldwide (Bachmann et al., 2014; Hálfdánarson et al., 2017; Klau et al., 2022) despite ongoing controversy over their use in paediatric patients (De Hert et al., 2011). Off-label prescribing is also common, as evidenced in a systematic review (Carton et al., 2015), in which 36%–93% of paediatric antipsychotic prescribing was off-label. Off-label prescribing is the prescribing of drugs for medical conditions for which they have not been approved by regulatory authorities (off-label by indication), as well as prescribing drugs for age-groups for which they have not been approved (off-label by age), which is particularly common in children/adolescents (Sharma et al., 2016). In the United States, in a study of office-based visits to psychiatrists and non-psychiatrist physicians from 2005 to 2009, 94.0% and 87.3% of children and adolescents, respectively, had no Food and Drug Administration (FDA) approved indication recorded for antipsychotic prescriptions (Olfson et al., 2012).

Studies in the United States (Edelsohn et al., 2017; Penfold et al., 2013) have found antipsychotics were predominantly prescribed to children/adolescents for attention deficit hyperactivity disorder (ADHD) and disruptive or aggressive behaviours. As age increased, antipsychotics were increasingly prescribed for depression in several U.S. studies (Edelsohn et al., 2017; Olfson et al., 2015) and a Finnish study (Varimo et al., 2020).

However, little is currently known about antipsychotic prescribing patterns in children/adolescents in Australia, nor the extent to which prescribing conforms with approvals by the Therapeutic Goods Administration (TGA), a key regulator in the Australian healthcare system (see Appendix 1). In Australia, some studies (e.g., Karanges et al., 2014) have examined psychotropic medication data from the Pharmaceutical Benefits Scheme (PBS), which provides information on prescriptions of subsidised medications, but no information on clinical indications.

Our literature search retrieved only four Australian studies that provided information about diagnoses. Firstly, an audit of case-notes at the Women's and Children's Hospital in South Australia in 2012 found most antipsychotic prescriptions were for children with intellectual disabilities or autism with behavioural problems (Ellis & Angley, 2013). The second study examined reasons for antipsychotic prescribing to 12–17-year-old attendees at a public mental health clinic in New South Wales (Dharni & Coates, 2018). Twenty-four precent of patients were prescribed antipsychotics, mostly with antidepressants, and primarily for anxiety disorders or sleep issues. However, in that study, patients with psychoses were excluded, and for missing diagnoses, reason for presentation was used as a proxy, casting doubt on the accuracy of diagnoses. The third and fourth studies, both retrospective file reviews, examined prescribing of all psychotropics in a Western Australian eating disorders inpatient unit (Moore et al., 2013), and a Brisbane child and youth mental health service (Dean et al., 2006). The main reasons for prescribing antipsychotics were agitation and/or anxiety (Moore et al., 2013) and behavioural disturbances (Dean et al., 2006). In all studies, the sample size was small and unrepresentative of prescribing in the wider community.

Key points

- Previous research shows high rates of off-label prescribing of antipsychotics to children/adolescents
- Most prescribing by Australian GPs appears to be off-label, and increasing—(70% 2011—80% 2017)
- The main diagnosis among children/adolescents prescribed antipsychotics was depression/anxiety
- Co-prescribing of other psychotropics was frequent (70% of patients)
- More support is needed for Australian GPs to improve antipsychotic prescribing practices to children/adolescents, and make alternative treatments more accessible.

The aims of this study are to examine (1) proportions of children/adolescents with mental health diagnoses who received antipsychotic prescriptions, across time and in different socioeconomic levels, age-groups and geographical locations, (2) most frequent diagnoses associated with antipsychotic prescriptions, (3) off-label prescribing frequencies, (4) most frequently prescribed antipsychotics, and (5) frequencies of co-prescription with other classes of psychotropic drugs.

METHODS

Study population and data source

This study analysed electronic health records (EHRs) of children/adolescents under 19 years attending Australian general practices in 2011 and 2017, using MedicineInsight, a large primary care database established in 2011. Australia has a universal healthcare system, with a mix of public and private healthcare services (Appendix 1). Patients covered by Medicare are entitled to subsidised medical services from the Medicare Benefits Scheme (MBS), and a wide range of medicines approved on the Pharmaceutical Benefits Scheme (PBS). General practitioners (GPs; family physicians) provide more MBS-subsidised mental health care than any other providers, with 38% of consultations in a typical week addressing mental health concerns (Thornley & Harris, 2021). Psychotropic drugs, with the exception of stimulants, are mostly prescribed by GPs (www.aihw.gov.au/mental-health/topic-areas/mental-health-prescriptions).

In the 2018/2019 financial year, a total of 569 general practices and 3255 general practitioners (GPs; family physicians) were registered with MedicineInsight, representing 7% of all practices and 9% of all GPs (NPS MedicineWise, 2020a). On joining MedicineInsight, practices have whole-of-practice de-identified clinical records, including patient sociodemographics, uploaded to a data warehouse using a secure third-party extraction tool (Havard et al., 2021). Information on all clinical encounters, including medications prescribed, diagnoses, medical tests and results, and reasons for encounters, are uploaded monthly, generating an ongoing record of patient encounters (Havard et al., 2021).

To improve data quality, only practices with at least 2 years of data and no interruptions of more than 6 weeks are provided to researchers by MedicineInsight. Additionally, we excluded practices with substantial variations in patient numbers over time (i.e., over five times higher in 2018 than 2011). 402 general practices met the quality standards for inclusion, and had antipsychotic prescriptions recorded for children or adolescents within the study period.

As a further quality measure, only patients classified as 'regular patients', at any time during the study period, were included. Regular patients were defined as those who attended a specific general practice at least three times within 2 years, with at least one visit each year. Patients may attend other practices outside and within MedicineInsight, resulting in some incomplete treatment records and some duplication of patients, the latter estimated as less than 4% in the database (NPS MedicineWise, 2020b). Including only regular patients maximises the likelihood that patient records are a more complete record of their attendance. As a sensitivity analysis, we also performed an analysis without restricting the sample to regular patients.

The final sample included 168,009 children/adolescents (regular patients) in 2011 and 301,643 in 2017.

Study variables

Antipsychotic prescriptions

We included recorded prescriptions of all antipsychotics listed in the Anatomical Therapeutic Chemical (ATC) index (World Health Organization [WHO], 2023), and available in Australia. A list of antipsychotics and indications approved by the TGA for use in children/adolescents in Australia is provided in Supporting Information Table S1.

Mental health diagnoses

GPs record health conditions using a drop-down list in EHR practice software and/or free-text fields in three variable fields within MedicineInsight: diagnosis, reason for visit, and reason for prescription. We used coding algorithms to extract diagnostic information based on keywords relating to mental health diagnoses (Supporting Information Table S2). In some cases, terms used in the algorithms represent symptoms; but, for mental health diagnoses, they are often also used to represent disorders (e.g., anxiety) (Havard et al., 2021). A mental health diagnosis was recorded for the patient if the algorithm identified the corresponding term/diagnosis in at least one of the three fields. This procedure for extracting diagnoses was validated by Havard et al. A recorded diagnosis was associated with an antipsychotic prescription if the diagnosis was recorded from 180 days before through to 90 days after the prescription, or both occurred within the same calendar year.

We used a hierarchical approach, adapted from Zito et al. (2013), to determine the most likely diagnoses for patients prescribed antipsychotics. Higher-level categories represent conditions with stronger clinical rationales for use of antipsychotics, based on existing clinical guidelines and Australian regulatory approvals. Ten mutually-exclusive levels were identified: psychoses, including schizophrenia; autism with behavioural problems; bipolar disorder; disruptive behaviour/conduct disorder (DBD/CD); autism without behavioural problems; ADHD; eating disorders; depression/anxiety; sleep disorders; and 'other' (post-traumatic stress disorder [PTSD], obsessive-compulsive disorder, personality disorders, communication disorders [language, learning], substance use disorders, enuresis/incontinence disorders).

Our preliminary analyses found 154 patients prescribed antipsychotics without associated mental health diagnoses in 2011, and 392 in 2017 (Supporting Information Table S3). A small percentage of these patients received prescriptions for approved neurological conditions such as Tourette's and epilepsy (7.1%, 2011; 3.6% 2017). A larger minority of patients had mental health plans or suicidal behaviours recorded, without specific mental health diagnoses (13.6%, 2011; 28.6%, 2017). However, the majority had no associated psychiatric or neurological reason for prescribing (79.2%, 2011; 68.4%, 2017). Some may have been diagnosed by paediatricians or child/adolescent psychiatrists, and the diagnostic records not captured in the dataset, or the diagnoses may have been recorded in doctors' progress notes, which, for confidentiality reasons, are not included in the database. In these circumstances, our diagnosis algorithm would associate non-psychiatric reasons with antipsychotic prescriptions. We cannot be confident that these reasons would provide a good representation of the primary reasons for prescribing. Therefore, we restricted our analyses to the subsample with mental health diagnoses.

Off-label prescribing

Prescription of antipsychotics was considered off-label if the drug was not approved by the TGA for the condition identified in the hierarchy of diagnoses and the age of the child. The algorithm for identifying off-label prescribing is provided in Supporting Information Table S4. A combined off-label variable for all prescriptions across all diagnoses was created. If more than one antipsychotic was prescribed in the calendar year, the diagnosis was considered to have an on-label antipsychotic if any of the prescriptions was on-label for the diagnosis.

Sociodemographic factors

We analysed gender, age, rurality and socioeconomic status. Gender was divided into male and female, and age was categorised into three groups: 0–9, 10–14, and 15-18-years. Rurality of patient residence was categorised as major cities, inner regional, or outer regional/remote/very remote, using the Australian Statistical Geography Standard (ASGS) (Australian Bureau of Statistics [ABS], 2016b). Socioeconomic status was analysed using the Index of Relative Socio-economic Advantage and Disadvantage (IRSAD), divided into quintiles. IRSAD is an indicator based on residential postcodes, developed by the Australian Bureau of Statistics using census data on income, education, employment status, and housing (Australian Bureau of Statistics [ABS], 2016a). If patient IRSAD was missing, practice IRSAD was used as a proxy.

Psychotropic co-prescribing

Psychotropic co-prescribing was defined as writing a prescription for at least one other class of psychotropic on the same day an antipsychotic was prescribed. The other medication classes, detailed in an earlier study by our team (Klau et al., 2022), were antidepressants, ADHD medications (stimulants, atomoxetine and alpha-2 agonists, which are approved in Australia for ADHD), anxiolytics and hypnotics/sedatives, with melatonin examined separately.

Statistical analysis

Proportions of patients with mental health diagnoses with associated antipsychotic prescriptions, and proportions receiving off-label prescriptions, were calculated for 2011 and 2017. Frequencies of associated diagnoses were also calculated. Results were adjusted for patient age, gender, and IRSAD, and practice characteristics (rurality, state, IRSAD). Differences in proportions from 2011 to 2017 were analysed using logistic regression, reporting marginal predicted percentages derived from odds ratios, with 95% confidence intervals, using practice as a cluster and robust standard errors. Differences according to sociodemographic characteristics were also analysed using a similar approach. Unadjusted percentages were calculated for the most frequently prescribed antipsychotics for each diagnostic group and for psychotropic co-prescribing.

Stata version 16 (StataCorp) was used for all analyses.

RESULTS

Sample characteristics

In 2011, 8418 of 168,009 (4.2%) children/adolescents had mental health diagnoses recorded (Table 1). In 2017 there were 27,412 of 301,643 (6.7%) (adjusted difference +2.5%, 95% CI [2.2, 2.8], $p < 0.001$; Supporting Information Table S5).

191 children/adolescents with mental health diagnoses were prescribed antipsychotics in 2011, and 893 in 2017.

In both years, children 0-9-years (approximately 58% of the total sample) were the most likely to receive any mental health diagnosis, but the least likely to receive antipsychotic prescriptions for a diagnosis (Table 1). Of the patients with mental health diagnoses receiving antipsychotic prescriptions, most resided in major cities (46.1%, 2011; 48.3%, 2017) or inner regional areas (40.3%, 2011; 37.2%, 2017). In both years, most patients who received antipsychotic prescriptions for their diagnoses, were male (57.6%, 2011; 53.4%, 2017). The distribution by IRSAD was similar both years, with most patients receiving prescriptions (70%) living in the lower three IRSAD quintiles (most disadvantaged).

Diagnoses

A higher proportion of patients with mental health diagnoses were given antipsychotic prescriptions in 2017 (2.0% in 2011; 2.9% in 2017, $p < 0.001$; Table 2).

TABLE 1 Sample characteristics.

	Total sample 0-18 year-olds		Sample with mental health diagnosis		Sample with mental health diagnosis prescribed antipsychotic	
	2011	2017	2011	2017	2011	2017
N	168,009	301,643	8418	27,412	191	893
Age group						
<10 years	57.1%	58.4%	44.2%	41.5%	15.2%	12.0%
10–14 years	23.9%	21.9%	23.4%	25.3%	27.2%	27.3%
15–18 years	19.0%	19.7%	32.4%	33.3%	57.6%	60.7%
Gender						
Male	48.0%	50.0%	53.3%	53.3%	57.6%	53.4%
Female	52.0%	50.0%	46.7%	46.7%	42.4%	46.6%
IRSAD						
1. Most advantaged	28.1%	28.0%	24.7%	25.3%	13.6%	16.4%
2	18.3%	18.5%	18.0%	18.1%	16.2%	13.8%
3	21.9%	21.9%	22.6%	23.2%	22.5%	26.0%
4	14.2%	14.9%	16.5%	16.8%	20.9%	23.0%
5. Least advantaged	17.6%	16.7%	18.1%	16.6%	26.7%	20.9%
Remoteness						
Major cities	61.4%	62.8%	60.0%	60.9%	46.1%	48.3%
Inner regional	25.2%	24.4%	29.5%	28.8%	40.3%	37.2%
Outer regional/remote/very remote	13.4%	12.8%	10.6%	10.3%	13.6%	14.5%

Abbreviation: IRSAD, Index of Relative Socio-economic Advantage and Disadvantage.

TABLE 2 Proportions of children and adolescents with mental health diagnoses prescribed antipsychotics, 2011 and 2017.

	2011		2017		Absolute difference 2017–2011	
	N with diagnosis	Adjusted[b] % of diagnostic group receiving antipsychotic prescriptions	*N* with diagnosis	Adjusted[b] % of diagnostic group receiving antipsychotic prescriptions	% (95% CI)	*p* value
All diagnoses[a]	8418	2.0	27,412	2.9	0.9 (0.5, 1.4)[b]	<0.001
Psychoses, including schizophrenia	67	45.7	209	34.0	−11.7 (−25.8, 2.5)	0.105
Autism with behavioural problems	63	10.8	244	8.9	−1.9 (−9.5, 5.7)	0.616
Bipolar disorder	82	21.6	156	41.5	19.9 (8.7, 31.0)	<0.001
Disruptive behaviour/conduct disorder	852	1.3	2798	2.9	1.6 (0.4, 2.9)	0.011
Autism without behavioural problems	1100	3.7	3086	6.1	2.4 (0.2, 4.5)	0.030
ADHD	893	0.9	3517	1.8	0.9 (0.1, 1.7)	0.022
Eating disorders	182	1.1	523	7.2	6.1 (3.1, 9.1)	<0.001
Depression or anxiety	2872	1.5	10,183	2.5	1.0 (0.4, 1.5)	0.001
Depression	1623	1.9	4710	3.9	2.0 (1.2, 2.9)	<0.001
Anxiety	1748	1.4	7776	2.1	0.8 (0.1, 1.4)	0.030
Depression and anxiety	499	2.1	2303	4.5	2.4 (1.0, 3.8)	0.001
Sleep disorders	729	0.9	2630	0.4	−0.4 (−1.1, 0.3)	0.210
Other mental health[c]	1578	0.2	4066	0.4	0.3 (−0.1, 0.5)	0.099

Abbreviation: ADHD, attention deficit hyperactivity disorder.

[a]Only one diagnosis is recorded per patient according to hierarchy. Highest level (1: psychosis) through to lowest level (10: other). Diagnoses higher in hierarchy have stronger clinical rationale for use of antipsychotics. Numbers adjusted for age, gender, patient IRSAD, and practice characteristics (state, rurality, practice IRSAD).

[b]Analysis using logistic regression adjusted for age, gender, patient IRSAD, and practice characteristics (state, rurality, practice IRSAD). IRSAD, Index of Relative Socio-economic Advantage and Disadvantage.

[c]'Other' includes obsessive-compulsive disorder, post-traumatic stress disorder, personality disorder, substance use disorder, incontinence disorder, including bedwetting, learning and language disorders.

Higher prescribing proportions were observed in 2017 for patients diagnosed with bipolar disorder, autism without behavioural problems, depression/anxiety or behavioural disorders (ADHD, DBD/CD). However, eating disorders had the largest difference of all diagnoses (6.5 times more likely to be prescribed antipsychotics in 2017 than in 2011). For some analyses, however, numbers were low, limiting the reliability of the findings.

Analysing diagnoses associated with antipsychotic prescriptions (Figure 1), showed most patients in 2011 had diagnoses of depression/anxiety (26.8%), followed by diagnoses of autism without behavioural problems (22.3%) and psychoses (17.8%). A similar pattern was found in 2017, with percentages of 30.8% (depression/anxiety) and 25.2% (autism without behavioural problems), but DBD/CD replaced psychoses in third place (9.8%).

Off-label prescribing

Table 3 presents the results for off-label prescribing among patients with mental health diagnoses who received antipsychotic prescriptions. The proportion of off-label prescribing was higher in 2017 (79.7%) than 2011 (69.8%), with the most marked increases occurring in 15-18-year-olds, females, those living in outer regional/remote/very remote areas or the most disadvantaged areas (lowest IRSAD quintile). Analysing by diagnosis, psychotic disorders had a higher frequency of off-label prescribing in 2017 (46.7% 2017 vs. 16.3% 2011; +30.4, 95% CI [15.4, 45.5], $p < 0.001$). Numbers were too low to reliably examine changes in other disorders for which antipsychotic approvals existed (bipolar disorder, behavioural problems in autism or DBD/CD). The higher level of off-label prescribing in 2017 was mostly attributable to diagnoses of autism without behavioural problems and diagnoses of depression/anxiety.

Sociodemographic characteristics of children/adolescents prescribed antipsychotics

Adjusted analyses comparing frequencies of antipsychotic prescribing to children/adolescents with mental health diagnoses for 2011 and 2017, by sociodemographic characteristics, are presented in Table 4. In most sociodemographic groups, the proportion of patients with mental disorders prescribed antipsychotics was higher in 2017. The greatest differences were for 15–18-year-olds (3.6%, 2011 vs. 5.5%, 2017), those living in outer regional/remote/very remote areas (2.1% vs. 3.6%) and in the middle IRSAD quintile (2.3% vs. 3.7%). The male/female ratio declined from 1.8 in 2011 to 1.5 in 2017.

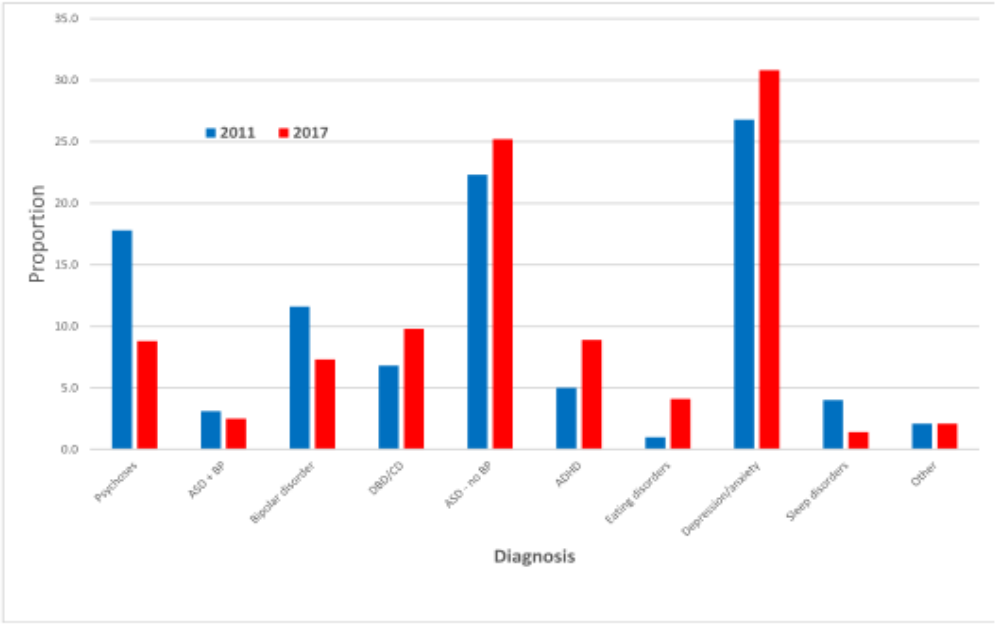


FIGURE 1 Main diagnosis among children and adolescents receiving antipsychotic prescriptions, 2011 and 2017. Only one diagnosis is recorded per patient according to hierarchy. Highest level (1: psychosis) through to lowest level (10: other). Diagnoses higher in hierarchy have stronger clinical rationale for use of antipsychotics. Numbers adjusted for age, gender, patient IRSAD, and practice characteristics (state, rurality, practice IRSAD). 'Other' includes obsessive-compulsive disorder, post-traumatic stress disorder, personality disorder, substance use disorder, incontinence disorders (including enuresis/bed wetting), learning disorder, language disorder. ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; BP, behavioural problems; CD, conduct disorder; DBD, disruptive behaviour disorder; IRSAD, Index of Relative Socio-economic Advantage and Disadvantage.

TABLE 3 Proportions of children and adolescents receiving off-label antipsychotic prescriptions by sociodemographic characteristics, 2011 and 2017.

	Adjusted prevalence[a] 2011 (%)	Adjusted prevalence[a] 2017 (%)	Overall absolute difference 2017–2011 (95% CI)[a]	*p* value
Total	69.8	79.7	10.0 (1.5, 18.4)	0.020
Age groups				
0–9 years	84.4	82.6	−1.8 (−17.7, 14.1)	0.827
10–14 years	**86.4**	81.1	−5.3 (−16.5, 5.9)	0.350
15–18 years	56.6	78.2	21.6 (10.4, 32.8)	<0.001
Gender				
Male	71.4	75.5	4.1 (−6.6, 14.8)	0.449
Female	66.9	**84.8**	17.8 (7.0, 28.6)	0.001
Rurality				
Major cities	76.7	78.4	1.6 (−9.2, 12.5)	0.767
Inner regional	69.6	80.0	10.4 (−3.6, 24.4)	0.145
Outer regional/remote/very remote	48.4	82.7	34.3 (15.1, 53.4)	<0.001
IRSAD quintile[b]				
1. Least disadvantaged	78.7	87.2	8.4 (−8.6, 25.4)	0.333
2	75.9	80.8	4.9 (−10.7, 20.5)	0.537
3	73.7	77.0	3.4 (−14.1, 20.8)	0.705
4	70.4	80.2	9.8 (−9.4, 28.9)	0.318
5. Most disadvantaged	57.7	77.4	19.7 (1.9, 37.6)	0.030

Note: Numbers marked in bold type indicate $p < .05$ (Bonferroni adjusted) for the difference between each category and the reference category for the given year. Reference categories were: 15–18 years, male, major cities and IRSAD quintile1 (Least disadvantaged).

[a]Analyses using logistic regression adjusted for age, gender, patient IRSAD, and practice characteristics (state, rurality, practice IRSAD), and reporting predicted probabilities.

[b]IRSAD, Index of Relative Socio-economic Advantage and Disadvantage.

Specific antipsychotics

For both years, the three most frequently prescribed antipsychotics were risperidone, quetiapine and olanzapine (Table 5). Risperidone was the most frequent in 2011 (48.8% of all prescriptions), and quetiapine (41.4%) in 2017. In both years, quetiapine was the most commonly prescribed antipsychotic for psychoses (37.2%, 2011; 33.0%, 2017), bipolar disorder (50.0%; 58.2%) and depression/anxiety (72.0%; 76.2%), but risperidone was the most commonly prescribed antipsychotic for autism, ADHD and disruptive behaviours. Olanzapine constituted 41.7% of antipsychotic prescriptions for eating disorders in 2017.

Psychotropic co-prescribing

Co-prescribing of other classes of psychotropic drugs was common (Supporting Information Table S6). In adjusted analyses, 69.7% of patients in 2011 and 69.4% in 2017 were prescribed different classes of psychotropics the same day as antipsychotics. In both years, antidepressants were the most co-prescribed psychotropic medications for most disorders, followed by ADHD medications. The third most frequently prescribed concurrent medication changed from anxiolytics in 2011 to melatonin in 2017.

Sensitivity analyses

Table 1 was replicated without restricting the sample to regular patients. The results are presented in Supporting Information, Table S7. Results were near identical, with very minor changes in predicted proportions, confidence intervals and *p*-values.

DISCUSSION

This study analysed patterns of antipsychotic prescribing to children/adolescents in Australian primary care in 2011 and 2017. There are three notable findings. Firstly, compared with 2011, patients with any mental health diagnosis in 2017 were more likely to be prescribed antipsychotics. Although frequencies of antipsychotic prescribing remained relatively stable for psychoses, autism with behavioural problems, and sleep disorders, patients with other diagnoses were more likely to be prescribed antipsychotics in

TABLE 4 Proportions of children and adolescents with mental health diagnoses prescribed antipsychotics, by sociodemographics, 2011 and 2017.

	2011		2017		Absolute difference 2017–2011	
	Number with mental health diagnosis	Diagnoses prescribed AP (%)[a]	Number with mental health diagnosis	Diagnoses prescribed AP (%)[a]	% (95% CI)[a]	*p* value
Total	8418	2.0	27,412	2.9	0.9 (0.5, 1.4)	<0.001
Age group						
0–9 years	3722	**0.6**	11,366	**0.9**	0.3 (−0.2, 0.8)	0.270
10–14 years	1971	**2.2**	6926	**3.1**	0.9 (0.03, 1.7)	0.043
15–18 years	2725	**3.6**	9120	**5.5**	1.8 (1.0, 2.7)	<0.001
Gender						
Male	4486	**2.6**	14,603	**3.5**	0.9 (0.2, 1.6)	0.016
Female	3928	**1.4**	12,791	**2.4**	0.9 (0.5, 1.4)	<0.001
Rurality						
Major cities	5049	**1.7**	16,695	**2.5**	0.8 (0.2, 1.4)	0.012
Inner regional	2481	**2.4**	7881	**3.3**	0.9 (0.1, 1.7)	0.024
Outer regional/remote/very remote	888	**2.1**	2836	**3.6**	1.5 (0.4, 2.6)	0.006
IRSAD quintile						
1. Least disadvantaged	2076	**1.1**	6929	**1.9**	0.8 (0.2, 1.3)	0.006
2	1516	**2.1**	4967	**2.6**	0.4 (−0.5, 1.4)	0.341
3	1904	**2.3**	6349	**3.7**	1.5 (0.4, 2.5)	0.005
4	1392	**2.2**	4614	**3.4**	1.2 (0.2, 2.2)	0.019
5. Most disadvantaged	1526	**2.3**	4543	**3.0**	0.7 (−0.1, 1.5)	0.097

Note: Numbers marked in bold type indicate $p < .05$ (Bonferroni adjusted) for the difference between each category and the reference category for the given year. Reference categories were: 15–18 years, male, major cities and IRSAD quintile1 (Least disadvantaged).

Abbreviations: AP, antipsychotic; IRSAD, Index of Relative Socio-economic Advantage and Disadvantage.

[a]Analyses using logistic regression adjusted for age, gender, patient IRSAD, and practice characteristics (state, rurality, practice IRSAD), and reporting predicted probabilities.

TABLE 5 Most prescribed antipsychotics associated with each diagnostic group, with clinical hierarchy[a], 2011 and 2017.

	2011					2017				
	AP total	N patients	AP type	n	%[b]	AP total	N patients	AP type	n	%[b]
All	209	191	RIS	102	48.8	963	893	QUE	399	41.4
			QUE	72	34.4			RIS	368	38.2
			OLAN	21	10.0			OLAN	103	10.7
Psychoses, including schizophrenia	43	33	QUE	16	37.2	103	81	QUE	34	33.0
			RIS	14	32.6			OLAN	24	23.3
			OLAN	10	23.3			ARIP	15	14.6
Autism with behavioural problems	7	7	RIS	7	100.0	26	23	RIS	19	73.1
								OLAN	<5	-
								QUE	<5	-
Bipolar disorder	24	21	QUE	12	50.0	79	66	QUE	46	58.2
			RIS	<5	-			OLAN	13	16.5
			OLAN	<5	-			RIS	8	10.1
Disruptive behaviour/conduct disorders	13	13	RIS	11	84.6	80	76	RIS	60	75.0
			QUE	<5	-			QUE	9	11.3
								OLAN	5	6.3
Autism spectrum disorders	47	44	RIS	42	89.4	217	206	RIS	177	81.6
			PAL	<5	-			QUE	18	8.3
			QUE/PER	<5	-			ARIP	10	4.6
Attention deficit hyperactivity disorders	10	10	RIS	8	80.0	79	78	RIS	57	72.2
			QUE/PER	<5	20.0			QUE	14	17.7
								ARIP	<5	-
Eating disorders	<5	<5	RIS	<5	-	36	34	QUE	20	55.6
			OLAN	<5	50.0			OLAN	15	41.7
								RIS	<5	-
Depression/anxiety	50	50	QUE	36	72.0	311	300	QUE	237	76.2
			RIS	14	28.0			OLAN	31	10.0
			OLAN	10	20.0			RIS	26	8.4
Sleep disorders	8	7	RIS	<5	-	14	14	QUE	10	71.4
			QUE	<5	-			RIS	<5	-
			OLAN/HAL	<5	-			OLAN/HAL	<5	-
Other[c]	5	<5	RIS	<5	-	18	15	QUE	9	50.0
			QUE	<5	-			RIS	<5	-
								OLAN	<5	-

Note: Numbers and percentages omitted where cell size <5 patients.

Abbreviations: AP, antipsychotic; ARIP, aripiprazole; HAL, haloperidol; MEL, melatonin; OLAN, olanzapine; PER, periciazine; QUE, quetiapine; RIS, risperidone.

[a] Only one diagnosis is recorded per patient according to hierarchy. Highest level (1: psychosis) through to lowest level (10: other). Diagnoses higher in hierarchy have stronger clinical rationale for use of antipsychotics.

[b]Percentages reported as unadjusted proportion of all patients on antipsychotics for each diagnostic group. Patients may have had more than one co-prescribed medication class.

[c]'Other' includes obsessive-compulsive disorder, post-traumatic stress disorder, personality disorder, substance use disorder, incontinence disorder, including bed-wetting, learning disorder, and language disorders.

2017. Secondly, off-label prescribing was higher in 2017 (79.7%) than 2011 (69.8%), especially for females, 15-18-year-olds, and patients living in disadvantaged areas and remote geographical regions. Thirdly, in both years, almost 70% of patients prescribed antipsychotics were co-prescribed other classes of psychotropics.

Diagnostic patterns associated with antipsychotic prescriptions

Consistent with international (Carton et al., 2015) and Australian (Dharni & Coates, 2018; Ellis & Angley, 2013) findings, we observed high levels of off-label prescribing, increasing from 69.8% in 2011 to 79.7% in 2017.

Most patients who were prescribed antipsychotics had off-label diagnoses of depression/anxiety, with comparatively low frequencies of prescribing associated with ADHD. This contrasts with international findings. Several studies examining antipsychotic prescription rates across all prescribers, and reporting diagnoses with hierarchy (Crystal et al., 2009), and without hierarchy in the United States (Edelsohn et al., 2017; Olfson et al., 2015), and Germany (Bachmann et al., 2014), have found ADHD was one of the two most frequent diagnoses. The difference likely reflects differing regulatory landscapes. ADHD patients in Australia are generally prescribed stimulants by specialists (Australian ADHD Professionals Association, 2023). Although GPs can co-manage treatment of children with ADHD, complex cases likely to be considered for non-routine medications such as antipsychotics may be solely managed by paediatricians or child psychiatrists. Even so, despite being low in number, the proportion of patients with ADHD prescribed antipsychotics in primary care doubled from 2011 to 2017.

Several studies have reported antipsychotic prescription frequencies associated with depression/anxiety diagnoses similar to those found in our study. A U.S. study (Edelsohn et al., 2017) and a Finnish study (Varimo et al., 2020) found depression was the most frequent diagnosis associated with antipsychotics in 13-17-year-olds, and a Norwegian study reported anxiety disorders and depression were the most common diagnoses in females 0-18-years (Nesvag et al., 2016). However, none of these studies used a hierarchical approach to associate diagnoses with prescriptions. It is possible that, for some patients, our diagnosis algorithm flagged comorbid depression/anxiety as the primary reason for antipsychotic prescribing when diagnoses higher in the hierarchy had not been captured in our dataset. However, our findings are consistent with international studies that used a range of techniques to link diagnoses with prescriptions, suggesting that the finding may be robust.

A Canadian study found GPs prescribed antipsychotics most often for depression and anxiety, whereas paediatricians prescribed them most often for ADHD, and child psychiatrists for psychotic disorders, in 2010/11 (Ronsley et al., 2013). Therefore, the high prescribing rates for depression/anxiety may indicate a prescribing pattern particular to general practice.

We also found increases in antipsychotic prescribing associated with bipolar disorder, DBD/CD, autism without behavioural problems, and eating disorders.

TGA approvals (Therapeutic Goods Administration, 2023) and guidelines for juvenile bipolar disorder (McClellan et al., 2007; Therapeutic Guidelines, 2021) recommend antipsychotics for treating manic symptoms. Therefore, the high percentage of patients (41.5% in 2017) with bipolar disorder prescribed antipsychotics is not surprising. However, bipolar disorder also had the greatest change (+19.9%) in prescribing from 2011 to 2017, which may indicate more liberal attitudes towards prescribing antipsychotics, or switching from epilepsy drugs such as valproate due to growing safety concerns (Medicines and Healthcare Products Regulatory Agency [MHRA], 2022).

More liberal prescribing practices may also apply to the other disorders showing an increase in prescribing. For example, the increase in prescribing for autism, without the behavioural problems required for on-label prescribing, may indicate a growing belief that antipsychotics are suitable for a range of autistic symptoms. Alternatively, GPs may have omitted mention of behavioural issues in diagnostic fields, resulting in misclassification of some autism diagnoses.

The increased off-label prescribing of antipsychotics for young patients with eating disorders is also concerning. Prescribing of medications to patients with eating disorders is problematic due to patients' poor nutritional status affecting drug metabolism and risk of adverse events (National Institute for Health and Care Excellence [NICE], 2017). The TGA has not approved antipsychotic use in eating disorders for any age-group. Nonetheless, the advantage of weight gain as an effect of antipsychotic use in anorexia nervosa has led to the recommendation of antipsychotics, in particular olanzapine, as a treatment with some supportive evidence (Aigner et al., 2011), and the Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for eating disorders (Hay et al., 2014) document level-II evidence supporting use of olanzapine and amisulpride.

Sociodemographic characteristics of children/adolescents prescribed antipsychotics

Antipsychotic prescribing was more prominent in older age-groups and increased monotonically with age, consistent with findings from 2007 to 2012 in the United States, United Kingdom, Denmark and Germany (Kalverdijk et al., 2017) and in Norway in 2010 (Nesvag et al., 2016).

The prescribing gap between the two genders decreased from 2011 to 2017 (male/female ratio declined from 1.8 to 1.5), and off-label prescribing was higher in females than males in 2017. Supporting our findings, a recent Norwegian study found incident antipsychotic prescribing for females exceeded that in males for the first time in 2011, with the trend continuing through to 2017 (Varimo et al., 2020). The researchers speculated this might be due to increased antipsychotic prescribing for anxiety, mood disorders and insomnia, which are usually more prevalent in adolescent females. In line with this, in our study, the proportion of patients with depression/anxiety diagnoses prescribed antipsychotics was higher in 2017 than 2011.

With respect to socioeconomic factors, those in the most advantaged areas (highest quintile), were least likely to have antipsychotics associated with mental disorders. Although the proportion of patients with diagnoses prescribed antipsychotics generally increased as disadvantage increased, only those in the middle quintile were statistically significantly more likely to be prescribed antipsychotics for their diagnoses. Off-label prescribing frequencies were similar across all quintiles in each year, except that they were markedly higher in the lowest quintile in 2017 compared with 2011. These results are suggestive of increased frequencies of prescribing to patients with increasing disadvantage, similar to that observed in

U.K. (Nunn et al., 2020) and Swedish (Crump et al., 2011) studies. This may be due to poorer access to non-pharmacological treatment options in socially disadvantaged areas (Nunn et al., 2020). However, the low numbers in our study did not permit analyses stratified by diagnosis and sociodemographics, limiting our understanding of the factors contributing to the observed pattern in antipsychotic prescribing. Future studies examining prescribing practices by age, rurality and socioeconomic status in more detail are needed.

Choice of antipsychotic

The three most frequently prescribed antipsychotic agents were risperidone, quetiapine and olanzapine, consistent with findings in 11 of 14 countries (Hálfdánarson et al., 2017).

In the United States, several European countries, and Australia from 2005/6 to 2014 (Hálfdánarson et al., 2017), risperidone predominated. As in our study, international studies found risperidone prescribed mostly for hyperkinetic disorders (ADHD/CD) and autism (Bachmann et al., 2014; Murphy et al., 2013). However, in our study, risperidone was replaced by quetiapine in 2017 as the most frequently prescribed antipsychotic. This shift to quetiapine prescribing may be related to high prescribing rates for depression/anxiety, as observed in Finland from 2008 to 2017 (Varimo et al., 2020).

Notably, olanzapine, which was prescribed mainly for eating disorders, is not approved in Australia for any child or adolescent disorders. It is the antipsychotic agent most strongly associated with weight gain, and consequent cardiometabolic problems in young patients, putting paediatric patients at high risk of adverse events and long-term harm (Maayan & Correll, 2011).

Psychotropic co-prescribing

Levels of concurrent psychotropic prescribing were high. In adjusted analyses, around 69% of patients were prescribed other psychotropics the same day as antipsychotics, in both 2011 and 2017. Corroborating our findings, a Finnish population-wide prescription registry reported 44.9% of antipsychotic users from 2008 to 2016 had at least one concomitant psychotropic, although in their study polypharmacy rates were higher in 2016 (51.0%) than in 2008 (41.0%) (Varimo et al., 2023).

Consistent with Varimo et al. (2023), and a systematic review of antipsychotic polypharmacy in children/adolescents (primarily in the United States) (Toteja et al., 2014), we found antidepressants were most frequently co-prescribed with antipsychotics. This was also congruent with findings from an earlier (2013) Pharmaceutical Benefits Scheme (PBS) report (Morrison et al., 2014), and a Canadian study characterising antipsychotic prescribing for young people up to 25 years from 2000 to 2007 (Murphy et al., 2013).

Drivers of off-label antipsychotic prescribing

In Australia, there are few reliable up-to-date resources to guide treatment of children/adolescents with psychotropic medications (Hazell, 2018), so clinicians must rely on alternative resources. These resources include consensus guidelines (Brett, 2015), adult guidelines (Doey et al., 2007), and international guidelines and approvals (Smogur et al., 2022). Prescribing patterns in our study may reflect advice provided in these resources.

For example, olanzapine is approved for adolescents with schizophrenia and bipolar disorder in the United States (Schulz & Haight, 2013), and for adults with these conditions in Australia (Eli Lilly & Co, 2019). Therefore, the relatively high prescribing in our study may be due to clinicians extrapolating medication effectiveness from these approvals. Similarly, quetiapine is TGA-approved for depression and anxiety disorders in Australian adults (Brett, 2015), and appears to be increasingly prescribed for anxiety in children/adolescents (Monasterio & McKean, 2013). Dharni and Coates (2018) found quetiapine prescribed for anxiety (23.5%) and insomnia (76.5%) in 12-17-year-olds—two conditions for which quetiapine is commonly prescribed for adults (Brett, 2015). Consistent with this, we found quetiapine was most frequently prescribed for depression/anxiety in both 2011 and 2017. Also, in the early 2000s, pharmaceutical companies in the United States actively promoted quetiapine for off-label conditions in children/adolescents, such as anxiety, depression, PTSD and insomnia (U.S. Department of Justice, 2010). Such marketing campaigns can impact perceptions of safety and efficacy of medications, resulting in more liberal attitudes to prescribing, and increased off-label prescribing (Fickweiler et al., 2017).

Increased off-label prescribing of antipsychotics to children/adolescents in the United States has prompted health authorities to implement programs aiming to improve antipsychotic prescribing to children/adolescents in primary care (Penfold et al., 2022). One such programme resulted in a 51% relative decrease in antipsychotic prescribing from 2006 to 2013 (Barclay et al., 2017). Concerns about antipsychotic use in Australia prompted the Drug Utilisation Subcommittee (DUSC) of the PBS to prepare reports on antipsychotic prescribing in adults (NPS Medicine Wise Professional, 2020), and children/adolescents (Morrison et al., 2014). The report on adult prescribing resulted in the initiation of a programme providing GPs support and advice on managing patients with and without antipsychotics (NPS Medicine Wise Professional, 2020), resulting in a 7.3% relative decrease in antipsychotic prescribing. Results from our study suggest the need for similar strategies to improve antipsychotic prescribing in children/adolescents.

Strengths and limitations

MedicineInsight is a large primary care database, covering 7% of GPs and 13% of patients who attended GPs in Australia in 2018/19. Although some states, regions, and higher IRSAD quintiles were overrepresented compared with census data, the patients in the database are considered representative of those attending Australian general practice (NPS MedicineWise, 2020a). MedicineInsight provides comprehensive data on medications prescribed, including both private and PBS-subsidised prescriptions, and reasons for encounters. However, numbers were low in some analyses, limiting the reliability of some statistical findings.

Some patients had multiple diagnoses within a year, so it was not always possible to determine the exact diagnosis for which antipsychotics were prescribed. In some cases, terms used in the diagnosis algorithm represent both symptoms and diagnoses, which could result in overestimated prevalences of some common diagnoses, such as anxiety or behavioural disorders. Medications are often initiated by psychiatrists or paediatricians (Kjosavik et al., 2017), and some specialists' diagnoses might not be captured in our dataset. Similarly, diagnostic information in GP progress notes would not be captured, and historical information might not routinely be recorded at each clinical encounter. Also, anecdotal evidence suggests physicians may be reluctant to formally diagnose young patients, to reduce the risk of stigma (Olfson et al., 2015). Therefore, some diagnoses may be absent from MedicineInsight records, resulting in underestimates of the numbers of prescriptions associated with approved indications, and overestimates of off-label prescribing. Furthermore, GP diagnoses may not match research criteria and may not be equivalent to diagnoses made by mental health specialists.

Medicine Insight records prescriptions written, not necessarily dispensed. Therefore, prescription frequencies may overestimate drug use. Finally, our findings only apply to general practice, and cannot be generalised to other settings.

CONCLUSION

This study fills a gap in current understandings of antipsychotic prescribing to children/adolescents in Australia. Overall, the findings suggest an increase in GP off-label prescribing from 2011 to 2017, especially for depression/anxiety.

There also appears to be an increasing tendency for patients in more disadvantaged areas to be prescribed antipsychotics for mental disorders, and a growing tendency to prescribe more to females. These changes in prescribing may be partly due to GPs having inadequate training and/or mentoring, and a lack of appropriate referral pathways. Future studies are needed to monitor antipsychotic prescribing trends, to assess the impact of COVID and other factors affecting mental health, and further investigate prescribing practices to paediatric patients in Australian primary care.

AUTHOR CONTRIBUTIONS

Julie Klau: Conceptualization; formal analysis; funding acquisition; methodology; project administration; writing—original draft. **David Gonzalez**: Data curation; formal analysis; funding acquisition; methodology; supervision; writing—review and editing. **Melissa Raven**: Funding acquisition; methodology; supervision; writing—review and editing. **Jon Jureidini**: Conceptualization; funding acquisition; methodology; project administration; supervision; writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors have declared that they have no competing or potential conflicts of interest.

DATA AVAILABILITY STATEMENT

The dataset used in this research is not publicly available due to privacy and ethical restrictions.

ETHICAL CONSIDERATIONS

The independent MedicineInsight Data Governance Committee approved this study (protocol 2019-029), and the Human Research Ethics Committee of the University of Adelaide exempted it from full ethical review due to the use of non-identifiable data.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX A

Australia's health system

- ✓ Medicare—a universal publicly-funded health insurance scheme available to all Australian and New Zealand citizens, permanent residents, and some overseas visitors
- ✓ Medicare Benefits Scheme (MBS) provides:
  - Low or no-cost medical services, including general practitioner (GP) consultations, tests, scans
  - Free public hospital care
  - Subsidies for some services in private hospitals
- ✓ Pharmaceutical Benefits Scheme (PBS) (and the Repatriation PBS [RPBS] for eligible war veterans and their dependents) provides:
  - Low or no-cost medicines for a large range of medicinal products that have been approved by Australia's regulatory authority - the Therapeutic Goods Administration (TGA)
- ✓ MBS and PBS 'safety net' that annually caps out-of-pocket expenses for patients
- ✓ Private health insurance is incentivised by the Australian Government by providing a means-tested rebate to assist with the cost of insurance.
- ✓ Private health insurance provides cover for private hospital patients and other health services not subsidised or partially subsidised by Medicare (e.g., dental, physiotherapy, non-PBS-subsidised medicines)

Mental health in primary care

- ✓ Mental health related issues are the most common reason for presentation to GPs
- ✓ GPs prescribe approximately 78% of all PBS-subsidised antipsychotics
- ✓ GPs prescribe approximately 35% of PBS-subsidised antipsychotics to children under 15 years

- ✓ GPs are the major providers of MBS-subsidised mental health services
- ✓ Since 2006, Medicare has subsidised psychological therapies via the Better Access initiative (capped at 10 sessions annually)

For more information on Medicare: https://www.health.gov.au/topics/medicare/about.

For more information on the PBS: https://www.pbs.gov.au/info/about-the-pbs.

5.7 Chapter 5 Supplementary information

Supporting Information

Article

Antipsychotic prescribing patterns in children and adolescents attending Australian general practice in 2011 and 2017.

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Table S1. Indications for use of antipsychotics in children and adolescents in Australia, as listed in Product Information documents approved by Australian Therapeutic Goods Administration

Medication	Medicine Name	Age range	Indicated use
Antipsychotics			
Chlorpromazine	Largactil	No age limits specified	Schizophrenia, mania, psychotic depression Severe behavioural disturbances in children with mental retardation or autism: treatment of self-injurious, aggressive behaviour or overactivity Nausea, vomiting
Clozapine	Clopine	> 16 years	Treatment resistant schizophrenia
Haloperidol	Serenace	> 2 years	Severely aggressive or hostile children, Tourettes
Lurasidone[a]	Latuda/Lupin	> 12 years	Schizophrenia
Periciazine	Neulactil	1-3 years	Not recommended – contraindicated < 1 year
Periciazine	Neulactil	3-6 years	Use reserved for exceptional situations in specialist units
Periciazine	Neulactil	> 6 years	Severe anxiety, impulsiveness, aggression, schizophrenia maintenance
Quetiapine	Seroquel	10-17 years	Monotherapy for treatment of acute mania associated with bipolar 1 disorder
Quetiapine	Seroquel	13-17 years	Schizophrenia
Risperidone	Risperdal	> 14 years	Schizophrenia
Risperidone	Risperdal	> 5 years	Treatment of conduct disorders or other disruptive behaviour disorders
Risperidone	Risperdal	Adolescents	Adolescents and adults with sub-average intellectual function or mental retardation and prominent destructive behaviours (e.g., aggression, impulsivity, self-injurious behaviours)
Risperidone	Risperdal	Children and adolescents	Behavioural disorders associated with autism in children and adolescents
Trifluoperazine	Stelazine[b]	>2 years (with caution)	Schizophrenia, manic depressive psychosis Relief of delusions, hallucinations and confusion Control of tremulousness and aggressive behaviour in alcoholics Nausea and vomiting Take particular care in administering Stelazine to children with acute illnesses (e.g. chicken pox, CNS infections, measles, gastroenteritis) or dehydration
Amisulpride	Solian		None
Aripiprazole	Abilify		None
Asenapine	Saphris		None
Brexpiprazole	Rexulti		None
Droperidol	Droleptan		Used only as injectable for anaesthesia in children 2 to 12 years
Flupenthixol	Fluanxol		None
Fluphenazine	Modecate		None
Olanzapine	Zyprexa		None
Paliperidone	Invega		None
Ziprasidone	Zeldox		None
Zuclopenthixol	Clopixol		None

a. Lurasidone was approved for schizophrenia in adolescents 13 to 17 years in April 2018

b. Stelazine is no longer registered on the Therapeutic Goods Administration (TGA) website. Last product information document updated 31 August 2016.

Table S2. Terms used to extract diagnostic information from MedicineInsight (diagnosis, reason for visit, reason for prescription)

Code	Diagnostic category	Relevant terms
SCHIZ	Psychoses, including schizophrenia	schizophrenia, schizoaffective, psychosis, delusions, hallucinations, paranoid, thought disorder, catatonic
BIP	Bipolar disorder	bipolar, manic depressive disorder, manic, mania, BPAD, bipolar affective disorder, mood swing
DBD	Disruptive behaviour disorder/ conduct disorder	CD, ODD, DBD, DMDD, disruptive, aggression, behaviour disorder, disruptive mood dysregulation disorder, defiance
ASD	Autism spectrum disorder	ASD, PDD, autism, asperger's, RETT syndrome
ADHD	Attention deficit hyperactivity disorder	ADHD, ADD, AHD, attention, hyperactive, hyperkinetic
ANX	Anxiety disorder	anxiety, anxious, phobia, GAD, generalised anxiety disorder, panic disorder/ panic attack, agoraphobia, neurotic
DEP	Depressive disorder	depression, dysthymia, melancholia, anhedonia, low moods, sad mood
ED	Eating disorder	anorexia, bulimia, binge eating disorder, body dysmorphia, orthorexia, PICA
PTSD	Post-traumatic stress disorder	PTSD, CPTSD, post-traumatic stress, complex trauma
OCD	Obsessive-compulsive disorder	OCD, obsessions, compulsions, trichotillomania,
PD	Personality disorder	PD, personality disorder, (antisocial, schizoid, schizoid, narcissistic, avoidant)
SUD	Substance use disorder	SUD, addiction, marijuana, cannabis, LSD, ecstasy, heroin, cocaine, MDMA
SLEEP	Sleep disorders, including insomnia	sleep, insomnia, narcolepsy, Willis-Ekbom, RLS, restless leg syndrome, hypersomnia
INCONT	Incontinence disorders, including enuresis	bed wetting, enuresis, incontinence
LD	Learning disorder	LD, learning disorder, dyslexia, dyscalculia, dysgraphia, reading problem,
LANG	Language disorder	language, apraxia, speech disorder

Note. After extracting diagnoses with key terms, all reasons from free text fields were manually checked to exclude non-diagnostic entries (e.g., "mother thinks child is…."; "without psychotic").

Misspellings were also examined and included where appropriate (e.g., "austism", "asbergers", "dislexia", "biopolar", etc.).

Table S3. Reasons associated with antipsychotic prescriptions where there was no record of any psychiatric diagnosis

	2011		2017	
Reason associated with diagnosis	Number of patients	%	Number of patients	%
Tourettes	3	1.9	4	1.0
Epilepsy	6	3.9	7	1.8
Intellectual disability	2	1.3	3	0.8
Suicide/self-harm	1	0.6	4	1.0
Mental health care plans/ referrals	20	13.0	106	27.0
Vomiting/nausea	2	1.3	4	1.0
Repeat scripts	18	11.7	57	14.5
Infections	27	17.5	38	9.7
Skin conditions	3	1.9	6	1.5
Pain/migraine	3	1.9	6	1.5
Asthma	1	0.6	1	0.3
Allergy	1	0.6	2	0.5
Checks up/follow-up	2	1.3	13	3.3
Vaccination	0	0.0	6	1.5
Contraception/reproductive	1	0.6	4	1.0
Miscellaneous	64	41.6	131	33.4
Total patients	154	100.0	392	100.0

Note: Analysis of diagnoses using hierarchy. Diagnoses with TGA approval near top of hierarchy (Tourettes syndrome, epilepsy, nausea).

For all categories, the antipsychotic may have been given for a psychiatric reason that had not been recorded in our dataset. For patients with mental health plans, the diagnosis may be recorded in progress notes or specialist records. For other prescriptions, where there was no neurological or psychiatric reason on record, the reason for visit to the GP was recorded (e.g., infection).

Table S4. Algorithm for determining off-label prescribing

Diagnosis	On-label	Off-label
Psychosis, including schizophrenia	QUE + age >12 years	QUE + age<13 years
	RIS + age>14 years	RIS + age<15 years
	LUR + age>12 years	LUR + age<13 years
	PER + age>6 years	PER + age<7 years
	CLOZ + age>17 years	CLOZ + age<17 years
	TRIFLU + age>2 years	TRIFLU + age<3 years
	CHLOR	AMIS, ARIP, ASEN, BREX, DROP, FLUX, FLUZ, HAL, OLAN, PAL, ZIP, ZUC
Autism with behaviour problems	RIS, CHLOR	HAL + age<3 years
	HAL + age>2 years	PER + age<7 years
	PER + age>6 years	AMIS, ARIP, ASEN, BREX, CLOZ, DROP, FLUX, FLUZ, LUR, OLAN, PAL, QUE, TRIFLU, ZIP, ZUC
Bipolar disorder[a]	QUE + age>9 years	QUE + age<10 years
	CHLOR	AMIS, ARIP, ASEN, BREX, CLOZ, DROP, FLUX, FLUZ, HAL, LUR, OLAN, PAL, PER, RIS, TRIFLU, ZIP, ZUC
Disruptive behaviour disorder/ conduct disorder	RIS + age>5 years	RIS + age<6 years
	PER + age>6 years	PER + age<7 years
	HAL + age>2 years	HAL + age<3 years
	CHLOR	AMIS, ARIP, ASEN, BREX, CLOZ, DROP, FLUX, FLUZ, LUR, OLAN, PAL, QUE, TRIFLU, ZIP, ZUC
Autism spectrum disorder		AMIS, ARIP, ASEN, BREX, CHLOR, CLOZ, DROP, FLUX, FLUZ, HAL, LUR, OLAN, PAL, PER, QUE, RIS, TRIFLU, ZIP, ZUC
Attention deficit hyperactivity disorder		AMIS, ARIP, ASEN, BREX, CHLOR, CLOZ, DROP, FLUX, FLUZ, HAL, LUR, OLAN, PAL, PER, QUE, RIS, TRIFLU, ZIP, ZUC
Eating disorders		AMIS, ARIP, ASEN, BREX, CHLOR, CLOZ, DROP, FLUX, FLUZ, HAL, LUR, OLAN, PAL, PER, QUE, RIS, TRIFLU, ZIP, ZUC
Depression or anxiety	PER + age>6 years + diagnosis of anxiety	PER + age<7 years
		AMIS, ARIP, ASEN, BREX, CHLOR, CLOZ, DROP, FLUX, FLUZ, HAL, LUR, OLAN, PAL, QUE, RIS, TRIFLU, ZIP, ZUC
Sleep problems		AMIS, ARIP, ASEN, BREX, CHLOR, CLOZ, DROP, FLUX, FLUZ, HAL, LUR, OLAN, PAL, PER, QUE, RIS, TRIFLU, ZIP, ZUC
Other[b]		AMIS, ARIP, ASEN, BREX, CHLOR, CLOZ, DROP, FLUX, FLUZ, HAL, LUR, OLAN, PAL, PER, QUE, RIS, TRIFLU, ZIP, ZUC

Abbreviations for medications: AMIS, amisulpride; ARIP, aripiprazole; ASEN, asenapine; BREX, brexpiprazole; CHLOR, chlorpromazine; CLOZ, clozapine; DROP, droperidol; FLUX, flupenthixol; FLUZ, fluphenazine; HAL, haloperidol; LUR, lurasidone; OLAN, olanzapine; PAL, paliperidone; PER, periciazine; QUE, quetiapine; RIS, risperidone; TRIFLU, trifluoperazine; ZIP, ziprasidone; ZUC, zuclopenthixol

a. Antipsychotics are approved for children/adolescents only for manic episodes within bipolar 1 disorder. For the purposes of this algorithm, any prescription of an antipsychotic with bipolar disorder was assumed to be for mania, and therefore, on-label.

b. Other diagnoses include obsessive-compulsive disorder, post-traumatic stress disorder, personality disorder, substance use disorder, incontinence disorders (including enuresis/bed wetting), learning disorder, language disorder.

Table S5. Changes in proportions of patients with diagnoses from 2011 to 2017, without hierarchy

	Predicted % 2011	Predicted % 2017	Difference 2011 to 2017 (95% CI)[a]	p value
Any mental health diagnosis	4.22	6.74	2.52 (2.21, 2.83)	<0.001
Psychosis	0.03	0.05	0.02 (0.01, 0.03)	0.001
Bipolar disorder	0.04	0.04	-0.001 (-0.02, 0.01)	0.550
ASD	0.63	0.82	0.20 (0.12, 0.27)	<0.001
DBD/CD	0.47	0.72	0.25 (0.18, 0.32)	<0.001
ADHD	0.55	1.12	0.57 (0.44, 0.70)	<0.001
ED	0.09	0.13	0.04 (0.02, 0.06)	<0.001
Depression	0.83	1.29	0.45 (0.38, 0.53)	<0.001
Anxiety	0.92	2.17	1.25 (1.14, 1.37)	<0.001
Sleep	0.44	0.95	0.51 (0.42, 0.60)	<0.001
OCD	0.08	0.09	0.01 (-0.01, 0.03)	0.186
PTSD	0.03	0.05	0.02 (0.01, 0.04)	<0.001
PD	0.02	0.02	0.004 (-0.005, 0.01)	0.375
SUD	0.06	0.06	-0.00 (-0.02, 0.02)	0.990
Incontinence/enuresis	0.39	0.40	0.01 (-0.03, 0.05)	0.726
Learning disorder	0.09	0.10	0.02 (-0.004, 0.04)	0.117
Language disorder	0.36	0.55	0.19 (0.13, 0.25)	<0.001

Abbreviations: ASD, autism spectrum disorder; DBD, disruptive behaviour disorder; CD, conduct disorder; ADHD, attention deficit hyperactivity disorder; ED, eating disorder; OCD, obsessive-compulsive disorder; PTSD, post-traumatic stress disorder; PD, personality disorder; SUD, substance use disorder

a. Analyses using logistic regression, adjusted for age, gender, patient IRSAD, and practice characteristics (state, rurality, practice IRSAD). IRSAD, Index of Relative Socio-economic Advantage and Disadvantage.

Table S6. Number of patients co-prescribed other classes of psychotropics with an antipsychotic, by diagnosis with hierarchy

	2011				2017		
Diagnoses	AP (N)	Any concurrent n (%)[a]	Most frequent concurrent (n[%])[a]		AP (N)	Any concurrent n (%)[a]	Most frequent concurrent (n[%])[a]
All	191	132 (69.1)	ADEP(108 [56.54])		893	660 (73.9)	ADEP (511[57.22])
			ADHD (24[12.57]) STIM(17[8.90]) ADREN(11[5.76])				ADHD (186[20.83]) STIM(135[15.12]) ADREN(92[10.30])
			ANXIO (24[12.57])				MEL (139[15.57])
Psychoses, including schizophrenia	33	27 (81.82)	ADEP (25[75.76])		81	45 (55.56)	ADEP (39[48.15])
			ANXIO (8[24.24])				ANXIO (9[11.11])
			SED <5				MEL (8[9.88])
Autism with behavioural problems	7	2 (28.57)	ADHD <5		23	14 (60.87)	ADEP (10[43.48])
			ANXIO <5				ADHD (6[26.09]) STIM(6[26.09]) ADREN <5
							MEL (2[8.70])
Bipolar disorder	21	12 (57.14)	ADEP (11[52.38])		66	45 (68.18)	ADEP (39[59.1])
			ANXIO (94[19.05])				ADHD (7[10.61]) STIM(6[9.09]) ADREN <5
			SED <5				ANXIO&SED(6[9.09])
Disruptive behaviour/conduct disorders	13	8 (61.54)	ADEP (6[46.15])		76	51 (67.11)	ADHD (30[39.47]) STIM (19[25.0]) ADREN (21[27.63])
			ADHD (5[38.46]) STIM <5 ADREN <5				ADEP (24[31.58])
			ANXIO <5				MEL (13[17.11])
Autism spectrum disorder	44	24 (54.55)	ADEP (13[29.55])		206	134 (65.05)	ADEP (84[40.78])
			ADHD (12[27.27]) STIM(8[18.18]) ADREN(5[11.36])				ADHD (66[32.04]) STIM(51[24.76]) ADREN(27[13.11])
			MEL <5				MEL (25[12.14])
Attention deficit hyperactivity disorder	10	5 (50.0)	ADHD <5		78	60 (76.92)	ADHD (51[65.38]) STIM (45[57.7]) ADREN (20[25.6])
			ADEP <5				ADEP (29[37.18])
							MEL (5[6.41])
Eating disorders	<5	<5	ADEP <5		34	30 (88.24)	ADEP (28[82.35])
							MEL (4[11.76])
							ANXIO <5
Depression/anxiety	50	42 (84.0)	ADEP (41[82.0])		300	263 (87.67)	ADEP (249[83.0])
			ANXIO (7[14.0])				MEL (67[22.33])
			SED <5				ANXIO (36[12.0])
Sleep	7	7 (100.0)	ADEP (5[71.4])		14	11 (78.57)	MEL (7[50.0])
			MEL <5				ADEP <5
			ANXIO&SED <5				ADHD <5
Other[b]	<5	<5	ADEP <5		15	7 (46.67)	ADEP (5[33.33])
							SED&MEL <5
							ADHD <5

Note: Numbers and percentages were omitted where cell size <5 patients

Abbreviations: AP, antipsychotic; ADEP, antidepressant; ANXIO, anxiolytic; ADHD, medication for attention deficit hyperactivity disorder, including stimulants and alpha2 agonists; STIM, stimulant; ADREN, alpha2 agonist; SED, hypnotic/sedative; RIS, risperidone; QUE, quetiapine; OLAN, olanzapine; ARIP, aripiprazole; HAL, haloperidol; PER, periciazine; MEL, melatonin.

a. Percentages reported as unadjusted proportion of all patients on antipsychotics for each diagnostic group. Patients may have had more than one co-prescribed medication class.
b. 'Other' includes obsessive-compulsive disorder, post-traumatic stress disorder, personality disorder, substance use disorder, incontinence disorder, including bed-wetting, learning and language disorders

Table S7. Sensitivity analysis – Proportions of all children and adolescents with mental health diagnoses prescribed antipsychotics, 2011 and 2017

	2011		2017		Absolute difference 2017 -2011	
	N with diagnosis	Adjusted[a] % of diagnostic group receiving antipsychotic prescriptions	N with diagnosis	Adjusted[a] % of diagnostic group receiving antipsychotic prescriptions	%(95% CI)	p value
All diagnoses*	8702	1.8	28814	2.8	0.9 (0.5, 1.4)[a]	<0.001
Psychoses, including schizophrenia	70	40.3	218	31.2	-9.1 (-22.5, 4.3)	0.183
Autism with behavioural problems	66	10.3	250	8.4	-1.9 (-8.8, 5.0)	0.584
Bipolar disorder	85	19.6	161	40.1	20.5 (9.6, 31.4)	<0.001
Disruptive behaviour/ conduct disorder	874	1.2	2943	2.9	1.7 (0.5, 3.0)	0.008
Autism without behavioural problems	1158	3.5	3291	5.9	2.3 (0.2, 4.4)	0.029
ADHD	933	0.8	3759	1.7	0.9 (0.2, 1.6)	0.015
Eating disorders	187	1.0	543	6.5	5.5 (2.7, 8.3)	<0.001
Depression or anxiety	2956	1.4	10642	2.4	1.0 (0.5, 1.6)	<0.001
Depression	1680	1.7	4941	3.7	1.9 (1.2, 2.7)	<0.001
Anxiety	1805	1.2	8110	2.1	0.9 (0.3, 1.5)	0.005
Depression and anxiety	529	1.7	2409	4.1	2.4 (1.2, 3.6)	<0.001
Sleep disorders	741	0.8	3359	0.6	-0.2 (-0.9, 0.4)	0.467
Other mental health[b]	1632	0.2	4250	0.4	0.2 (-0.1, 0.5)	0.113

Note. Analysis including all children and adolescents attending general practices, not restricted to 'regular patients' (i.e., patients with visits 3 times within 2 years, and 1 visit in each year)

* Only one diagnosis is recorded per patient according to hierarchy. Highest level (1: psychosis) through to lowest level (10: other). Diagnoses higher in hierarchy have stronger clinical rationale for use of antipsychotics. Numbers adjusted for age, gender, patient IRSAD, and practice characteristics (state, rurality, practice IRSAD).

Abbreviations: ADHD, attention deficit hyperactivity disorder.

a. Analysis using logistic regression adjusted for age, gender, patient IRSAD, and practice characteristics (state, rurality, practice IRSAD). IRSAD, Index of Relative Socio-economic Advantage and Disadvantage.

b 'Other' includes obsessive-compulsive disorder, post-traumatic stress disorder, personality disorder, substance use disorder, incontinence disorder, including bedwetting, learning and language disorders.

Table 5.1 Crude frequencies of paediatric mental disorder diagnoses for each year from 2011 to 2018

	2011	2012	2013	2014	2015	2016	2017	2018
Any diagnosis	5.01%	5.80%	6.67%	7.15%	7.67%	8.41%	9.09%	9.11%
Psychosis	0.04%	0.05%	0.06%	0.05%	0.05%	0.06%	0.07%	0.05%
BD	0.05%	0.04%	0.05%	0.05%	0.05%	0.05%	0.06%	0.04%
ASD	0.70%	0.77%	0.82%	0.90%	0.93%	0.99%	1.11%	1.11%
DBD/CD	0.55%	0.63%	0.71%	0.81%	0.85%	0.98%	1.01%	1.04%
ADHD	0.65%	0.79%	0.91%	0.97%	1.07%	1.24%	1.44%	1.53%
ED	0.11%	0.14%	0.16%	0.16%	0.15%	0.15%	0.18%	0.18%
Depression	1.05%	1.27%	1.44%	1.45%	1.57%	1.62%	1.75%	1.68%
Anxiety	1.15%	1.46%	1.79%	2.11%	2.40%	2.73%	2.96%	3.04%
Sleep	0.56%	0.68%	0.81%	0.92%	1.03%	1.15%	1.32%	1.29%
OCD	0.09%	0.10%	0.12%	0.12%	0.12%	0.12%	0.12%	0.13%
PTSD	0.03%	0.04%	0.04%	0.04%	0.04%	0.06%	0.07%	0.07%
PD	0.02%	0.02%	0.03%	0.02%	0.02%	0.04%	0.03%	0.03%
SUD	0.06%	0.06%	0.07%	0.06%	0.07%	0.09%	0.08%	0.08%
INCONT	0.44%	0.49%	0.56%	0.56%	0.54%	0.58%	0.55%	0.56%
LD	0.10%	0.12%	0.13%	0.14%	0.14%	0.14%	0.15%	0.13%
LANG	0.40%	0.45%	0.53%	0.60%	0.64%	0.73%	0.82%	0.81%

Abbreviations: ASD, autism spectrum disorder; BD, bipolar disorder; DBD, disruptive behaviour disorder; CD, conduct disorder; ADHD, attention deficit hyperactivity disorder; ED, eating disorder; OCD, obsessive-compulsive disorder; PTSD, post-traumatic stress disorder; PD, personality disorder; SUD, substance use disorder; INCONT, incontinence/enuresis; LD, learning disorder; LANG, language disorder.

6 Cardiometabolic monitoring in children and adolescents prescribed antipsychotics in Australian primary care, 2011 to 2017.

6.1 Publication status

This chapter is the third paper included in this thesis, which has been submitted for publication in the Journal of Drug Safety.

6.2 Preface

Chapter 4 highlighted an increasing trend for prescribing of antipsychotics to children and adolescents across the study period. Prescribing increased 6.2% annually, with an absolute increase of 95.8% from 2011 to 2018. Chapter 5, examining off-label prescribing, recorded high levels of off-label antipsychotic prescribing that increased from 69.8% of all children prescribed antipsychotics in 2011 to 79.9% in 2017. Adverse events associated with antipsychotic prescribing can be particularly problematic, especially for children and adolescents. They can experience more rapid and severe adverse effects than adult users [405]. Furthermore, adverse effects can result in a reduced benefit/harm ratio when antipsychotics are used off-label [34]. Consequently, paediatric guidelines recommend regular monitoring of cardiometabolic parameters in all antipsychotic users. Parameters examined in this chapter included measurement of weight, blood glucose and lipids, blood pressure, prolactin, and lever function.

This chapter answers the following research questions:

1). How frequently are children and adolescents monitored for antipsychotic-related adverse effects within 12 months following their first antipsychotic prescription?
2). Are children and adolescents receiving antipsychotic prescriptions monitored more often than patients not receiving antipsychotics?

6.3 Key findings

1. There were low rates of cardiometabolic monitoring in children and adolescents prescribed antipsychotics during the study period 2011 to 2017.
2. 55.9% of children or adolescents were monitored at least once on at least one parameter within 12 months of their incident antipsychotic prescription.
3. Weight was the most frequently monitored parameter (39.1% monitored at least once in 12 months) but monitoring requiring blood testing was rarely performed.

4. Compared to patients attending general practices who were never prescribed antipsychotics, users of antipsychotics were monitored slightly more frequently.

6.4 Statement of Authorship

Title of Paper	Cardiometabolic monitoring in children and adolescents prescribed antipsychotics in Australian primary care, 2011 to 2017
Publication Status	☐ Published ☐ Accepted for Publication ☑ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Submitted for publication to journal "Drug Safety"

Principal Author

Name of Principal Author (Candidate)	Julie Klau		
Contribution to the Paper	JK contributed to the conceptualisation and design of the study, analyses and interpretation of results, and wrote the original manuscript. JK also assisted with the preparation of variables in the database, engaged in ongoing editing and refinements, and submitted the article to the journal as primary and corresponding author.		
Overall percentage (%)	80%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature	80%	Date	29 April 2024

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Associate Professor David Gonzalez-Chica		
Contribution to the Paper	DG assisted with database preparation and advice on statistical analyses. DG also provided critical revisions of the manuscript, contributing to intellectual content.		
Signature	5%	Date	12 April 2024
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Contribution to the Paper	MR assisted with major critical revisions of the manuscript, contributing to intellectual content.		
Signature	5%	Date	11 April 2024

Name of Co-Author	Dr Natalie Aboustate		
Contribution to the Paper	NA assisted with major critical revisions of the manuscript, contributing to intellectual content. NA assisted with the submission process to the academic journal.		
Signature	5%	Date	12 April 2024

Name of Co-Author	Professor Jon Jureidini		
Contribution to the Paper	JJ assisted with conceptualisation and design of the study, and provided critical revisions of the manuscript, contributing to intellectual content.		
Signature	5%	Date	11 April 2024

6.5 Main paper

Cardiometabolic monitoring in children and adolescents prescribed antipsychotics in Australian primary care, 2011 to 2017

6.6 Abstract

6.6.1 Introduction and Objective

Antipsychotic medications are associated with serious cardiometabolic adverse effects, which are more pronounced in children and adolescents. Australian and international guidelines recommend regular monitoring of physical and metabolic parameters when patients are prescribed antipsychotics. This study examined rates of cardiometabolic monitoring of paediatric patients prescribed antipsychotics in Australian primary care from 2011 to 2017.

6.6.2 Methods

A retrospective analysis using electronic health records (EHRs) in a large primary care database, MedicineInsight, examined rates of measurements of weight, waist circumference, blood glucose, lipid profiles, blood pressure, prolactin, and liver function in children under 19 years. Monitoring for metabolic syndrome, defined as measurement of weight, blood pressure, and glucose, was also examined. The measurement period was 365 days post-incident antipsychotic prescription, inclusive of baseline. A secondary analysis using four different definitions for baseline was also performed. Target trial methodology was used to examine whether rates of monitoring were higher in a sample of patients prescribed antipsychotics compared to patients not receiving antipsychotics. Sensitivity analyses examined the impact of being overweight or obese at baseline and patients' duration of antipsychotic use.

6.6.3 Results

55.9% of patients using antipsychotics were monitored at least once on at least one parameter during the study period. Weight was most frequently measured (39.1% of patients measured at least once), followed by blood pressure (29.0%), blood glucose (12.9%), liver function (9.1%) and cholesterol (8.1%). Baseline measurements showed a similar pattern. From 90 days before to 14 days after incident antipsychotic prescription, 36.0% of patients had at least one measurement of at least one parameter recorded. Weight was measured most frequently (23.8%), followed by blood pressure (17.4%) and glucose (7.0%). Monitoring for parameters comprising metabolic syndrome occurred at least once in

only 1.5% of patients. Adjusted analyses comparing antipsychotic users with non-users revealed a significant, albeit small, increased rate of monitoring in antipsychotic users (1.157 monitoring visits within 12-months, versus 0.691 visits for non-users; $p<0.001$). Patients who were overweight or obese at baseline were monitored more frequently, especially if starting antipsychotics (3.492 visits; $p = 0.001$), but duration of antipsychotic use had no significant effect on monitoring rates.

6.6.4 Conclusions

Rates of paediatric cardiometabolic monitoring associated with antipsychotic prescribing in Australian general practice were low. Although monitoring rates were higher for patients using antipsychotics, the difference was small. While some children and adolescents may be monitored in specialist settings, the low rates of monitoring observed in this study suggest that a coordinated system-wide approach to monitoring is needed for paediatric patients.

6.7 Introduction

Antipsychotic prescribing to children and adolescents is on the rise worldwide [4, 406], with increasing numbers of children receiving these drugs for off-label conditions, or conditions for which there are no approvals by regulatory authorities [48, 407]. Concerns about the cardiometabolic adverse effects of second-generation antipsychotics (SGAs) have been noted since the US Food and Drug Administration (FDA) placed a warning on these drugs in 2003 [408]. However, first-generation antipsychotics (FGAs) also cause significant weight gain [409] and have been associated with cardiometabolic adverse events [410] and metabolic syndrome in adults [411]. Therefore, all antipsychotics have been examined in the present study.

6.7.1 Cardiometabolic adverse effects in children and adolescents

Children and adolescents taking antipsychotics are especially vulnerable to adverse metabolic effects; they experience more rapid changes in weight and drug-induced lipid and glucose abnormalities compared with adults [9]. Childhood metabolic syndrome (MetS) is defined by being overweight or obese, having high blood glucose levels, low levels of high-density lipoproteins (HDLs), high triglycerides, and high blood pressure [98]. Childhood MetS predicts adult MetS from as young as 5 years of age and adult type 2 diabetes and subclinical atherosclerosis from age 8 [99]. This raises concerns that antipsychotics, due to their effect on metabolic parameters, could propel children and adolescents into lifelong health problems and premature mortality.

Concerns about the cardiometabolic effects of SGAs have prompted many jurisdictions around the world to develop protocols for monitoring metabolic health to detect problematic changes early and implement strategies to manage the adverse effects [72, 106, 107, 276, 279]. The Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children (CAMESA) has developed evidence-based medication-specific guidelines [72]. In Australia, the Women's and Children's Health Network (WCHN), in collaboration with the University of South Australia, developed an evidence-based program in 2005 [107]. This program recommends regular monitoring of weight, blood pressure, glucose levels, lipid profiles, and liver function when commencing antipsychotics in children and adolescents [107].

6.7.2 International studies examining cardiometabolic monitoring in children and adolescents prescribed antipsychotics

Despite the existence and implementation of cardiometabolic monitoring guidelines in many countries, monitoring rates of recommended clinical and laboratory parameters in children and adolescents across all health settings remain low [412]. A recent systematic review of research on metabolic monitoring in children and adolescents taking antipsychotics included all studies in children aged under 19 years attending mental health services [412]. The review included fifteen studies published up to 2020, including four self-reports by clinicians [413-416], six chart reviews [417-422], and five data linkage studies [102, 423-426]. In a majority of cases, despite clinicians reporting high levels of awareness of monitoring requirements and rates of monitoring, adherence to guideline recommendations for baseline and follow-up testing was low, especially for blood monitoring [412]. For example, one Canadian study by Chen and colleagues [427] examining under-18-year-olds prescribed antipsychotics in 2014 found only 17% had at least one laboratory measure at baseline and 35% at follow-up (between 3 months and 12 months post antipsychotic prescription). Less than 5% received lipid and glucose testing at baseline and less than 22% at follow-up [427]. A study using a UK general practice database, the Clinical Practice Research Datalink (CPRD), similarly found low rates of monitoring in paediatric antipsychotic users [428]. This study examined monitoring from 2000 to 2017 [428] and found less than 25% of patients aged up to 18 years were monitored for physical measures (weight, body mass index [BMI], waist circumference, and blood pressure) and less than 15% for laboratory parameters (glucose, lipids, prolactin, and glycated haemoglobin [HbA1c]) during the first six months following an incident antipsychotic prescription. In the US, despite improvements following FDA warnings in 2003, American Diabetes Association (ADA) recommendations in 2004 [423, 429-431], and the introduction of monitoring guidelines or programs [432-434], paediatric monitoring rates remained suboptimal overall [408, 422, 424, 425, 430, 432, 435].

6.7.3 Australian studies examining cardiometabolic monitoring in children and adolescents prescribed antipsychotics

Australian studies examining metabolic monitoring of children and adolescents receiving antipsychotics are sparse, with only two studies including children under 15 years: a small pilot study involving 10 doctors (psychiatrists, paediatricians) and 17 patients published in 2008 [436], and a prospective 3-month audit of patients under 18 undertaken at the Women's and Children's Hospital in Adelaide, South Australia [62]. Of the 60 patients

reviewed in this study, 54 were classified as long-term antipsychotic users (>1 month) and deemed in need of monitoring. Only 11 (20%) had a monitoring chart in their records, and four (7.4%) patients had been monitored according to South Australian recommendations.

Other Australian studies have surveyed child psychiatrists about the safe use of SGAs, including metabolic monitoring [416, 437]. Walter and colleagues surveyed 126 child psychiatrists, most of whom (86%) expressed a high level of concern about the risks for children taking SGAs and the need for regular cardiometabolic monitoring [416]. However, their actual practices did not coincide with published guidelines nor match expressed concerns. For example, changes in waist circumference (WC) were reported by psychiatrists to be "always or usually" observed in 58% of survey respondents, yet only 24% reported actually measuring this parameter at baseline and 28% measured it on a regular basis.

A 2017 Australian study examined which medical specialty initiated antipsychotic prescriptions in a sample of concession card holders from 2010 to 2013 [438]. General practitioners (GPs) initiated approximately 70% of all antipsychotic prescriptions, but in children under 15 years, 47% of prescriptions were initiated by paediatricians and 17% by psychiatrists, with the remaining 36% initiated by GPs or other health practitioners [438]. In this sample, GPs may have prescribed antipsychotics in collaboration with specialists, but the researchers were unable to determine this, nor the role of GP prescribing to patients in their later teens. Although GPs are not the main initiators of antipsychotic prescribing for children and adolescents in Australia, they are still actively and increasingly engaged in paediatric antipsychotic prescribing [406]. Further, no studies to date have examined the extent to which metabolic monitoring of children and adolescents is carried out in Australian primary care. This study aims to examine the extent to which children and adolescents who are prescribed antipsychotics in Australian general practice are receiving cardiometabolic monitoring. Results are reported descriptively, and differences in monitoring rates compared between antipsychotic users and non-users are analysed using target trial methodology [439].

6.8 Methods

6.8.1 Study design and data source

A retrospective study of de-identified electronic health records (EHRs) was conducted using MedicineInsight, a large longitudinal Australian primary care database. MedicineInsight was established in 2011 with funding from the Australian government to monitor medicine

safety and quality use of medicines. In the 2018/2019 financial year, the database included 569 general practices and 3,255 general practitioners (GPs, family physicians), representing 7% of all Australian practices and 9% of all GPs [355]. De-identified information on patient demographics, reasons for clinical encounters, medications prescribed, diagnoses, medical tests, and results is uploaded monthly to MedicineInsight using a secure third-party extraction tool. Results of pathology tests may be entered manually or loaded electronically directly from external sources. All patients in the database receive a unique identifier, which allows for tracking their data over time and across different datasets. To improve data quality, MedicineInsight only provides researchers with data from general practice sites established for at least two years without interruptions of more than six weeks to data provision and a consistent volume of transactions [354].

6.8.2 Study samples

The MedicineInsight sample covered 854,312 children and adolescents aged under 19 years who attended 547 general practices from 2011 to 2018.

6.8.2.1 Antipsychotic subsample

For the descriptive analysis, we defined a sub-population of incident antipsychotic users as any patient receiving an antipsychotic prescription during the study period, where there was a minimum of 12 months antipsychotic-free prior to their first recorded prescription. We restricted the sample to patients who had an incident antipsychotic prescribed from 1 January 2011 to 31 December 2017, to ensure a 12-month follow-up period was available for all patients. Australian monitoring guidelines for children and adolescents are not specifically restricted to SGAs [107, 109], therefore FGAs (4.2% of antipsychotics in our sample) were included in our study. The final sample included 3,840 patients from 488 practices.

6.8.2.2 Target trial sample

For the target trial analysis, the sample was restricted to children and adolescents aged 3-18 years. The sample of 555,440 patients from 547 practices included 3,829 who were prescribed an antipsychotic.

6.8.3 Data extraction

6.8.3.1 Antipsychotic prescriptions

Information about antipsychotic prescriptions was extracted from the “prescription issued table” in MedicineInsight that records generic and brand names of drugs. The sample included all antipsychotics, both first- and second-generation, available in Australia and

listed in the Anatomical Therapeutic Chemical (ATC) index (electronic supplementary material [ESM], Supplementary Table 1).

6.8.3.2 Monitoring information

Monitoring information was extracted from two sources in the MedicineInsight database: the pathology dataset containing records of laboratory tests and the observations dataset containing records of blood pressure, height, weight, BMI, random blood glucose, and lipid levels.

6.8.4 Outcomes

6.8.4.1 Primary outcomes

Monitoring parameters were determined by reference to guidelines created by the WCHN in South Australia [107] and an algorithm provided by the Health, Education, and Training Institute (HETI) in New South Wales, Australia [109]. Recommended metabolic measures and monitoring frequencies by both guidelines are presented in Table 6.1.

Table 6.1 Summary of two recommended algorithms for monitoring cardiometabolic health in children and adolescents taking psychotropic medications in Australia

	Baseline	2-Weekly	Monthly	3 months	6 months	9 months	12 months	Total
Health, Education, and Training Institute (HETI)[a] recommendations for adolescents using any psychotropic medications								
Weight	✓	1st 6-8 weeks	after 6-8 weeks	✓	✓	✓	✓	9
BMI (kg/m²)	✓				✓		✓	3
Waist circumference	✓			✓	✓	✓	✓	5
Blood pressure	✓			✓	✓		✓	4
FPG/RPG/HbA1c	✓			✓	✓		✓	4
Total cholesterol	✓			✓	✓		✓	4
HDL	✓			✓	✓		✓	4
LDL	✓			✓	✓		✓	4
Triglycerides	✓			✓	✓		✓	4
Liver function	✓				✓		✓	3
Prolactin	if symptoms present							
Women's and Children's Health Network (WCHN)[a] recommendations for children or adolescents using antipsychotic medications								
Weight	✓		1st 3 months	✓	✓	✓	✓	7
BMI (kg/m²)	✓		1st 3 months	✓	✓	✓	✓	7
Waist circumference								
Blood pressure	✓				✓		✓	3
FPG/RPG/HbA1c	✓			✓			✓	3
Total cholesterol	✓			✓			✓	3
HDL	✓			✓			✓	3
LDL	✓			✓			✓	2
Triglycerides	✓			✓			✓	3
Liver function	✓			✓			✓	3
Prolactin	✓			✓			✓	3

Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; HbA1c, haemoglobin A1c; HDL, high density lipoprotein; LDL, low density lipoprotein; RPG, random plasma glucose.

Notes:

a. Other baseline investigations that may need to be performed, if clinically required, include TFT (thyroid function tests), FBC (full blood count), ECHO (echocardiogram), UEC (urea, electrolytes and creatinine) and vitamin D.

Outcome parameters included weight, BMI, waist circumference, blood pressure, glucose (fasting and random blood glucose, HbA1c), lipids (total cholesterol, HDL), triglycerides, and prolactin levels. Liver function testing reported levels of alkaline phosphatase (ALP). We also created a combined variable to determine if any of the parameters were measured at least once within a 12-month period. The measurement period was 365 days after the incident antipsychotic prescription, inclusive of baseline, using the date of the incident antipsychotic prescription as baseline.

As children and adolescents are particularly prone to developing antipsychotic-induced MetS, we created two variables to examine its rate of measurement. MetS, as defined by the International Diabetes Federation (IDF), includes obesity, high triglycerides, low HDL, high blood pressure, and high blood glucose [98]. The IDF further defines MetS as present in children or adolescents if waist circumference, and at least two of the remaining four parameters have levels recorded outside pre-defined thresholds [98]. Specifically, IDF-defined parameters in children over 9 years of age consist of obesity (defined as waist circumference exceeding the 90th percentile for gender and age) and the presence of at least two other abnormal clinical measures. The first MetS variable we created consisted of all five parameters. Rates of measurement for waist circumference were very low in our sample, so we created the second three-factor variable from the three most frequently measured MetS parameters (weight, blood pressure, and blood glucose).

6.8.4.2 Secondary outcomes

Our secondary outcomes consisted of measurements taken at baseline using four different definitions: (1) the date an antipsychotic was first prescribed, (2) from the date of the incident antipsychotic prescription to 14 days after (BL_14), (3) from 30 days before to 14 days after (BL30_14), and (4) from 90 days before to 14 days after the incident prescription (BL90_14).

6.8.5 Statistical analysis

6.8.5.1 Antipsychotic subsample

Using the sub-sample of patients prescribed antipsychotics, crude descriptive statistics were used to report the percentage of patients who had a given metabolic parameter measured within 12 months, inclusive of the day of incident prescription, reported in categories of once, twice, or 3 or more times.

6.8.5.2 Total sample

Target trial methodology [439] was used to determine if rates of monitoring were higher in children and adolescents prescribed antipsychotics compared to those who attended a MedicineInsight practice with no recorded antipsychotic prescription prior to 2011 and during the study period. The incident date for the comparison group was the date of first attendance at the practice. Target trial methodology emulates a randomised controlled trial using epidemiological data by employing augmented inverse probability weighting (AIPW) [382]. Inverse probability weighting (IPW) is a regression technique used for examining causal effects in epidemiological studies [383]. AIPW is a doubly robust procedure that estimates causal effects by specifying two regression models: one for the outcome and one for the exposure [382]. The exposure regression estimates a propensity score or the probability of exposure conditional on covariates (the probability of being prescribed antipsychotics). In the doubly robust model, only one of the models needs to be correctly specified to produce unbiased results. We used logistic regression for the treatment (exposure) variable and Poisson regression for the outcome variable. Although all outcome variables were overdispersed, AIPW for count variables does not require alternative analyses for overdispersed or zero-inflated outcomes [389].

There were very few children aged under 3 years receiving an antipsychotic (11 patients), so to facilitate the AIPW analysis, we restricted the sample to ages 3 and over.

6.8.5.3 Sensitivity analyses

Overweight/obesity at baseline was considered an important covariate to include in AIPW analyses but was excluded from the primary analyses due to high levels of missing data (89.5%). Therefore, we performed sensitivity analyses on a subsample with weight recorded at baseline and a subsample of patients who were overweight/obese at baseline.

We also performed a sensitivity analysis of patients regularly attending the practice. For this analysis, we restricted the sample to patients who had at least two GP visits in the 12-month follow-up period (i.e., at least two GP visits during the study period, inclusive of the day of the incident event), where a monitoring event occurred.

A further analysis examined duration of antipsychotic use, comparing patients prescribed antipsychotics once with those receiving two or more prescriptions.

6.8.6 Covariates

Potential confounding covariates for the target trial analysis were selected based on factors known to be related to the treatment and outcome and use of a directed acyclic graph (DAG) generated using an online tool available at daggity.net [386, 440]. The DAG used in the current analysis is provided in Supplementary Figure 1 (see ESM).

Covariates included in the AIPW analysis included age (years), gender, state, socio-economic status (Index of Relative Socio-economic Advantage and Disadvantage [IRSAD]) of the practice and the patient, Indigenous status, presence of allergies, smoking status, and health conditions.

6.8.6.1 Health conditions

The variable for health conditions contained 3 levels related to likelihood of receiving an antipsychotic for the condition: (1) conditions for which antipsychotics are approved by the Australian Therapeutic Goods Administration (TGA) for children and adolescents, (2) non-TGA-approved conditions, and (3) no diagnosis on record (ESM, Supplementary Table 2 lists diagnoses included in each level). As we were primarily interested in monitoring triggered by the prescription of antipsychotics, we excluded all antipsychotic users who had diagnoses of diabetes, hypertension, or dyslipidaemia on record prior to the incident antipsychotic prescription.

6.8.6.2 Sociodemographic covariates

Age was recorded in years, and gender was divided into male and female. Socio-economic status was derived from the IRSAD, divided into quintiles. IRSAD is an indicator that summarises information derived from census data on individual and household conditions, including income, education, employment, occupation, and housing [441] within specific geographical areas [365]. Rurality was divided into major cities, inner regional, and outer regional/remote/very remote areas. Indigenous status was divided into three categories: Indigenous, non-Indigenous, or not stated/recorded.

6.8.6.3 Weight at baseline

The overweight/obesity at baseline variable used in sensitivity analyses was calculated using percentiles based on age and gender from World Health Organization (WHO) guidelines [367, 368]. As age was only provided as year of birth by MedicineInsight, figures for calculation of centiles were calculated for mid-year. For example, age 1 year used 18-month centile figures, and age 5 used 5 year and 6-month figures. Centiles were calculated using the algorithm provided by the WHO using weight-for-age data considered appropriate for 0-

9-year-olds and BMI-for-age percentiles for 10-18-year-olds [368]. Weight at baseline was measured on the day of the incident event up to 14 days after. Children and adolescents were classified as overweight/obese if their weight-for-age or BMI-for-age centiles were recorded as the 85th centile or above, as defined by the WCHN [107]. A dichotomous variable classifying patients as overweight/obese at baseline was created for analyses.

6.8.7 Ethics approval

The independent MedicineInsight Data Governance Committee approved this study (protocol 2019-029), and the Human Research Ethics Committee of the University of Adelaide exempted it from full ethical review due to the use of non-identifiable data.

6.9 Results

6.9.1 Sample characteristics

There were 3,840 patients aged 0-18 years in the antipsychotic sub-sample (Table 6.2). In the AIPW sample that was restricted to 3-18-year-olds, there were 3,829 antipsychotic users and 551,611 non-users. 52% of antipsychotic users were male, compared with 48% of non-users, with a higher mean age in the antipsychotic group (14.3 [3.6] vs 8.8 [5.1]). Patients with an antipsychotic prescription were more likely to reside in inner regional areas (34.1% vs 22.7%) and more disadvantaged areas (67.7% versus 52.3% in the lower three IRSAD quintiles). Antipsychotic users were also more likely to be overweight/obese at baseline (32.3% vs 22.1%), smokers (15.5% vs 2.9%), have recorded allergies (26.7% vs 16.0%), and have recorded diagnoses both for conditions with antipsychotic approvals (27.2% vs 1.5%) and non-approved conditions (29.0% vs 12.3%). 63% of children and adolescents prescribed antipsychotics received more than one prescription.

Table 6.2 Patient characteristics of samples from MedicineInsight examined for paediatric health monitoring according to analysis and antipsychotic prescriptions

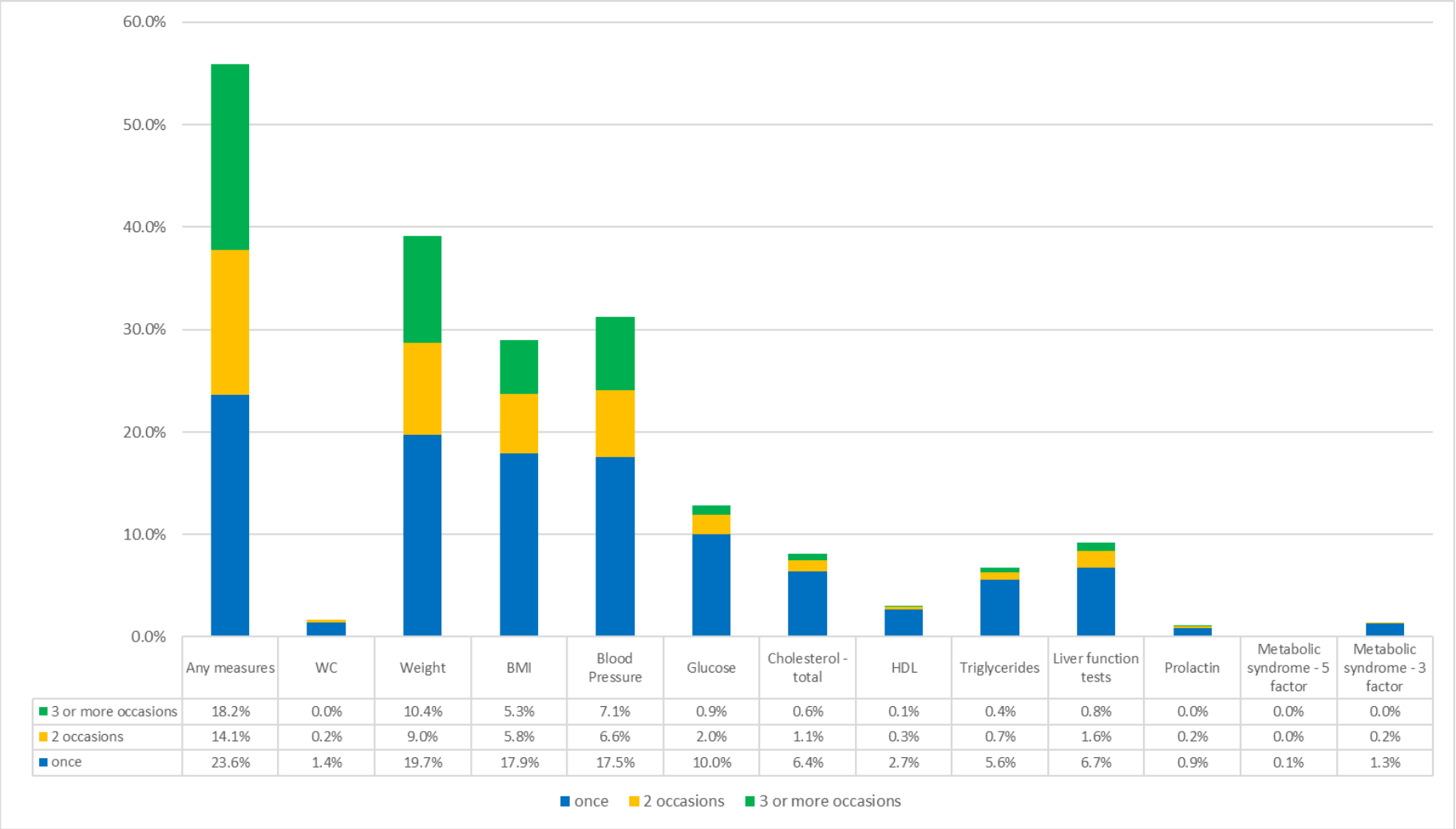
		AP subsample	AIPW sample (3-18 years)		AIPW sample with weight at baseline		AIPW sample with at least 1 follow-up visit	
			No antipsychotic N (%)	Antipsychotic prescribed N (%)	No antipsychotic N (%)	Antipsychotic prescribed N (%)	No antipsychotic N (%)	Antipsychotic prescribed N (%)
	Total N	3,840	551,611	3,829	58,213	365	425,967	3,547
Variable	**Level**							
Gender	Male	2,014 (52.5%)	264,722 (48.1%)	2,006 (52.4%)	28,216 (48.5%)	216 (59.2%)	204,425 (48.0%)	1,834 (51.7%)
	Female	1,823 (47.5%)	286,129 (51.9%)	1,820 (47.6%)	29,955 (51.5%)	149 (40.8%)	221,114 (52.0%)	1,710 (48.3%)
Age at baseline (mean [sd])	Years	14.3 [3.7]	8.8 [5.1]	14.3 [3.6]	8.6 [5.0]	13.6 [3.8]	8.5 [5.1]	14.2 [3.6]
Age group (3 category) at baseline	<10 years	546 (14.2%)	315,736 (57.2%)	535 (14.0%)	35,129 (60.3%)	76 (20.8%)	255,226 (59.9%)	508 (14.3%)
	10-14 years	984 (25.6%)	126,943 (23.0%)	984 (25.7%)	12,396 (21.3%)	100 (27.4%)	92,085 (21.6%)	930 (26.2%)
	15-18 years	2,310 (60.2%)	108,932 (19.7%)	2,310 (60.3%)	10,688 (18.4%)	189 (51.8%)	78,656 (18.5%)	2,109 (59.5%)
Patient IRSAD (5 category)	1 - least disadvantaged	646 (16.8%)	153,642 (27.9%)	641 (16.7%)	12,237 (21.0%)	53 (14.5%)	118,952 (27.9%)	591 (16.7%)
	2	597 (15.6%)	111,022 (20.1%)	596 (15.6%)	12,957 (22.3%)	67 (18.4%)	85,786 (20.1%)	545 (15.4%)
	3	981 (25.6%)	122,293 (22.5%)	980 (25.6%)	13,471 (23.2%)	87 (23.8%)	94,624 (22.2%)	919 (25.9%)
	4	789 (20.6%)	80,973 (14.7%)	786 (20.5%)	10,500 (18.0%)	89 (24.4%)	62,248 (14.6%)	732 (20.6%)
	5 - most disadvantaged	826 (21.5%)	83,387 (15.1%)	825 (21.6%)	9,018 (15.5%)	69 (18.9%)	64,134 (15.1%)	759 (21.4%)
Rurality	Major cities	2,012 (52.4%)	361,913 (65.6%)	2,006 (52.4%)	36,554 (62.8%)	206 (56.4%)	281,780 (66.2%)	1,862 (52.5%)
	Inner regional	1,310 (34.1%)	125,421 (22.7%)	1,305 (34.1%)	14,885 (25.6%)	131 (35.9%)	96,061 (22.6%)	1,210 (34.1%)
	Outer regional, remote, very remote	518 (13.5%)	64,266 (11.7%)	518 (13.5%)	6,774 (11.6%)	28 (7.7%)	48,126 (11.3%)	475 (13.4%)
Diagnosis	Approved diagnosis	1,044 (27.2%)	8,199 (1.5%)	1,042 (27.2%)	1,150 (2.0%)	138 (37.7%)	6,298 (1.5%)	957 (27.0%)
	Not approved diagnosis	1,112 (29.0%)	67,919 (12.3%)	1,111 (29.0%)	7,088 (12.2%)	120 (32.8%)	53,523 (12.6%)	1,048 (29.5%)
	No diagnosis recorded	1,684 (43.9%)	475,493 (86.2%)	1,676 (43.8%)	49,792 (85.8%)	108 (29.5%)	366,146 (86.0%)	1,542 (43.5%)

		AP subsample	AIPW sample (3-18 years)		AIPW sample with weight at baseline		AIPW sample with at least 1 follow-up visit	
Duration of AP use	No AP	-	551,611 (100%)	-	58,213 (100%)	-	425,967 (100%)	-
	1 AP	1,439 (37.5%)	-	1,431 (37.4%)	-	120 (32.9%)	-	1,186 (33.4%)
	>1 AP	2,401 (62.5%)	-	2,398 (62.6%)	-	245 (67.1%)	-	2,361 (66.6%)
Allergy recorded	No known allergy	2,577 (67.1%)	438,700 (79.5%)	2,571 (67.1%)	47,283 (81.2%)	222 (60.8%)	339,351 (79.7%)	2,365 (66.7%)
	Allergy/reaction	1,026 (26.7%)	88,088 (16.0%)	1,023 (26.7%)	8,491 (14.6%)	81 (22.2%)	71,080 (16.7%)	972 (27.4%)
	Not recorded	237 (6.2%)	24,283 (4.5%)	235 (6.1%)	2,439 (4.2%)	62 (17.0%)	15,536 (3.6%)	210 (5.9%)
Smoking status	Non-smoker	2,014 (52.4%)	312,588 (56.7%)	2,009 (52.5%)	35,856 (61.7%)	187 (51.2%)	244,831 (57.5%)	1,887 (53.2%)
	Smoker	593 (15.4%)	15,736 (2.9%)	593 (15.5%)	1,446 (2.5%)	41 (11.2%)	11,273 (2.6%)	535 (15.1%)
	Ex-smoker	102 (2.7%)	4,520 (0.8%)	102 (2.7%)	442 (0.8%)	12 (3.3%)	3,323 (0.8%)	86 (2.4%)
	Not stated/not recorded	1,131 (29.5%)	218,318 (39.6%)	1,125 (29.4%)	20,347 (35.0%)	125 (34.2%)	166,438 (39.1%)	1,039 (29.3%)
Overweight or obese at baseline	No	248 (67.8%)	45,337 (77.9%)	247 (67.7%)	45,337 (77.9%)	247 (67.7%)	36,630 (78.0%)	240 (68.6%)
	Yes	118 (32.2%)	12,876 (22.1%)	118 (32.3%)	12,876 (22.1%)	118 (32.3%)	10,348 (22.0%)	110 (31.4%)
Follow-up visits within 12 months	At least 1 visit	3,558 (92.7%)	425,967 (77.2%)	3,547 (92.6%)	46,978 (80.7%)	350 (95.9%)	425,967 (100%)	3,547 (100%)
	None	282 (7.3%)	125,644 (22.8%)	282 (7.4%)	11,235 (19.3%)	15 (4.1%)	-	-

Abbreviations: AP, antipsychotic; IRSAD, index of relative socio-economic advantage and disadvantage; SD, standard deviation.

6.9.2 Analysis of antipsychotic sub-sample

The frequencies of cardiometabolic monitoring within 12 months of the incident antipsychotic prescription, inclusive of baseline (the follow-up period), are shown in Figure 6.1. 55.9% of patients were measured at least once on at least one measure. Weight was the most frequently measured (39.1% at least once during the follow-up period), but only 10% of patients were measured on three or more occasions, despite guidelines suggesting 7-9 times (Table 6.1). Blood pressure was the next most frequently monitored (31.2% at least once during the follow-up period), with 7% monitored on three or more occasions. Most measures requiring pathology testing were monitored less frequently, ranging from 1% for prolactin to 13% for glucose within 12 months. Full metabolic syndrome monitoring occurred once in 0.1% of patients, while measuring on the three most frequently measured parameters in MetS occurred once in 1.3% of patients and twice in 0.2% during the follow-up period. None were measured on more than two occasions for either definition of metabolic syndrome.



	Any measures	WC	Weight	BMI	Blood Pressure	Glucose	Cholesterol - total	HDL	Triglycerides	Liver function tests	Prolactin	Metabolic syndrome - 5 factor	Metabolic syndrome - 3 factor
3 or more occasions	18.2%	0.0%	10.4%	5.3%	7.1%	0.9%	0.6%	0.1%	0.4%	0.8%	0.0%	0.0%	0.0%
2 occasions	14.1%	0.2%	9.0%	5.8%	6.6%	2.0%	1.1%	0.3%	0.7%	1.6%	0.2%	0.0%	0.2%
once	23.6%	1.4%	19.7%	17.9%	17.5%	10.0%	6.4%	2.7%	5.6%	6.7%	0.9%	0.1%	1.3%

Figure 6.1 Proportion of patients (%) with cardiometabolic measurements taken within 12 months of incident antipsychotic prescription, by number of occasions. Metabolic syndrome – 5 factor includes (1) Weight, BMI or WC; (2) HDL; (3) blood pressure; (4) triglycerides; (5) Glucose (random or fasting or HbA1c). Metabolic syndrome – 3 factor includes (1), (3) and (5) of the 5-factor definition above. Number inclusive of measurement on day of incident event.
Abbreviations: BMI, body mass index; HbA1c, haemoglobin A1c; HDL, high density lipoprotein cholesterol; WC, waist circumference.

The number of patients measured at baseline for all parameters is shown in Table 6.3. On the day of the incident antipsychotic prescription, only weight (11.9%), BMI (8.1%), and blood pressure (6.7%) were measured in more than 1% of patients. As the definition of baseline expanded from 14 days to between 44 days and 104 days, the number of patients being measured increased monotonically for all parameters, peaking at 23.8% of patients being measured for weight, followed by 17.4% for blood pressure and 7% for glucose.

Table 6.3 Proportions of patients (%) with baseline measurements recorded during four different timespans before and after incident antipsychotic prescription

Measurement	Baseline	Baseline + 14 days after	30 days before to 14 after	90 days before to 14 after
Any measures recorded	15.9%	20.5%	26.9%	36.0%
Waist circumference	0.3%	0.3%	0.5%	0.7%
Weight	11.9%	14.3%	17.8%	23.8%
BMI	8.1%	9.7%	12.4%	17.0%
Glucose	1.0%	2.3%	4.2%	7.0%
Total cholesterol	0.6%	1.3%	2.4%	3.9%
HDL	0.1%	0.4%	0.7%	1.2%
Triglycerides	0.5%	1.1%	2.0%	3.2%
Blood pressure	6.7%	8.7%	12.5%	17.4%
Liver function tests	0.6%	2.1%	3.5%	5.2%
Prolactin	0.0%	0.1%	0.2%	0.3%
Metabolic syndrome (5 factor)	0.0%	0.0%	0.0%	0.1%
Metabolic syndrome (3 factor)	0.2%	0.3%	0.6%	0.8%

Abbreviations: BMI, body mass index; HDL, high density lipoprotein.

6.9.3 AIPW analysis of full sample

For the AIPW analysis, aggregated measures were used for weight and lipids. The aggregated weight measure included records for weight, BMI, or waist circumference, while aggregated lipids included total cholesterol, HDL, or triglycerides.

Antipsychotic users were almost twice as likely as non-users to be measured on any metabolic measure during the follow-up period (Potential Outcome Mean [POM] = 1.157 with antipsychotic, vs POM = 0.691 no antipsychotic; Table 6.4). For individual parameters, measurement of weight was one-third more likely to be measured during the follow-up period for antipsychotic users. The average treatment effect (ATE), defined as the mean

outcome difference between the treatment and control groups, was 0.323. Measurement of blood pressure had the next highest ATE, at one-seventh (ATE=0.165). All other ATEs were negligible, around 0.050.

Table 6.4 Comparison[a] of the frequency of monitoring events for incident antipsychotic users compared to non-users aged 3 to 18 years

Monitoring event	ATE (95% CI)	POM - antipsychotic prescribed	POM - no antipsychotic prescribed	% increase	p value
N		3,829	551,611		
Any metabolic measure	0.466 (0.271, 0.660)	1.157	0.691	67	<0.001
Weight – any measure[b]	0.323 (0.153, 0.492)	0.867	0.545	59	<0.001
Glucose	0.059 (0.027, 0.090)	0.108	0.050	118	<0.001
Lipids[c]	0.050 (0.022, 0.077)	0.076	0.026	189	<0.001
Blood pressure	0.165 (0.121, 0.209)	0.304	0.139	118	<0.001
Liver function tests	0.051 (0.030, 0.072)	0.083	0.032	160	<0.001

Abbreviations: AIPW, Augmented Inverse Probability Weighting; ATE, average treatment effect; BMI, body mass index; HDL, high density lipoprotein; IRSAD, index of relative socio-economic advantage and disadvantage; POM, potential outcome mean; SE, standard error.
Notes:
a. Analysis using AIPW, including covariates of age, gender, Indigenous status, patient IRSAD, health conditions, smoking status, allergy, and practice characteristics (practice IRSAD, state, rurality).
b. Measures recorded for weight, or BMI or waist circumference.
c. Measures recorded for total cholesterol or HDL or triglycerides.

6.9.4 Sensitivity analyses

The analysis restricted to patients with a record of weight at baseline exhibited almost double the rates of monitoring for any measure for patients prescribed antipsychotics (POM with antipsychotic = 3.282 versus no antipsychotic = 1.735; Table 6.5(a)). The POMs for all measures analysed were higher for both users and non-users of antipsychotics when a weight measurement was recorded at baseline, although POMs for patients prescribed antipsychotics ranged from 1.8 times higher for weight assessments to 3.9 times higher for liver function tests. A sample of patients who were overweight/obese at baseline showed similar results (Table 6.5(b)).

A sensitivity analysis examining results for those who attended their general practice at least twice during the study period showed similar results, although the ATE for all measures was lower (see Table 6.5(c)).

Table 6.5 ATEs and POMs from sensitivity analyses[a] comparing the frequency of monitoring events for antipsychotic users and non-users aged 3 to 18 years: (a) Sample with weight measured at baseline; (b) Sample overweight/obese at baseline; (c) Sample with at least one follow-up visit that included a monitoring event.

Monitoring event	ATE (95% CI)	POM - antipsychotic prescribed	POM - no antipsychotic prescribed	% increase	p value
(a) **Sample with weight measured at baseline**					
N		365	58,213		
Any metabolic measure	1.548 (0.862, 2.233)	3.282	1.735	89	<0.001
Weight – any measure[b]	1.310 (0.745, 1.875)	2.885	1.575	83	<0.001
Glucose[d]	0.064 (-0.031, 0.161)	0.155	0.091	70	0.202
Any lipids[c,e]	0.076 (-0.003, 0.156)	0.121	0.044	173	0.059
Blood pressure	0.367 (0.162, 0.571)	0.671	0.304	121	<0.001
Liver function	0.146 (0.032, 0.259)	0.196	0.050	289	0.012
(b) Sample overweight or obese at baseline					
N		118	12876		
Any metabolic measure[f]	1.736 (0.741, 2.731)	3.492	1.757	98.8	0.001
Weight – any measure[b,f]	1.564 (0.389, 2.739)	3.108	1.544	101.3	0.009
Glucose[e]	0.656 (-0.540, 1.852)	0.786	0.130	506	0.282
Any lipids[c,g]	0.296 (-0.400, 0.992)	0.356	0.060	493	0.404
Blood pressure[f]	0.816 (0.355, 1.276)	1.251	0.435	187.5	<0.001
Liver function[e]	0.191 (-0.053, 0.436)	0.247	0.056	344.1	0.125
(c) Sample with at least 1 follow-up visit that included a monitoring event					
N		3,547	425,967		
Any metabolic measure	0.389 (0.174, 0.604)	1.231	0.842	46	<0.001
Weight – any measure[b]	0.269 (0.080, 0.457)	0.929	0.660	41	0.005
Glucose	0.049 (0.015, 0.083)	0.112	0.062	79	0.005
Lipids[c]	0.046 (0.016, 0.075)	0.079	0.026	137	0.003
Blood pressure	0.141 (0.098, 0.185)	0.310	0.132	84	<0.001
Liver function tests	0.045 (0.023, 0.068)	0.086	0.040	113	<0.001

Abbreviations: AIPW, augmented inverse probability weighting; ATE, average treatment effect; BMI, body mass index; HDL, high density lipoprotein; IRSAD, index of relative socio-economic advantage and disadvantage; LDL, low density lipoprotein; POM, potential outcome mean; SE, standard error.

Notes:

a. Analyses using AIPW, including covariates of age, gender, Indigenous status, patient IRSAD, health conditions, smoking status, allergy, and practice characteristics (practice IRSAD, state, rurality).

b. Measures recorded for weight, or BMI or waist circumference.

c. Measures recorded for total cholesterol or HDL or LDL or triglycerides.

d. State omitted as a variable in this analysis.

e. IRSAD recategorized as 3 groups and state omitted in this analysis.

f. State recategorized to 6 groups for this analysis.

g. IRSAD recategorized as 3 groups and state recategorized into 5 groups for this analysis.

Analysing metabolic monitoring by the number of antipsychotics prescribed (Figure 6.2) showed no significant difference for any measure for longer duration of use, although all but lipids showed a trend towards increasing monitoring with increasing duration of use. However, for all comparisons, ATEs were very small.

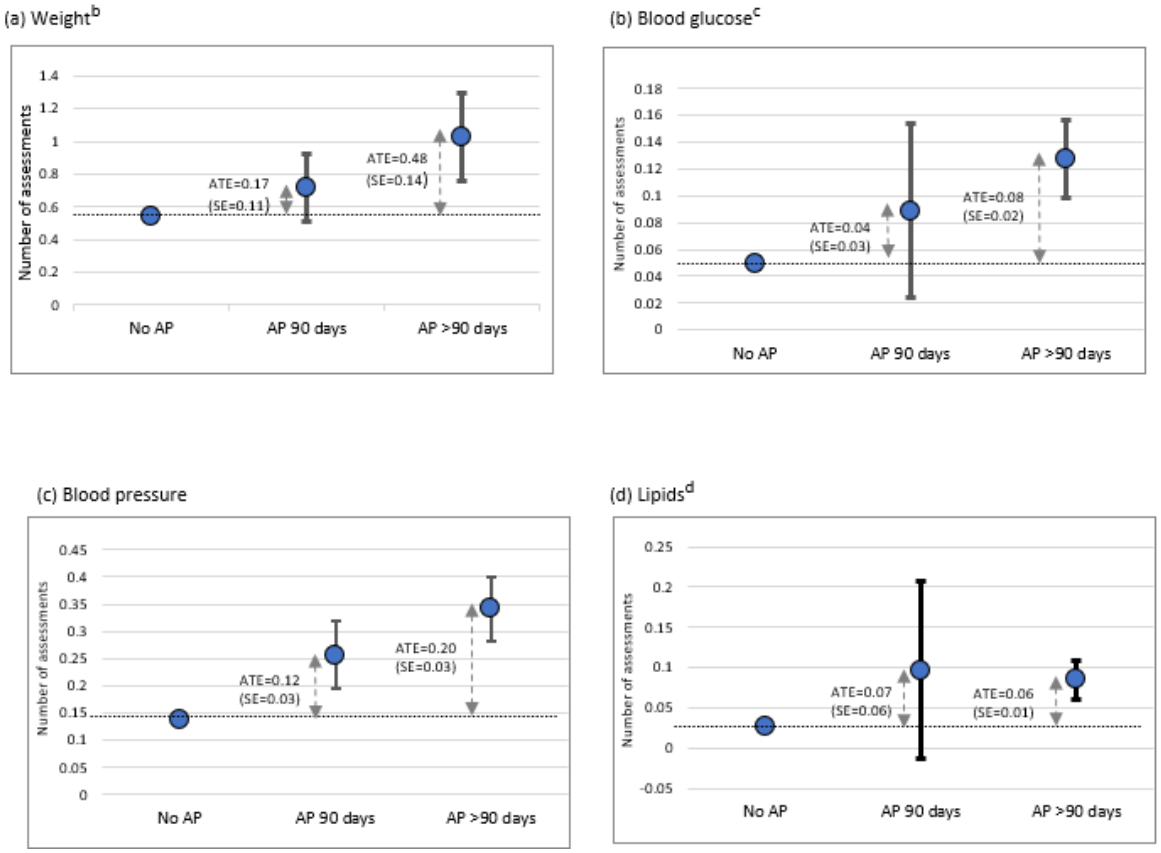


Figure 6.2 The number of assessments[a] recorded for (a) weight, (b) blood glucose, (c) blood pressure and (d) lipids for adolescents within 12 months of incident antipsychotic prescription according to duration of antipsychotic exposure: un-exposed, 90days exposure or greater than 90 days exposure.
Abbreviations: AP, antipsychotic; AIPW, augmented inverse probability weighting; ATE, average treatment effect; BMI, body mass index; HbA1c, haemoglobin A1c; HDL, high density lipoprotein; IRSAD, index of relative socio-economic advantage and disadvantage; LDL, low density lipoprotein; SE, standard error.
Notes:
a. Analyses using AIPW adjusted for age, gender, Indigenous status, patient IRSAD, health conditions, smoking status, allergy and practice characteristics (practice IRSAD, state, rurality).
b. Measures included weight, BMI or waist circumference.
c. Measures included fasting or random glucose tests, oral glucose tolerance tests, or HbA1c.
d. Measures included total cholesterol, HDL, LDL or triglycerides.

6.10 Discussion

This study examined rates of monitoring of metabolic parameters in children and adolescents within 12 months of receiving their first antipsychotic prescription, using a large primary care database, MedicineInsight. Monitoring rates were well below recommended Australian and international guidelines. Weight was the most frequently monitored parameter, being measured at least once in 39.1% of patients within the follow-up period.

Despite these low rates, however, we found some evidence that patients receiving antipsychotics were more likely to be monitored than patients not receiving antipsychotics.

6.10.1 Monitoring within 12 months of incident antipsychotic prescribing

Rates of monitoring within the 365-day measurement period in our study were suboptimal and below those found in international studies. For comparability to our study, we recalculated figures from a study using the UK CPRD database to include only a subsample of 0-18-year-olds [428, Table 2, p.40]. The researchers found rates of monitoring in the first 6 months of an antipsychotic prescription to be similar to our 12-month figures for glucose (12.0% vs 12.9% our study) and lipid (7.6% vs 8.1%) testing, but superior for prolactin (6.2% vs 1.1%). Although we had higher percentages monitored for weight (39.1% versus 22.8%) and blood pressure (31.2% versus 20.9%), this was likely due to the differing follow-up period (6 months versus our 12-month period). Indeed, the longer follow-up period may also suggest Australian rates of glucose and lipid testing were poorer.

In a Canadian study of almost 7,000 children under 19 years [427], glucose monitoring rates 3-12 months post antipsychotic prescription (13.0%) matched those found in our study's 12-month follow-up period, inclusive of baseline measures (12.9%), but rates for lipid (15% versus 8.1% in our study) and prolactin (7.5% versus 1.1%) monitoring were much lower in our dataset. Our low rates of prolactin monitoring are particularly concerning. Although some guidelines suggest monitoring prolactin only if patients are symptomatic [105, 109], others recommend regular monitoring [72, 102, 107]. Symptoms of hyperprolactinaemia do not correlate closely with prolactin levels [416] and are associated with endocrine disturbances and serious adverse effects, including hypogonadism, gynaecomastia, and osteoporosis [442]. Walter et al. (2008) [416] therefore recommended monitoring prolactin changes from baseline as an essential part of good monitoring practices.

A US study using the GE Centricity primary care database that included 3,090 children and adolescents 0-19 years and covered a 425-day measurement period (30 days before to 395 days after an incident antipsychotic prescription) [429] reported monitoring rates around 2.5 times higher than ours for BMI, blood pressure, and glucose. The GE Centricity database, similar to MedicineInsight, is an electronic medical record primary care database. However, one third of data in the GE Centricity database is from specialists, which may explain the comparatively higher monitoring observed in their study. In Australia, most antipsychotics

are prescribed by paediatricians and child psychiatrists [438], and any metabolic monitoring performed by these specialists may not be captured in the monitoring data in our study.

It is also notable that waist circumference was rarely measured despite being included in all Australian and international guidelines and being recommended as a critical measure by the IDF [98]. We found only four studies with any record of waist circumference monitoring [416, 443-445]. The highest rate of monitoring (74%) was reported by a Canadian inpatient mental health unit post-implementation of monitoring guidelines [444]. Much lower rates were observed in a Canadian outpatient clinic [445]. Before implementation of a metabolic monitoring program in January 2009, waist circumference was measured in 2.3% of patients at baseline, 0.7% at 3 months, with no measurements taken at 6-months and 12-months post-incident antipsychotic prescription [445]. Our rates of GP monitoring of waist circumference were even lower than those observed in this Canadian outpatient study, with at most 0.7% measured at baseline (BL90_14) and only 1.1% of patients measured during the 12-month follow-up period when including the day of initial prescription in the measurement period.

6.10.2 Comparison with non-antipsychotic users

Although crude figures for monitoring were all suboptimal and well below recommended guidelines, we found some evidence that patients receiving antipsychotics were more likely to be monitored during GP visits than the comparison group of non-users. In our adjusted AIPW analyses, all parameters were significantly higher in the antipsychotic sample, although this translated into a mere half measurement occasion difference for at least one measurement on at least one parameter within the follow-up period.

This finding is generally consistent with, although much lower than, that observed in a US study of 12-19-year-olds using the GE Centricity primary care database and a control group matched on age and gender [430]. The researchers (Ghate and colleagues) examined monitoring rates 395 days post-prescription (including baseline) of four metabolic parameters: weight, blood pressure, cholesterol, and blood glucose levels, from 2004 to 2009 [430]. The rates of monitoring were low, with less than 1% of all patients exposed to antipsychotics having all four metabolic parameters monitored. Similar to our study, the frequency of monitoring of BMI, blood pressure, total cholesterol, and blood glucose was higher for patients receiving antipsychotics, but the frequency increase for laboratory

parameters (lipids and glucose) was very low, despite their statistical significance. However, our results from the analysis of the MedicineInsight dataset are difficult to compare to the Ghate study, which included specialist prescribers and was restricted to adolescents.

Another study that similarly compared metabolic monitoring rates for antipsychotic users to a control group was a US study of Medicaid-insured 6-17-year-olds [425]. Monitoring rates in this study, using patients on albuterol as a comparison group, were much higher than those recorded by Ghate and colleagues and our study. Morrato and colleagues [425], using a narrower measurement period of 30 days before and six months after an incident prescription, found 31.6% of antipsychotic users monitored for glucose and 13.4% for lipids, compared to 12.6% and 3.1% in the albuterol group. However, the prevalence of antipsychotic prescribing is higher in Medicaid-insured youth than in privately-insured youth in the US [4, 446, 447], and higher than most other countries [4]. There are also programs aimed at improving the safe and effective use of antipsychotics in Medicaid-insured youth [433, 447]. This may account for the higher rates of metabolic monitoring reported by Morrato and colleagues [425], albeit still at suboptimal rates. Additionally, the differences in monitoring rates used in the Morrato et al. study were analysed using unadjusted chi-square analyses, further limiting the comparability between studies.

6.10.3 Baseline monitoring

Baseline metabolic monitoring is recommended in all Australian and international guidelines and emphasised as a critical precursor to antipsychotic treatment for youth with first-episode psychosis by the Orygen Specialist Program (formerly Orygen Youth Health) [448]. Baseline measures can help detect existing metabolic problems and guide the choice of medication where antipsychotics are indicated [426, 448]. Using the most liberal definition of baseline (recorded from 90 days before to 14 days after an incident antipsychotic prescription [BL90_14]), 36% of patients in our study had a parameter measured at baseline, 17% had weight and blood pressure measured, 7% glucose, 3.9% cholesterol, and 0.7% waist circumference. Compared to many other studies, baseline monitoring we observed was poorer [102, 422, 427, 443, 445, 449].

Our rates were similar to those reported in a recent Canadian chart review of 294 patients 4-18 years attending a child and adolescent psychiatric outpatient program from 2014 to 2016 [418]. For ease of comparison, we recalculated percentages from Table 3 from their

published paper to create one group of 4-18-year-olds. The researchers recorded 23.5% of patients with any baseline measure (any of weight, height, blood pressure, glucose, electrocardiogram, lipids, insulin, or prolactin) using a liberal definition of 180 days before to 30 days after antipsychotic prescription. Our result of 36% for any parameter using our definition of BL90_14 compares favourably to this finding. Similarly, our findings were superior for weight (15.3% versus 23.8% in our study) and blood pressure (10.2% versus 17.4%). However, this Canadian study [418] sampled the monitoring practices of only four psychiatrists in a limited setting, so it has limited comparability with our study.

A large (N = 16,304) US study [426] restricted analyses to baseline monitoring of glucose in 2-18-year-olds using the Mini-Sentinel Distributed Database, specifically designed by the FDA to monitor medication safety. The researchers used three different definitions of baseline: 14 days before to 3 days after, 90 days before to 3 days after, and 90 days before to 30 days after. Rates of monitoring were 6%, 11%, and 15% for each respective period. In comparison, our glucose baseline measure was 7% using the BL90_14 definition, or approximately half that observed in the US study spanning a similar timeframe (90 days before to 30 days after antipsychotic prescription).

Several other international studies reported higher baseline monitoring rates for multiple parameters than found in our study [102, 422, 427, 443, 445, 449].

6.10.4 Sensitivity analyses

6.10.4.1 Analysis with weight measured at baseline

In our sensitivity analysis using weight status at baseline as a covariate, there was an increase in the number of times monitoring took place for both antipsychotic and control groups, with a significantly higher level of monitoring in patients prescribed antipsychotics. Patients on antipsychotics recorded an additional 1.5 visits where some form of metabolic monitoring took place within the follow-up period. The additional analysis of those recorded as overweight/obese at baseline showed similar results, but high levels of missing data for weight mean the results need to be interpreted with caution. The results from this sensitivity analysis suggest being overweight may trigger monitoring of weight and other metabolic parameters in all children and adolescents, but that GPs recognise a greater need for monitoring if patients are also prescribed antipsychotics.

We found only two papers that considered weight at baseline when assessing metabolic monitoring rates [422, 430]. A chart review of 149 patients 5-18 years attending family physicians and specialists at a US university clinic from 2013 to 2014 observed a statistically significant effect on monitoring of glucose at baseline and lipids at 3 months post-incident prescription in patients with elevated baseline BMI [422]. The differences, however, were small: for glucose, 22.73% of patients with elevated BMI were measured at baseline compared to 20.87% for normal weight, and for lipids, at three months post-incident prescription, 9.09% of patients were monitored if BMI was elevated versus 8.47% for normal weight. In the second US study using the GE Centricity database, consisting predominantly of primary care physicians and a sample of 12-19-year-olds, the researchers found an increase in monitoring of BMI and blood pressure if adolescents were obese at baseline, but no change in monitoring of total cholesterol and glucose [430]. These results corroborate our findings, but our results were comparatively much lower. The impact of weight issues at baseline remains an important topic for future research.

6.10.4.2 Analysis of patients with at least two GP visits during the study period

Our second sensitivity analysis using the subsample of children and adolescents with at least two visits to the GP within 12 months, inclusive of the incident antipsychotic prescription, generated numbers that were only slightly lower than those in the full analysis, with no change in direction or significance of any results.

6.10.4.3 Duration of antipsychotic use

Our study found very small, non-significant increases in monitoring of weight, blood pressure, and glucose and a small decrease for lipids in patients who received more than one antipsychotic prescription compared to patients with only one prescription during the follow-up period. We found only two studies that reported monitoring rates for children and adolescents on antipsychotics for differing durations: one US study [434] and one Canadian study [427]. In both studies, percentage changes were not directly comparable to our study, but, as with other findings, rates of monitoring were higher than in our study.

The US study by Nunez and colleagues [434] examined glucose and lipid monitoring in children in foster care and found 56.6% of longer-term users were monitored in 2017 and 51.2% in 2020, higher than rates for incident users (26.2%, 2017; 18.5%, 2020). However, the definition of “user” in this study was patients with two antipsychotic prescriptions within 12 months, and long-term use was defined as receiving antipsychotics for more than 12

months. Our definition of long-term was receiving more than one antipsychotic prescription during the 12-month study period. The differing methodologies in our study and that of the Canadian study by Chen and colleagues [427] prevented comparisons being drawn with our work.

Given the increased risk of cardiometabolic effects with long-term antipsychotic use [450, 451], the paucity of research on monitoring long-term users of antipsychotics in children and adolescents is concerning. Although our findings suggest a possibility of some increase in monitoring in small pockets of primary care within Australia, future studies using a larger dataset are needed to verify if long-term antipsychotic users are receiving adequate monitoring.

6.10.5 Future directions

Overall, the findings of our study point to low levels of cardiometabolic monitoring for children and adolescents being prescribed antipsychotics in Australian primary care. In Australia, the eTG Complete electronic clinical practice guidelines for childhood schizophrenia specify regular monitoring [175] and guidelines for autism [294] refer readers to the recommended adult monitoring schedule. Both guidelines state a key person should be identified to be responsible for ongoing monitoring, be that a paediatrician, child psychiatrist, or GP. More specific guidelines that clearly delineate the responsibilities of primary and secondary care providers may be needed. In the UK, the National Institute for Health and Care Excellence (NICE) guidelines [106] specify that GPs refer children to specialists, who would be responsible for initiating antipsychotics and monitoring the child for the first 12 months or until the condition is stabilised, after which time monitoring can be transferred to GPs under shared care arrangements.

However, improving guidelines is likely to have only a marginal effect on metabolic monitoring practices [412, 452, 453]. A systematic review of metabolic monitoring in child and adolescent mental health services found no evidence of an increase in guideline adherence from 2008 to 2020 [412]. Indeed, despite the development of clinical practice guidelines in most jurisdictions, clinician uptake of the recommendations has been suboptimal [412, 417, 454]. To improve rates of metabolic monitoring, strategies are also needed to encourage widespread implementation [412, 453], such as the provision of

educational resources [408, 412, 429, 432, 436, 455], hands-on training with regular feedback on performance [429, 432, 436, 452, 455], and electronic reminders [71, 429, 437].

Even in jurisdictions with implementation strategies in place, rates of metabolic monitoring tend to be low [432, 445, 454, 455]. Reasons for the poor rates include refusal by children or their carers due to children's fear of needles [71, 96, 445] or a sense of futility because the drug is considered essential to managing the child's condition [416, 427]. Consequently, some researchers have suggested a more realistic, targeted approach to monitoring whereby blood testing is undertaken only when there are apparent changes in weight or waist circumference [427]. Waist circumference is a particularly useful measure that has been shown to be a better predictor of MetS than BMI [444]. However, this targeted, stepwise approach to engaging patients in metabolic monitoring may also have limitations [95, 453]. For example, in a Danish study, two of 15 children met the criterion for MetS at 12 months post-initiation of antipsychotic treatment but had registered a normal BMI at baseline and at 12-month follow-up [95]. Therefore, using obesity as a trigger to engage in routine blood monitoring may not detect important metabolic changes and deny patients timely treatment.

In the Australian setting, it is unclear whether there is a lack of awareness of the importance of cardiometabolic monitoring for patients prescribed antipsychotics, a lack of resources, or a lack of effective communication between specialists and GPs. In a recent survey of ten child psychiatrists working in Child and Youth Mental Health Services in Queensland, 40% cited a lack of good communication with GPs as a barrier to implementing cardiometabolic monitoring [437]. Overall, what is clear is that for unknown reasons, inadequate monitoring is occurring in general practice settings when antipsychotics are prescribed.

6.11 Strengths and limitations

MedicineInsight is a large database that covered 9% of Australian GPs and 13% of GP patients in 2017/18. Although some states, regions, and IRSAD quintiles are over-represented compared to census data, patients in the database are considered representative of those attending Australian general practice [357]. MedicineInsight also provides extensive pathology and physical examination records, which can be linked chronologically with medication prescriptions. However, we were unable to determine if the monitoring that was observed was specifically related to the use of antipsychotics or for other physical conditions.

Medications are often initiated by psychiatrists or paediatricians [438], so the date of incident prescribing may be inaccurate in some cases. It is possible that monitoring was carried out in other settings, such as mental health clinics, hospitals, and specialist clinics, without being recorded in MedicineInsight, so rates may not represent a complete record of the monitoring being undertaken by the Australian medical community. GP progress notes may also have included some results from the clinical encounter that were not available in MedicineInsight records. It is also possible that other important covariates have been omitted from AIPW analyses.

6.12 Conclusions

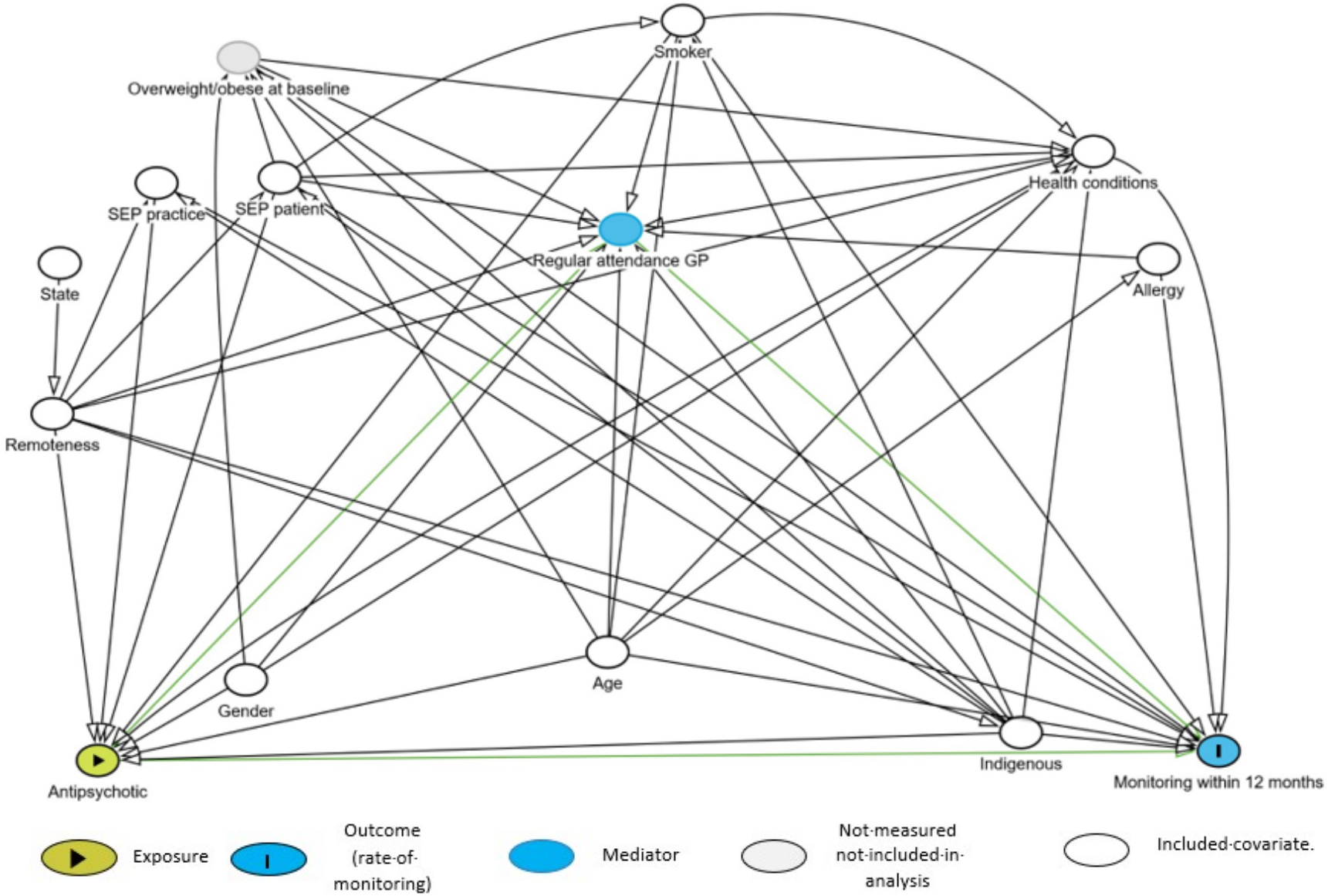
Rates of cardiometabolic monitoring in children and adolescents prescribed antipsychotics in Australian general practice are poor and well below recommended guidelines. Increasing awareness of the adverse health impacts of antipsychotics using education and training and improving guidelines to clearly delineate the role of psychiatrists, paediatricians, and GPs in paediatric monitoring are required. Consideration also needs to be given to less invasive monitoring methods and periodic assessment of the continued need for antipsychotics.

6.13 Supplementary information

Supplementary Table 1 Antipsychotics included in analyses

Antipsychotics			
ATC[a] class code	**Sub-class**	**Generic name**	**ATC sub-class code**
NO5A	Typical (first generation)		
		Chlorpromazine	NO5AA
		Droperidol	N05AD
		Flupenthixol	NO5AF
		Haloperidol	NO5AD
		Periciazine	NO5AC
		Trifluoperazine	N05AB
		Zuclopenthixol	NO5AF
NO5A	Atypical (second generation)		
		Amisulpride	NO5AL
		Aripiprazole	NO5AX
		Asenapine	NO5AH
		Brexpiprazole	NO5AX
		Clozapine	NO5AH
		Lurasidone	NO5AE
		Olanzapine	NO5AH
		Paliperidone	NO5AX
		Quetiapine	NO5AH
		Risperidone	NO5AX
		Ziprasidone	NO5AE

Abbreviations: ATC Anatomical Therapeutic Chemical.
Notes:
a. Antipsychotic classes as defined by the WHO ATC classification system. Includes all antipsychotics available in Australia.



Supplementary Figure 1 Directed acyclic graph showing proposed confounding structure for AIPW analyses.

Abbreviations: GP, general practitioner; SEP, socio-economic position.
Note: Weight recorded at baseline had 89.5% missing data and was not used in primary analyses. Overweight/obese at baseline was used in sensitivity analyses.

Supplementary Table 2. Diagnoses included in levels of "Health Conditions" variable

Approved for antipsychotic prescribing[a]	Not approved for antipsychotic prescribing[b]
Psychosis, including schizophrenia	Depression
Bipolar disorder	Anxiety
Autism spectrum disorder	Post-traumatic stress disorder (PTSD)
Disruptive behaviour disorder	Obsessive-compulsive disorder (OCD)
Tourette's/ Tics	Attention deficit hyperactivity disorder (ADHD)
Nausea	Substance use disorder (SUD)
Intellectual disability	Eating disorder (ED)
	Personality disorder (PD)
	Sleep disorders
	Language disorder
	Learning disorder
	Incontinence
	Ischemic heart disease
	Stroke
	Chronic pulmonary Obstructive Disease (COPD)
	Polycystic Ovary Syndrome (PCOS)
	Dyslipidaemia
	Chronic Kidney Disease (CKD)
	Hypertension
	Obstructive Sleep Apnoea (OSA)
	Cancer
	Osteoporosis
	Arthritis
	Peripheral Artery Disease (PAD)
	Musculoskeletal pain (MSK)
	Back pain
	Fracture
	Tenosynovitis
	Myofascial pain
	Pain management
	Fatigue syndrome
	Paget's disease
	Heart conditions
	Asthma
	Lung conditions
	Epilepsy

	Dermatitis

Notes:
a. These diagnoses may not all be approved for antipsychotics due to age limitations, or symptom restrictions (e.g., autism is only approved if severe destructive behaviours are a symptom, and only manic symptoms of bipolar disorder have medications approved).
b. These conditions may be comorbid with conditions approved for antipsychotics.

7 Prevalence of mental health disorders in general practice

7.1 Preface

This chapter explores the prevalence of paediatric mental disorder diagnoses observed and recorded in general practice, drawing comparisons with other studies of national and international mental health surveys. This chapter addresses the following research question:

1). Has the prevalence of mental disorder diagnoses changed in Australian general practice from 2011 to 2017?

Prevalence rates were previously summarised in Tables 1.1 and 1.2 in the introduction (Chapter 1). To facilitate discussion, these tables have been reproduced in this chapter with columns added to include data from Chapter 5 on the prevalence of mental disorder diagnoses recorded in MedicineInsight (data from Table 5.1).

7.2 Prevalence of mental disorder diagnoses in general practice 2011 to 2018

The reported prevalence of common paediatric mental disorders in Australia and internationally is summarised in Table 7.1, with added columns summarising the findings of this thesis for comparison.

The prevalence rates recorded in MedicineInsight and analysed in this thesis are markedly different from both the CAMHW survey, two international surveys [14, 17], and a meta-analysis of worldwide prevalence studies [21]. The 12-month prevalence rate for all disorders measured in the 2013/2014 CAMHW survey was higher than that recorded in MedicineInsight. For all disorders, the CAMHW survey reported 3.3 times higher rates of diagnosis than the 2011 rate in Australian primary care and 2.1 times the 2017 primary care rate. The prevalence for any anxiety disorder was 7.5 times higher in 2011 and 3.2 times higher in 2017. For OCD, the prevalence was 10 times higher in both years.

The difference in rates in the CAMHW survey and MedicineInsight may be partly due to differences in data collection processes. Diagnoses recorded in MedicineInsight were extracted from three data fields (reason for diagnosis, reason for encounter, and reason for prescription) using a diagnostic extraction algorithm (see Chapters 3 and 5). The CAMHW survey assessed the presence of mental disorders using the Diagnostic Interview Schedule for Children (DISC-IV), a parent/carer-reported structured set of interview questions based on the APA Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV) classifications [15]. In addition, children aged 11 years and over completed a self-report questionnaire, which also included a DISC-IV module [15]. The CAMHW survey covered a

representative sample of children attending a variety of healthcare settings, including general practices, and would also include children with diagnosable conditions currently not in contact with any health services or using school services or telephone counselling services [15]. Therefore, the CAMHW survey could capture diagnoses not recorded by general practices. This would be particularly relevant to ADHD diagnoses, which are discussed later in this section.

Another possible explanation for the low prevalence of mental disorder diagnoses in MedicineInsight is missing information. It is possible that some diagnoses from paediatric specialists, where diagnoses are commonly recorded [111], were not transferred to MedicineInsight. Also, as mentioned in previous chapters, GPs may not have recorded diagnoses in EHRs when cognisant of harms caused by the stigma of a mental disorder diagnostic label [456, 457]. Sensitive information is mostly recorded in progress notes and not captured in MedicineInsight data fields [355], possibly contributing to the apparently lower rates of diagnosis recorded in the dataset used in this thesis.

The difference in rates of ADHD diagnoses between the CAMHW survey and MedicineInsight showed much higher rates in CAMHW. The 2013/2014 CAMHW prevalence of ADHD was 13.5 times higher than ADHD diagnoses recorded in MedicineInsight in 2011 and 6.6 times higher than MedicineInsight's 2017 prevalence. This likely reflects the strict regulations for diagnosing and prescribing ADHD medications to children and adolescents [458, 459]. Stimulant drugs are classified as Schedule 8 drugs by the PBS due to their high potential for abuse and addiction [459]. In many Australian states and territories, stimulant prescriptions must be initiated and/or exclusively managed by paediatric specialists [458, 459]. In some situations, GPs are able to co-manage patients but need to apply for authority to prescribe stimulants according to state legislation [458, 459].

Table 7.1 Summary of Australian and international studies reporting on the prevalence of mental disorders in children and adolescents, with columns reporting on MedicineInsight data

Author	Lawrence (2015)[1]					Sadler et al (2018)[2]	Bitsko (2022)[3,a]	Barican (2022)[4]	Polanczyk (2015)[5]	2011 - Medicine-Insight	2017 - Medicine-Insight
Age range	4-17 years					5-19 years	3-17 years	4-18 years	6-18 years	0-18 years	0-18 years
Time period	2013/2014					2017	2013-2019	1993-2017	1983-2006	2011-2017	2011-2017
Population	Australia					England	United States	High income countries	All countries	Australian primary care	Australian primary care
Prevalence period	30 day %	12 month %	12 month % mild	12 month % moderate	12 month % severe	Unspecified[b]	Varied	Most 12-month	Varied	12-month	12-month
Any disorder	9.3	13.9	8.3	3.5	2.1	12.8[c]	13.9[d,e] [2017]	12.7	13.4	4.2	6.7
Schizophrenia						<0.1		0.1		0.03	0.05
Bipolar disorder						<0.5		0.3		0.04	0.04
Disruptive behaviour disorders							8.9 [7.0][e]	4.6	5.7	0.47	0.72
Behaviour disorders[f]						4.6					
Oppositional defiance disorder						2.9		3.3	3.6		
Conduct disorder	2.1	2.1	1.2	0.5	0.4	1.7		1.3	2.1		
Autism spectrum disorder						1.3	3.1 [2.9][e]	0.4		0.63	0.82
Attention-deficit/hyperactivity disorder	5.9	7.4	4.9	1.8	0.8	1.6	9.8 [8.7][e]	3.7	3.4	0.55	1.12
Any "emotional" disorder[g]						8.1					
Any depressive disorder						2.1	4.4 [3.4][e]	1.5	2.6	0.83	1.29

Author	Lawrence (2015)[1]					Sadler et al (2018)[2]	Bitsko (2022)[3,a]	Barican (2022)[4]	Polanczyk (2015)[5]	2011 - Medicine-Insight	2017 - Medicine-Insight
Prevalence period	30 day %	12 month %	12 month % mild	12 month % moderate	12 month % severe	Unspecified[b]	Varied	Most 12-month	Varied	12-month	12-month
Major depressive disorder	0.7	2.8	0.6	1.0	1.2	1.5		1.3	1.3		
Dysthymia						0.6		0.2	1.3		
Any anxiety disorder	3.4[h]	6.9[h]	3.7[h]	1.9[h]	1.3[h]	7.2[i]	9.4 [7.8][e,j]	5.2[k]	6.5[l]	0.92[m]	2.17[m]
Specific phobia						0.8		3.4			
Social phobia	1.1	2.3				0.8		1.2			
Separation anxiety disorder	1.7	4.3				0.7		1.6			
Reactive attachment disorder											
Generalised anxiety disorder	1.1	2.2				1.5		0.9			
Panic disorder						1.1		0.1			
Agoraphobia						0.5		0.1			
Post-traumatic stress disorder						0.6		0.1		0.0	0.05
Obsessive-compulsive disorder	0.5	0.8				0.4		0.3		0.08	0.09
Other less common disorders[n]						2.1					
Eating disorders						0.4		0.2		0.09	0.13
Substance use disorder							4.1	2.3		0.06	0.06
Sleep disorder										0.44	0.95
Personality disorder										0.02	0.02
Enuresis										0.39	0.40

Abbreviations: CAMHW, Child and Adolescent Mental Health and Wellbeing.

References included in this table:

1. Lawrence et al. (2015) The mental health of children and adolescents: report on the second Australian child and adolescent survey of mental health and wellbeing. Canberra: Department of Health. [15]

2. Sadler et al. (2018) Mental health of children and young people in England, 2017: trends and characteristics. Leeds (UK): NHS Digital. [17]

3. Bitsko et al. (2022) Mental health surveillance among children - United States, 2013-2019. [14]
4. Barican et al. (2022) Prevalence of childhood mental disorders in high-income countries: a systematic review and meta-analysis to inform policymaking. [19]
5. Polanczyk et al. (2015) Annual research review: a meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. [21]

Notes:

a. Nine surveillance systems examining child and adolescent mental health were used in this analysis: 1). Autism and Developmental Disabilities Monitoring Network (ADDM), 2). National Health and Nutrition Examination Survey (NHANES), 3). National Health Interview Survey (NHIS), 4). National Survey of Children's Health (NSCH), 5). National Survey on Drug Use and Health (NSDUH), 6). National Violent Death Reporting System (NVDRS), 7). National Vital Statistics System (NVSS), 8). School-Associated Violent Death Surveillance System (SAVD-SS), 9). Youth Risk Behavior Survey (YRBS).

b. The NHS digital survey did not specify the prevalence period. The survey used the Development and Wellbeing Assessment tool based on DSM-IV and ICD-10 criteria. Developers of the DABWA believed it preferable to focus on the present and recent past when assessing prevalence of mental disorders, mainly focussing on the previous month. (see Goodman et al. (2008), [18, p.647]).

c. The prevalence figure for 2017 comprises disorders included in previous surveys in 1999 and 2004, plus body dysmorphic disorder (BDD) and a few low prevalence conditions including bipolar affective disorder, both added in 2017.

d. The US mental health surveillance report did not give a figure for the prevalence of any disorder. For comparison, an estimate was obtained from a paper by Tkacz and Brady (2021) [22], examining mental health prevalence in children 4-17 years in the US, using the MarketScan commercial claims database. As the report by Bitsko et al. (2018) used nine different surveillance systems this figure may not be a good comparison.

e. Format x[y] shows the weighted prevalence for "Ever" (x) having the disorder (parent ever told by health care provider child had the problem) and [y] – "current" weighted prevalence (parent reported child currently had problem).

f. Behavioural disorders include conduct disorder (CD), oppositional defiant disorder (ODD), unsocialised and socialised CD, other CD.

g. Any "emotional" disorder includes separation anxiety disorder, different phobias (specific phobia, social phobia, agoraphobia), obsessive-compulsive disorder (OCD), panic disorder, post-traumatic stress disorder (PTSD), generalised anxiety disorder (GAD) and other anxiety disorders, depressive disorders, bipolar affective disorder, and body dysmorphic disorder.

h. Anxiety disorders in this category were social phobia, separation anxiety disorder, GAD or OCD.

i. Anxiety disorders in this category were: separation anxiety disorder, different phobias, OCD, panic disorder, PTSD, GAD, or other anxiety disorders.

j. Anxiety was defined as "anxiety problems", as measured by the NSCH survey.

k. Anxiety disorders in this category were: separation anxiety disorder, specific phobia, social anxiety disorder, GAD, panic disorder, agoraphobia. Six of the 14 studies in the meta-analysis also included PTSD and/or OCD.

l. This metanalysis covered a wide range of countries, methodologies and timespans. No list of included diagnoses in the "any anxiety disorder" was given.

m. Anxiety disorders were extracted from the MedicineInsight database using the following keywords: anxiety, phobia, generalised anxiety/GAD, panic disorder/panic attack, agoraphobia.

n. Other less common disorders include autism spectrum disorder, eating disorder, tic disorder, selective mutism and psychosis.

7.3 Changes in prevalence of mental disorder diagnoses

For ease of comparison, Table 7.2 combines information from Chapter 1 (Table 1.2) with Chapter 5's reported rates of recorded diagnoses from MedicineInsight (Table 5.1). Although comparability between studies was limited by differences in prevalence periods, patient age, and data collection methodology, the prevalence of mental disorders in children and adolescents using population surveys appears generally stable across several decades [21, 23]. In contrast, data from MedicineInsight showed a marked increase in the prevalence of most mental disorders from 2011 to 2017 (Table 7.3 replicates supplementary Table S5 in Chapter 5 and is also included for convenience). This could reflect a genuine increase in child and adolescent mental health problems encountered in general practice. Policy changes, such as the introduction of the Better Access initiative, may also explain the increase in recorded diagnoses. A brief discussion of policy changes that have occurred in the Australian health system is discussed in the next section.

Table 7.2 A summary of changes in Australian and international prevalence of child and adolescent mental disorders, with columns reporting on MedicineInsight data

Source	CAMHW survey (Lawrence)[1]			NHS Digital (Sadler)[2]				CDC (Bitsko)[3]			MedicineInsight		
Age range	1998	2013/14	Change %	5-15 years[a]	5-15 years[a]	5-15 years[a]	Change %	3-17 years	3-17 years	Change %	0-18 years	0-18 years	Change %
Time period	6-17 years	6-17 years		1999	2004	2017		2005-2011	2013-2019		2011-2017	2011-2017	
Prevalence period	12 month %	12 month %		Undefined[b]	Undefined[b]	Undefined[b]		Varied	Varied		2011	2017	
Any disorder[c]	12.5	11.1	-11.2%	9.7	10.1	11.2	15.5%[d]	11.0[e] [2012]	13.9[e] [2017]	26.4%	4.2	6.7	59.7%
Schizophrenia											0.03	0.05	66.7%
Bipolar disorder											0.04	0.04	0.0%
Behaviour disorders[f]				5.4	6.2	5.5	1.9%	4.6 [3.5][g]	8.9 [7.0][g]	93.5%[100.0][g]	0.47	0.72	53.2%
Oppositional defiance disorder													
Conduct disorder	2.7	2.1	-22.2%										
Autism spectrum disorder					1.0	1.3	30.0%	1.2 [1.1][g]	2.8 [2.5][g]	133.3% [127.3][g]	0.63	0.82	30.2%
Attention-deficit/hyperactivity disorder	9.8	7.8	-20.4%	1.5	1.5	1.9	26.7%	8.4 [6.8][g]	9.7 [8.5][g]	15.5% [25.0][g]	0.55	1.12	103.6%
Any "emotional" disorder[g]				4.3	3.9	5.8	34.9%[h]						
Any depressive disorder								3.9 [2.1][g]	4.4 [3.4][g]	12.8% [61.9][g]	0.83	1.29	55.4%
Major depressive disorder	2.1	3.2	52.4%										
Dysthymia													
Any anxiety disorder								4.7 [3.0][g,j]	9.4 [7.8][g.j]	100.0% [160.0][g,j]	0.92[k]	2.17[k]	135.9%
Post-traumatic stress disorder											0.0	0.05	66.7%
Obsessive-compulsive disorder											0.08	0.09	12.5%
Eating disorders					0.2	0.4	100.0%[l]				0.09	0.13	44.4%
Substance use disorder											0.06	0.06	0.0%
Sleep disorder											0.44	0.95	115.9%
Personality disorder											0.02	0.02	0.0%

Abbreviations: CAMHW, Child and Adolescent Mental Health and Wellbeing; CDC, Centers for Disease Control; NHS, National Health Service.

References included in this table:

1. Lawrence et al. (2015) The mental health of children and adolescents: report on the second Australian child and adolescent survey of mental health and wellbeing. Canberra: Department of Health.[15]
2. Sadler et al. (2018) Mental health of children and young people in England, 2017: trends and characteristics. Leeds (UK): NHS Digital.[17]
3. Bitsko et al. (2022) Mental health surveillance among children - United States, 2013-2019. [14]

Notes:

a. Disorders were assessed in 5-15-year-olds in 1999, 5-16-year-olds in 2004, and 5-19-year-olds in 2017. To examine trends the age group was restricted to 5-15 years. Disorders excluded from trend analyses include all disorders added since 1999, - body dysmorphic disorder, bipolar affective disorder, mania (emotional disorders), attachment disorder, feeding disorder, sleep disorder, eliminating disorder (other less common disorders).

b. The NHS digital survey did not specify the prevalence period. The survey used the Development and Wellbeing Assessment tool based on DSM-IV and ICD-10 criteria. Developers of the DABWA believed it preferable to focus on the present and recent past when assessing prevalence of mental disorders, mainly focussing on the previous month. (see Goodman et al. (2008), [18, p.647]).

c. For trend analyses, "any disorder" included all disorders measured for ach time period. CAMHW included depression, ADHD and conduct disorders; NHS Digital included behaviour disorders (defined in footnote e), autism spectrum disorders, ADHD and any "emotional" disorder (defined in footnote g); the US surveillance report only specified "behavioural or conduct problem" and "anxiety problem" without recording a specific diagnosis.

d. While the confidence intervals around the 1999 and 2017 rates of any disorder overlapped t-tests indicated an increase in the prevalence of any disorder over this period. However, there was no significant difference in prevalence rates between 2004 and 2017.

e. The US mental health surveillance report did not give a figure for the prevalence of any disorder. For comparison, an estimate was obtained from a paper by Tkacz and Brady (2021), examining mental health prevalence in children 4-17 years in the US, using the MarketScan commercial claims database. As the report by Bitsko et al. (2018) used nine different surveillance systems this figure may not be a good comparison.

f. For NHS Digital, behavioural disorders included oppositional defiant disorder (ODD), conduct disorder (CD), unsocialised CD, socialised CD and other CD.

g. Format x[y] shows the weighted prevalence for "Ever" (x) having the disorder (parent ever told by health care provider child had the problem) and [y] – "current" weighted prevalence (parent reported child currently had problem).

h. Any "emotional" disorder includes separation anxiety disorder, different phobias, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, generalised anxiety and other anxiety disorders, and depressive disorders. Disorders included for the first time in 2017 are excluded (bipolar affective disorder and body dysmorphic disorder).

i. Rates of "emotional" disorders were stable between 1999 and 2004 but increased significantly between 2004 and 2017.

j. Anxiety was defined as "anxiety problems", as measured by the National Survey of Children's Health.

k. Anxiety disorders were extracted from the MedicineInsight database using the following keywords: anxiety, phobia, generalised anxiety/GAD, panic disorder/panic attack, agoraphobia.

l. Eating disorders were not measured in 1999. Trends could only be examined from 2004 to 2017. The sample size for eating disorders was too small to reliably detect any changes.

Table 7.3 Changes in proportions of paediatric patients with mental disorder diagnoses recorded in MedicineInsight from 2011 to 2017 (reproduction of Chapter 5, Supplementary Table S5)

Mental disorder diagnosis	**Predicted % 2011**	**Predicted % 2017**	**Difference 2011 to 2017 (95% CI)[a]**	**% Change**	**p value**
Any mental health diagnosis	4.22	6.74	2.52 (2.21, 2.83)	59.7%	<0.001
Psychosis	0.03	0.05	0.02 (0.01, 0.03)	66.7%	0.001
Bipolar disorder	0.04	0.04	-0.001 (-0.02, 0.01)	0.0%	0.550
ASD	0.63	0.82	0.20 (0.12, 0.27)	30.2%	<0.001
DBD/CD	0.47	0.72	0.25 (0.18, 0.32)	53.2%	<0.001
ADHD	0.55	1.12	0.57 (0.44, 0.70)	103.6%	<0.001
ED	0.09	0.13	0.04 (0.02, 0.06)	44.4%	<0.001
Depression	0.83	1.29	0.45 (0.38, 0.53)	55.4%	<0.001
Anxiety	0.92	2.17	1.25 (1.14, 1.37)	135.9%	<0.001
Sleep	0.44	0.95	0.51 (0.42, 0.60)	115.9%	<0.001
OCD	0.08	0.09	0.01 (-0.01, 0.03)	12.5%	0.186
PTSD	0.03	0.05	0.02 (0.01, 0.04)	66.7%	<0.001
PD	0.02	0.02	0.004 (-0.005, 0.01)	0.0%	0.375
SUD	0.06	0.06	-0.00 (-0.02, 0.02)	0.0%	0.990
Incontinence/enuresis	0.39	0.40	0.01 (-0.03, 0.05)	2.6%	0.726
Learning disorder	0.09	0.10	0.02 (-0.004, 0.04)	11.1%	0.117
Language disorder	0.36	0.55	0.19 (0.13, 0.25)	52.8%	<0.001

Abbreviations: ASD, autism spectrum disorder; DBD, disruptive behaviour disorder; CD, conduct disorder; ADHD, attention deficit hyperactivity disorder; ED, eating disorder; OCD, obsessive-compulsive disorder; PTSD, post-traumatic stress disorder; PD, personality disorder; SUD, substance use disorder. IRSAD, Index of Relative Socio-economic Advantage and Disadvantage.

Notes:

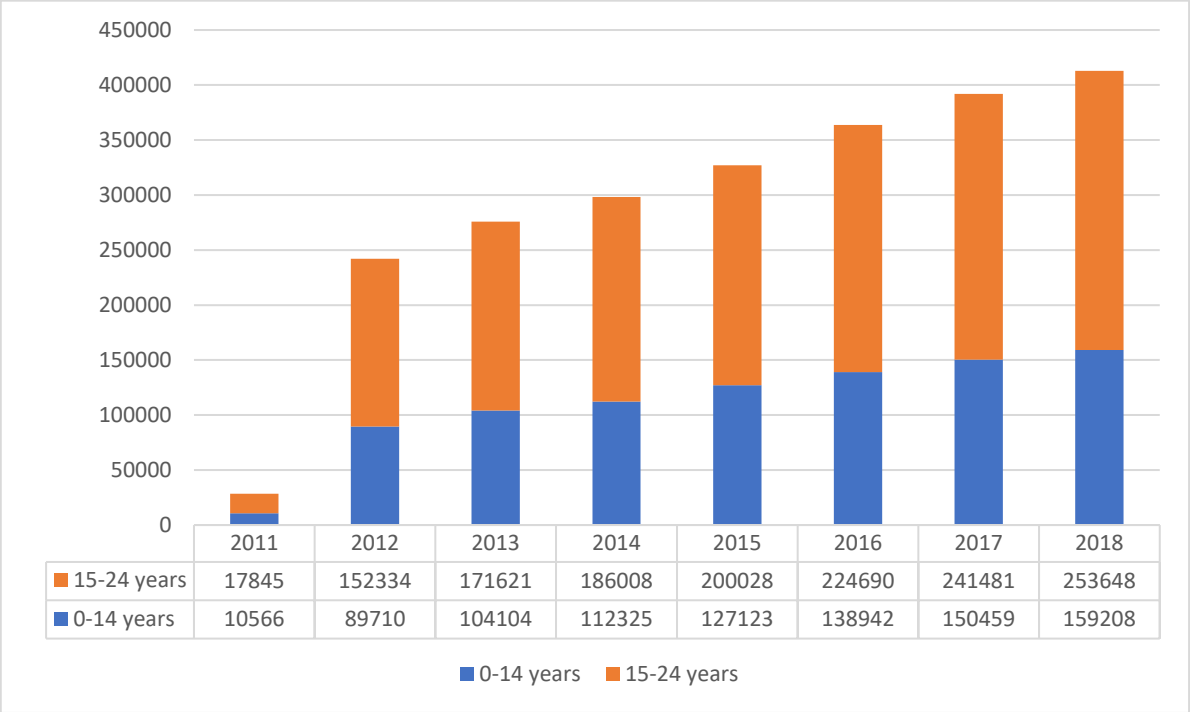
a. Analyses using logistic regression, adjusted for age, gender, patient IRSAD, and practice characteristics (state, rurality, practice IRSAD).

7.3.1 The Better Access Initiative

Several initiatives to address the unmet need for mental health treatment have been implemented by the Australian government, including the Better Outcomes in Mental Health Care program (introduced in 2001) [460] and Better Access initiatives (introduced in 2006) [461, 462]. Both schemes have provided patients with Medicare-subsidised non-drug treatments for mental disorders [460]. When Better Access was introduced, there was a rapid increase in GP billing for MBS mental health items [460, 461, 463]: from one in 500 patients with depression being treated under Better Outcomes in Mental Health Care to one in six being treated under Better Access [460].

To claim Medicare rebates under the Better Access initiative, GPs are required to undertake a biopsychosocial history, conduct a mental state examination, and make a diagnosis and/or formulation [464]. GP training is provided by the General Practice Mental Health Standards Collaboration (GPMHSC), a government-funded body established in 2002 to provide GPs with education and training in mental health (available at: https://gpmhsc.org.au/) [465]. GPs can undertake basic mental health skills training (MHST) or further upskill to train in focussed psychological strategies (FPS) [466]. Practitioners trained in FPS are able to provide some evidence-based psychological therapies, including cognitive behavioural therapy (CBT), interpersonal therapy (ITP), relaxation strategies, and training in problem-solving [466]. Medicare rebates are minimal for GPs with no mental health training, higher if GPs have undertaken MHST, and higher again if trained in FPS [466]. Under the Better Access initiative, GPs are required to develop a general practice mental health treatment plan (MHTP) for each patient, which assists in assessment, treatment planning, and the coordination of patient care between general practice and other health professionals [466].

Preparation of MHTPs by GPs increased steadily in the first 10 years of the scheme [463]. By 2010, most GPs were providing Better Access services, and by 2014, over 1.5 million MHTPs were prepared by GPs, with numbers continuing to rise steadily [463]. In 2022, the majority of Australian GPs (90%) had completed basic mental health skills training, while only 3.5% had undertaken the advanced FPS training [467]. Age-group data extracted from Medicare online shows the rapidly increasing trend in the provision of MHTPs by GPs during the study period also occurred in young patients (Figure 7.1).



	2011	2012	2013	2014	2015	2016	2017	2018
15-24 years	17845	152334	171621	186008	200028	224690	241481	253648
0-14 years	10566	89710	104104	112325	127123	138942	150459	159208

Figure 7.1 Numbers of young patients accessing Better Access GP MHTPs 2011 to 2018.
Abbreviations: GP, general practitioner; MHTP, mental health treatment plan.
Notes: Data for GP mental health treatment plans were not available from 2006 to 2010, and partial for 2011.

Widespread mental health training, undertaken by the majority of GPs since the inception of the Better Access initiative, would have likely resulted in increased recognition of mental health disorders by GPs. Furthermore, formulation of a diagnosis is required when generating a MHTP [457, 464]. This could partly explain the increase in the numbers of diagnoses recorded in MedicineInsight. There was a 57.1% increase in mental disorder diagnoses from 2012 to 2018 in MedicineInsight (Table 5.1) and according to data extracted from Medicare online (Figure 7.1), there was a 66.5% increase in 15-24-year-olds and a 77.5% increase in 0-14-year-olds with MHTPs during the same period. Although age groupings are not directly comparable, Figure 7.1 illustrates clearly that the provision of MHTPs was increasing similarly in children and adolescent/young adults.

7.4 Future directions in data collection of mental disorder prevalence

The accuracy of mental disorder prevalences in paediatric populations remains unreliable as data are sparse [468]. There have been only two surveys in Australia, in 1998 and 2013/2014, and only a handful of diagnoses were examined [23]. Contrasting and comparing the prevalence of mental disorders from the Australian CAMHW survey [15], international studies [14, 17], and the MedicineInsight database is difficult. Differing methodologies, assessment procedures, symptom informants (e.g., parent, child), age ranges [21], observation periods [469], and questionnaire phrasing [470] make the comparisons difficult.

Indeed, variability in methodologies is a well-recognised barrier to progress in the field of child and adolescent mental health [21, 471, 472].

Collishaw and Sellers (2020) have noted that the "development of robust methodologies to allow valid, reliable comparisons of prevalence, risk factors, and outcomes across time" [472, p.69] is an important priority to enable accurate tracking of the mental health burden in young people and assess the effectiveness of treatments. A team of Australian researchers, Lycet and colleagues [473], have suggested the limited availability of data on prevalence of mental disorders in Australian young people could be improved by combining three key health surveys: the triennial National Health Survey that collects data on multiple physical and mental health conditions (ages 2 and over), the National Survey of Child and Adolescent Mental Health and Wellbeing (ages 4-17 years), and the National Survey of Mental Health and Wellbeing (ages 16-85 years). Their proposed new combined triennial survey would cover all ages from 2 years and enable tracking of physical and mental health conditions, overweight/obesity, developmental outcomes, and both positive and negative health outcomes. Further, Lycet et al. suggest including measures for social determinants of health [473]. A new, more comprehensive, and regular health survey, in conjunction with the expanding use of electronic health records in large primary care databases [474] such as MedicineInsight, would significantly improve the monitoring of child and adolescent health outcomes when receiving psychotropic drugs.

In Chapter 8, the prevalence of mental disorders recorded in MedicineInsight is discussed in relation to prescribing for all the main classes of psychotropic drugs, to establish the degree to which prescribing follows TGA approvals and clinical guideline recommendations.

8 Off-label prescribing of psychotropics

8.1 Preface

In this chapter, off-label prescribing for all the main classes of psychotropics is reviewed and compared to TGA approvals and clinical practice guideline (CPG) recommendations. Discrepancies between these two sources of clinical guidance are discussed further in Chapter 9, Section 9.5.

The following research questions are addressed by this chapter:

1. Is prescribing of psychotropics concordant with TGA approvals for paediatric populations?
2. Is prescribing of psychotropics concordant with recommendations made by paediatric CPGs?

The prescribing of antipsychotics examined in Chapter 5 is discussed in greater detail in this chapter (Section 8.2). Other psychotropic drugs (antidepressants, ADHD drugs, anxiolytics, sedatives/hypnotics, and melatonin) are discussed in Sections 8.3 to 8.7 by comparing trends of psychotropic prescribing across the study period reported in Chapter 4 to trends of diagnoses reported in Chapter 5. To help facilitate these comparisons, trends are illustrated graphically and using data tables.

8.2 Antipsychotics

Off-label prescribing of antipsychotics to children and adolescents was examined in detail in Chapter 5. Antipsychotics are TGA-approved for paediatric patients with psychoses, manic episodes in bipolar disorder, autism spectrum disorder (ASD) with severe behavioural problems (e.g., self-destructive, self-injurious behaviour), and conduct disorder (CD), disruptive behaviour disorder (DBD), or severe aggression (see Supplementary Table S1, Chapter 5). Using a precise algorithm that considered the mental health condition, age of the child, and the specific antipsychotic drug recommended by the TGA, off-label prescribing was shown to increase from 2011 to 2017 by 10% overall, reaching 79.7% in 2017. However, the analysis in Chapter 5 did not consider whether prescribing was concordant with guidelines. Sections 8.2.1.1 to 8.2.1.3 briefly discuss guideline-concordance for the three main off-label diagnoses among children and adolescents receiving antipsychotics: depression/anxiety, ASD, and ADHD. Section 8.2.1.4 examines guideline-concordance with metabolic monitoring for patients receiving antipsychotics.

8.2.1 TGA concordant and guideline-concordant prescribing of antipsychotics in primary care

8.2.1.1 Depression and anxiety diagnoses

For psychotic depression, antipsychotics are recommended in two Australian [171] and two international paediatric depression guidelines [188, 189], but there are no TGA approvals for this indication. In the off-label antipsychotic study (Chapter 5), the process by which diagnoses were associated with prescriptions used a hierarchical method, such that all mentions of depression or anxiety comorbid with diagnoses higher up in the hierarchy were not classified as depression or anxiety diagnoses. Psychotic depression was included in the first category of "psychoses, including schizophrenia" and not included in depression diagnoses. For anxiety, only one antipsychotic, the FGA, periciazine, is approved in Australia for the treatment of severe anxiety in children over 6 years of age [475]. There were no prescriptions for this FGA in the MedicineInsight paediatric dataset.

No Australian paediatric guidelines recommend antipsychotics, but three international child and adolescent guidelines include them as non-first-line options for PTSD [255], obsessive-compulsive disorder (OCD) [256], and for adjunctive use in treatment-resistant depression (TRD) [189]. OCD and PTSD diagnoses had low rates recorded in MedicineInsight (see Table 5.1, Chapter 5) and are therefore an unlikely explanation for the high rates of antipsychotic prescribing to children and adolescents with anxiety reported in this thesis[h]. Further, the BMJ Best Practice guidelines emphasised that no paediatric controlled studies had been done using SGAs to treat TRD and that antipsychotics "should only be commenced by specialists who are experts in managing depression in childhood" [189, p.34]. Therefore, it is also unlikely that the high use of antipsychotics would be for augmentation in TRD in this thesis.

The records of depression and anxiety disorder associated with antipsychotic prescriptions recorded in MedicineInsight indicate a lack of concordance with Australian and international paediatric guidelines and TGA approvals.

[h] Note that PTSD and OCD were categorised under anxiety disorders in the DSM-IV but have been listed as separate disorders in the most recent version (DSM-5), which was published in 2013. In the present thesis, anxiety disorders have been grouped using DSM-IV categories.

8.2.1.2 Autism spectrum disorders (ASD)

In Australia, risperidone [476] and chlorpromazine [477] are approved for children and adolescents with behavioural disorders associated with ASD and intellectual retardation, in whom destructive behaviours are prominent (e.g., aggression, impulsivity, self-injury). Risperidone is also approved by the FDA, EMA, and MHRA for behavioural disorders in children and adolescents with ASD and is the most commonly prescribed antipsychotic for this indication in many countries [478]. In line with regulatory approvals, the Australian eTG Complete guidelines [294] and most other international guidelines (summarised in Appendix 10) also recommend risperidone to treat behavioural disorders in paediatric patients with ASD. No guidelines recommend antipsychotics for any core symptoms of ASD.

This thesis observed a diagnosis of ASD without behavioural problems was the second most common diagnosis among children and adolescents prescribed antipsychotics, and risperidone was the most prescribed for ASD both with and without behavioural problems. Of all patients with a recorded diagnosis of ASD in 2011 and 2017, 10.8% (n = 7) and 8.9% (n = 22) respectively, also had aggression or self-destructive behaviours recorded in the database. For autism without behavioural problems 3.7% (n = 41) of patients in 2011 and 6.1% (n = 188) of patients in 2017 were prescribed an antipsychotic. Therefore, the majority of antipsychotic prescriptions for patients with a diagnosis of ASD were neither TGA-approved nor guideline-concordant.

8.2.1.3 ADHD

There are no TGA-approved antipsychotics for ADHD. Australian [214] and international [214, 221, 225, 228, 229, 232] ADHD guidelines also make few recommendations for antipsychotics. SGAs are only recommended if ADHD is comorbid with other conditions, including aggressive or behavioural conditions (e.g., CD, oppositional defiant disorder [ODD]) [214, 221, 225, 228, 232], ASD [225], or learning disorders [225]. In hierarchical analyses of MedicineInsight data, an ADHD diagnosis was recorded at level 6, aggressive or behavioural conditions at level 4, and ASD at level 5. Therefore, behavioural conditions and ASD comorbid with ADHD would have been captured in levels higher up the hierarchy and not recorded as the primary diagnosis associated with the antipsychotic prescription. Learning disorders were recorded at low levels in the dataset (see Table 5.1). Therefore, absent the above comorbid conditions, the prescribing of antipsychotics to children and adolescents

diagnosed with ADHD during the study period occurred off-label and was not guideline-concordant.

8.2.1.4 Cardiometabolic monitoring for antipsychotic prescriptions

The examination of cardiometabolic monitoring for antipsychotic users reported in Chapter 6 shows a low adherence to guidelines. Guidelines suggest weight measurements should have been monitored 7 to 9 times in the year following the commencement of antipsychotics (Table1, Chapter 6). However, only 10.4% of patients had their weight measured more than twice during this timeframe. Measurements requiring more invasive procedures, such as venepuncture, were recommended three to four times in the year following the initiation of an antipsychotic, but only 0.9% of patients had any blood parameters tested more than twice.

Although monitoring rates were poor in general practice, monitoring may have occurred in other settings, such as hospitals and specialist psychiatric or paediatric services. The implications of the cardiometabolic monitoring results obtained in the MedicineInsight GP dataset are discussed further in Chapter 9.

8.3 Antidepressants

8.3.1 Off-label prescribing and depression and anxiety disorders

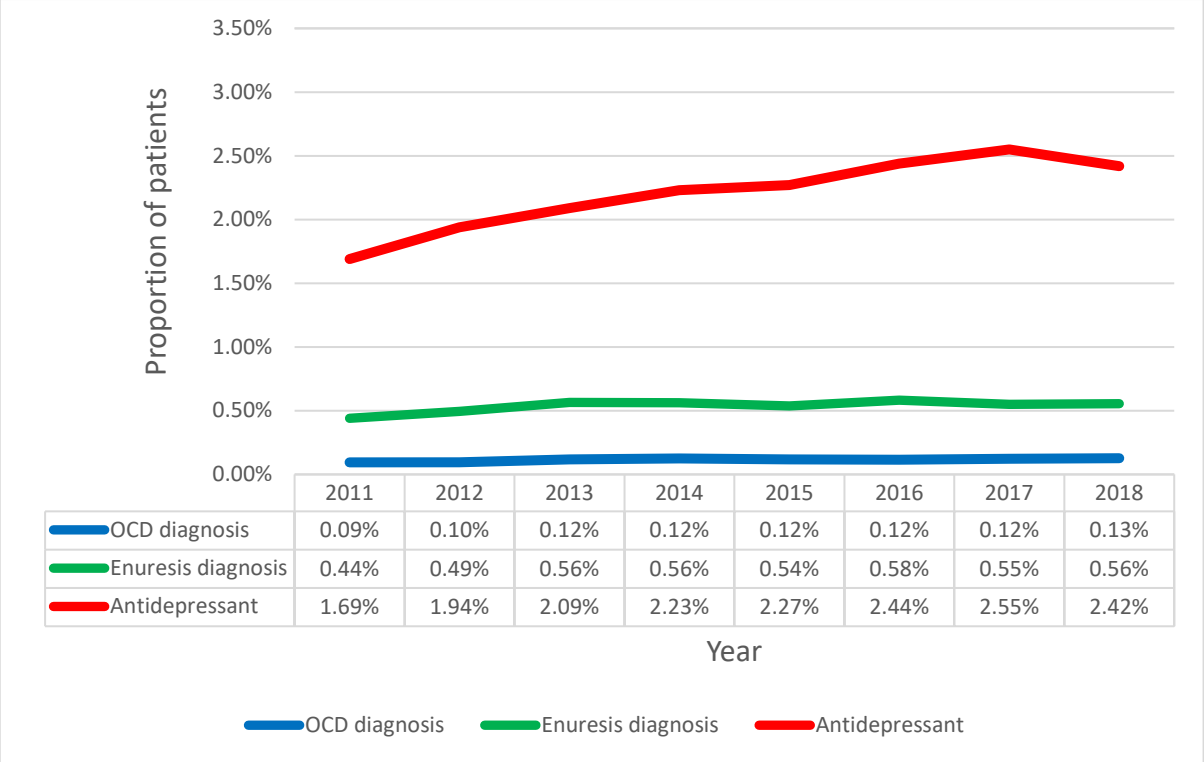
The diagnoses for which antidepressants are approved[i] for Australian children and adolescents are: OCD (fluvoxamine [479] and sertraline [480]), and enuresis (amitriptyline [481] and imipramine [332]). These two diagnoses were recorded in MedicineInsight at low rates in both 2011 and 2018. Nine in 10,000 patients in 2011 and 13 in 10,000 in 2018 had an OCD diagnosis recorded. 44 in 10,000 patients recorded a diagnosis of enuresis in 2011 and 56 in 10,000 in 2018 (see Chapter 5, Table 5.1).

All depression guidelines (Appendix 2), including the Australian NHMRC-approved *beyondblue* guidelines [171] and multiple anxiety disorder guidelines (see Appendix 7), recommend antidepressants as first-line pharmacological treatment after an initial trial of non-drug therapies.

Figure 8.1 shows crude proportions of patients prescribed an antidepressant and crude proportions of patients with diagnoses for which antidepressants are approved across the study period. Prescriptions were substantially higher than diagnoses, indicating the majority

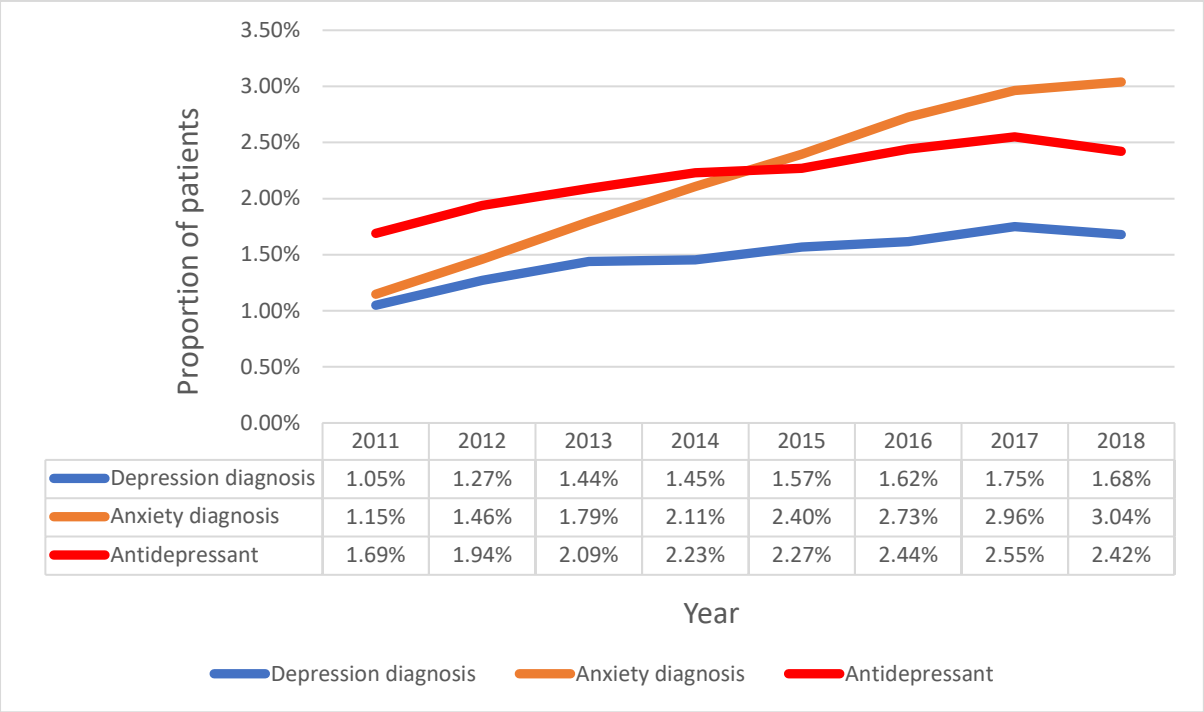
[i] Lithium was included in the antidepressant class in this thesis. Although approved for mania and psychotic disorders, lithium was prescribed in very low numbers in this analysis and is therefore not reported.

of antidepressant prescriptions were prescribed off-label. Figure 8.2 plots crude proportions of patients receiving antidepressants alongside the crude proportions of patients receiving a diagnosis of anxiety or depression for each year of the study period. The trend lines for the number of patients receiving antidepressants and depression diagnoses are remarkably similar. Although the number of patients with prescriptions is higher than depression diagnoses, diagnoses for anxiety outnumbered prescriptions after 2014. The general pattern suggests a close to 1:1 prescription of antidepressants and diagnosis of depression and/or anxiety. Considered together, Figures 8.1 and 8.2 suggest the majority of antidepressants are prescribed for non-TGA-approved depression and anxiety disorders. However, this is concordant with all guidelines summarised in this thesis.



	2011	2012	2013	2014	2015	2016	2017	2018
OCD diagnosis	0.09%	0.10%	0.12%	0.12%	0.12%	0.12%	0.12%	0.13%
Enuresis diagnosis	0.44%	0.49%	0.56%	0.56%	0.54%	0.58%	0.55%	0.56%
Antidepressant	1.69%	1.94%	2.09%	2.23%	2.27%	2.44%	2.55%	2.42%

Figure 8.1 Crude proportions of patients prescribed antidepressants and crude proportions of patients with diagnoses with TGA antidepressant approvals recorded in MedicineInsight from 2011 to 2018. Illustration of trends is not comparable to other figures due to differing percentage ranges Graph axes have been restricted to 0.0% to 3.5% to aid the visualisation of trends. Abbreviation: OCD, obsessive-compulsive disorder.



	2011	2012	2013	2014	2015	2016	2017	2018
Depression diagnosis	1.05%	1.27%	1.44%	1.45%	1.57%	1.62%	1.75%	1.68%
Anxiety diagnosis	1.15%	1.46%	1.79%	2.11%	2.40%	2.73%	2.96%	3.04%
Antidepressant	1.69%	1.94%	2.09%	2.23%	2.27%	2.44%	2.55%	2.42%

Figure 8.2 Crude proportions of patients prescribed antidepressants and crude proportions of patients with diagnoses of anxiety or depression recorded in MedicineInsight from 2011 to 2018.
Illustration of trends is not comparable to other figures due to differing percentage ranges. Graph axes have been restricted to 0.0% to 3.5% to aid the visualisation of trends.

8.3.2 Off-label prescribing and enuresis

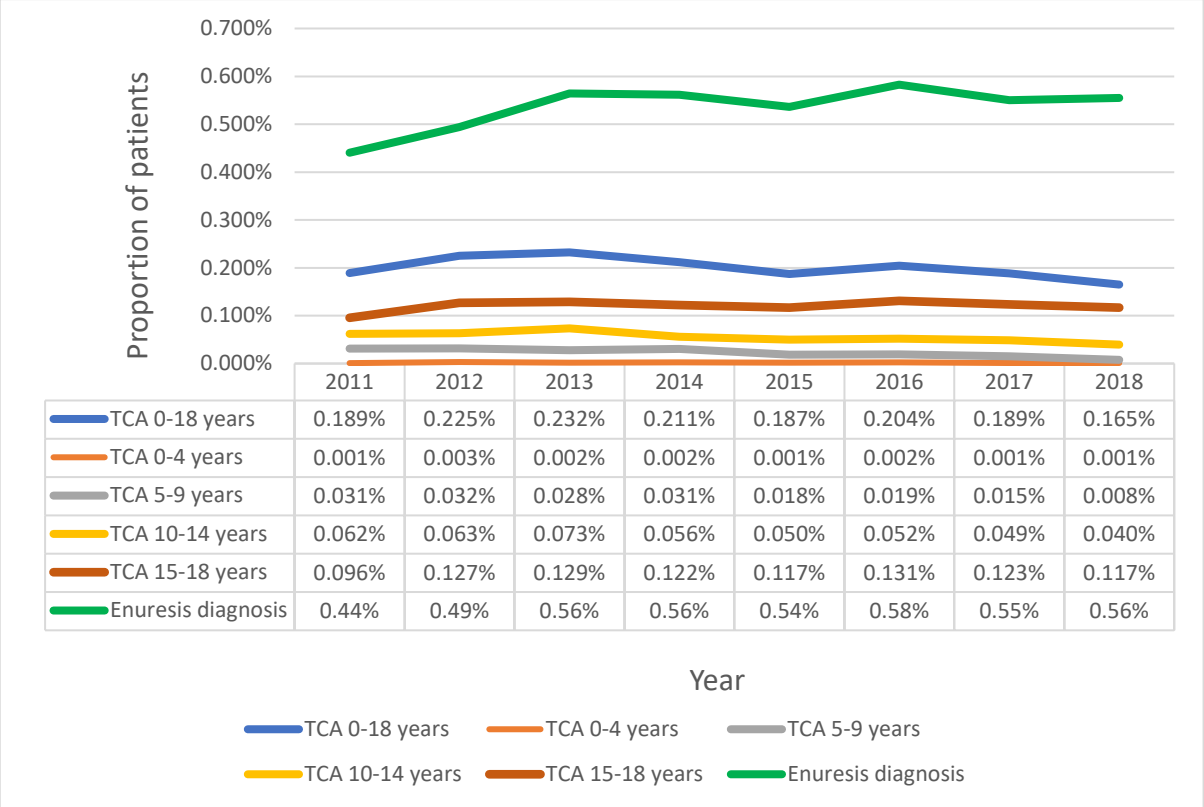
Two TCAs, amitriptyline [481] and imipramine [332], are approved by the TGA for bedwetting disorders. However, guidelines summarised in Appendix 13 mention only imipramine [325-328, 330, 331] or explicitly state that TCAs are no longer used to treat bedwetting [329]. The TGA has approved amitriptyline for all ages, but clinical guidelines do not recommend pharmacological treatment before age 6 (see Appendix 13).

The prevalence of bedwetting is around 30% in 4-year-olds [329], 10% in 6-year-olds [329], and has a spontaneous remission rate of approximately 15% each year throughout childhood [327]. Therefore, to help identify off-label prescribing trends, Figure 8.2 includes a breakdown of TCA prescribing by age group.

There were low proportions of patients prescribed TCAs in comparison to diagnoses of enuresis. Amitriptyline was the most prescribed antidepressant for 0-4-year-olds in 2018 and the only drug TGA-approved for this indication for this young age group, suggesting some prescribing was “on-label”. However, amitriptyline was not recommended in any enuresis guidelines, indicating a lack of guideline-concordance. All guidelines recommend the

hormonal drug desmopressin as a first-line treatment for enuresis (see Appendix 13), which is a non-psychotropic drug and therefore beyond the scope of this thesis.

The overall low proportions of patients with enuresis prescribed TCAs may indicate high levels of guideline-concordant prescribing. GPs may be using non-pharmaceutical options for most children and reserving treatment with TGA-approved drugs for small numbers of children who do not respond to non-pharmacological interventions. As age increases and the prevalence of bedwetting declines, TCAs are likely prescribed for other disorders that are not TGA-approved (e.g., depression).



	2011	2012	2013	2014	2015	2016	2017	2018
TCA 0-18 years	0.189%	0.225%	0.232%	0.211%	0.187%	0.204%	0.189%	0.165%
TCA 0-4 years	0.001%	0.003%	0.002%	0.002%	0.001%	0.002%	0.001%	0.001%
TCA 5-9 years	0.031%	0.032%	0.028%	0.031%	0.018%	0.019%	0.015%	0.008%
TCA 10-14 years	0.062%	0.063%	0.073%	0.056%	0.050%	0.052%	0.049%	0.040%
TCA 15-18 years	0.096%	0.127%	0.129%	0.122%	0.117%	0.131%	0.123%	0.117%
Enuresis diagnosis	0.44%	0.49%	0.56%	0.56%	0.54%	0.58%	0.55%	0.56%

Figure 8.3 Crude proportions of patients prescribed TCA antidepressants by age group and crude proportions of patients with diagnoses of enuresis recorded in MedicineInsight from 2011 to 2018.
Illustration of trends is not comparable to other figures due to differing percentage ranges. Graph axes have been restricted to 0.0% to 0.7% to aid the visualisation of trends. Abbreviation: TCA, tricyclic antidepressant. Diagnosis covers 0-18-year-olds, but most diagnoses of enuresis (bedwetting) apply to the younger age groups. Guidelines recommend children under 6 years of age should not receive drugs. Age groups are illustrated separately to easily identify prescribing trends.

8.4 ADHD drugs

Like all other diagnoses of childhood mental disorders, treatment guidelines for ADHD recommend non-drug options as first-line, with stimulants preferred when pharmacological treatment is indicated (see Appendix 5). TGA-approved stimulants (methamphetamine, dexamphetamine, and lisdexamphetamine) are strictly regulated in Australian states and territories [458, 459]. In most cases, GPs must refer patients to specialists to diagnose the

disorder and initiate drug treatment, after which GPs can be involved as co-prescribers [458, 459]. Other TGA-approved drugs for ADHD in children and adolescents include atomoxetine and guanfacine[j]. Figure 8.4 shows crude proportions of patients prescribed ADHD drugs and crude proportions of patients with ADHD diagnoses.

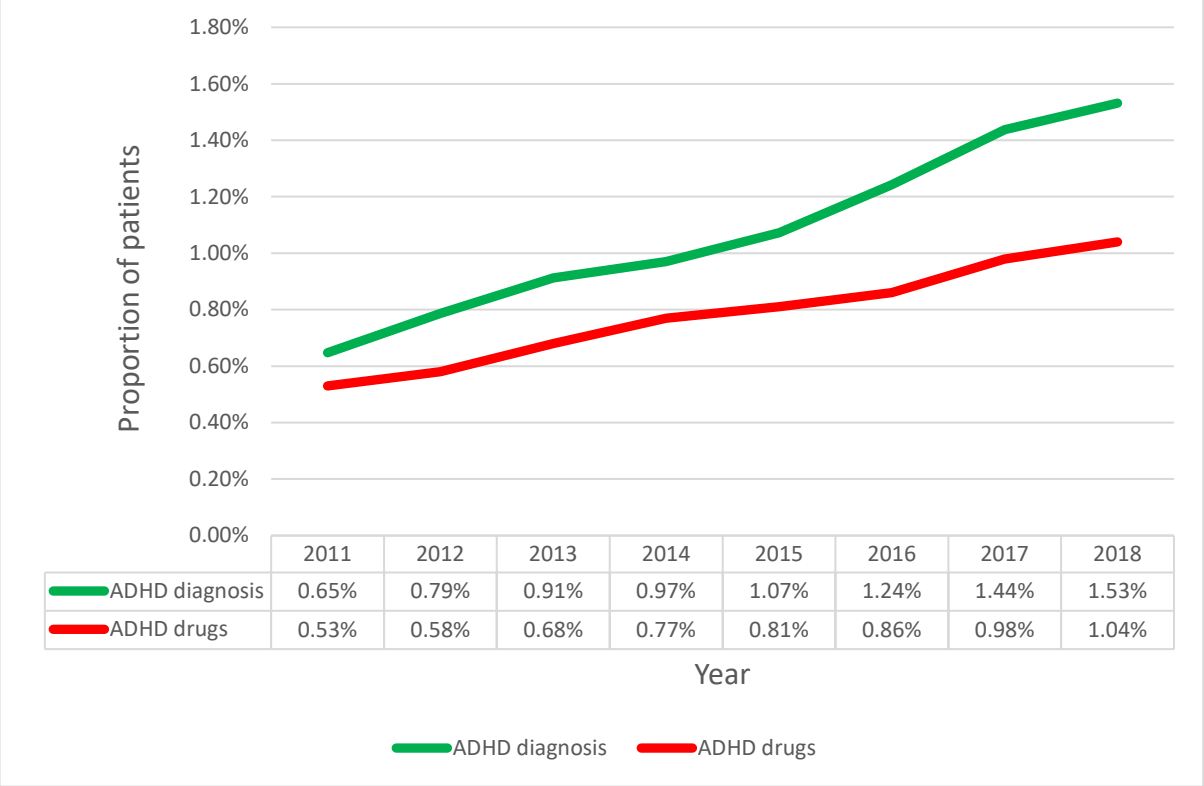


Figure 8.4 Crude proportions of patients prescribed ADHD drugs and crude proportions of patients with diagnoses of ADHD recorded in MedicineInsight from 2011 to 2018. Illustration of trends is not comparable to other figures due to differing percentage ranges. Graph axes have been restricted to 0.0% to 1.8% to aid the visualisation of trends. Abbreviation: ADHD, attention-deficit hyperactivity disorder.

Notably, Figure 8.4 shows more diagnoses were recorded than prescriptions written by GPs. This could occur if GPs are recording ADHD diagnoses in patients' medical records but treatment for ADHD remains under specialist care. Alternatively, this may be an artefact of the algorithm used to extract diagnoses from the database. Specifically, the severity of disorders was not available in MedicineInsight, resulting in the diagnostic algorithm attaching an ADHD diagnosis to children with severe, moderate, or mild attention/hyperactivity problems. The observed difference in prescriptions and diagnoses could represent guideline-concordant practices by GPs who first engage in "watchful waiting" or non-drug therapies when symptoms are not severe. Given strict regulations

j. Guanfacine is an alpha-2 agonist/anti-hypertensive drug. It was approved for ADHD in children over 5 years in August 2017.

around diagnosing and treating paediatric ADHD, prescribing by GPs recorded in MedicineInsight would mostly be consistent with TGA approvals and guideline concordant.

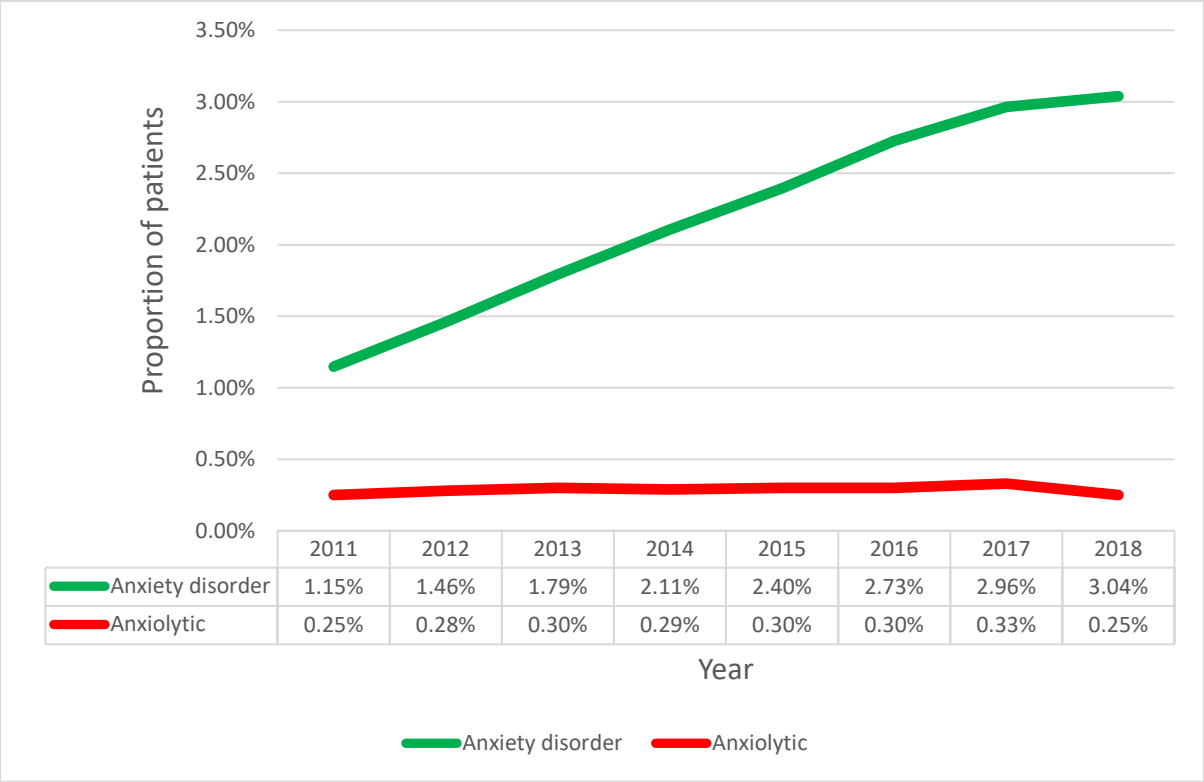
8.5 Anxiolytics

In Australia, the TGA has approved three anxiolytic benzodiazepines[k] for treating anxiety disorders in children and adolescents: diazepam [482], oxazepam [483], and lorazepam [484]. These drugs are approved for children aged over 6 months (diazepam) and adolescents over 15 years (oxazepam, lorazepam). However, due to problems with drug dependence and serious adverse events (including cognitive blunting, disinhibition, and risk of seizures on discontinuation), benzodiazepines are not considered first-line treatments for paediatric anxiety [485]. Treatment guidelines recommend SSRIs as first-line drugs for anxiety [486] (see Appendix 7 for a summary of guidelines).

There were no recommendations for benzodiazepines in Australian anxiety disorder guidelines[l] and few in international guidelines. Alprazolam and clonazepam are mentioned as possible treatments for children and adolescents with panic disorder in Canadian [264, 265] and US [258] clinical practice guidelines (CPGs), and lorazepam is mentioned for OCD and PTSD in Canadian CPGs [264]. Notably, all guidelines summarised in Appendix 7, including adult ones, do not recommend anxiolytics as first-line options for treating any anxiety disorders, and Canadian guidelines specifically contra-indicate alprazolam and clonazepam for some paediatric anxiety disorders [264, 265]. Figure 8.5 shows crude proportions of patients prescribed anxiolytics and crude proportions of patients with diagnoses of anxiety disorders across the study period.

k. Benzodiazepines are included in both anxiolytics and sedatives/hypnotics. The WHO ATC codes classify the N05B class of drugs as anxiolytics and include alprazolam, bromazepam, diazepam, oxazepam, lorazepam, and clobazam. The N05C class of benzodiazepines is classified as sedatives/hypnotics and includes flunitrazepam, midazolam, nitrazepam, temazepam, and the Z-drugs zopiclone and zolpidem.

l. The Melbourne Children's Campus Mental Health Strategy Anxiety Guideline Development Group published a clinical practice guideline for anxiety in children and young people in October 2023. [250].



	2011	2012	2013	2014	2015	2016	2017	2018
Anxiety disorder	1.15%	1.46%	1.79%	2.11%	2.40%	2.73%	2.96%	3.04%
Anxiolytic	0.25%	0.28%	0.30%	0.29%	0.30%	0.30%	0.33%	0.25%

Figure 8.5 Crude proportions of patients prescribed anxiolytics, and crude proportions of patients with anxiety disorder diagnoses recorded in MedicineInsight from 2011 to 2018. Illustration of trends is not comparable to other figures due to differing percentage ranges. Graph axes have been restricted to 0.0% to 3.5% to aid the visualisation of trends.

The small proportion of patients prescribed anxiolytics in conjunction with higher and increasing proportions of patients with diagnoses of anxiety disorders suggests prescribing is largely concordant with TGA approvals and clinical practice guidelines. Indeed, this stable low level of prescribing may be explained by guideline-concordant prescribing for non-psychiatric conditions such as seizures and status epileptics, for which benzodiazepines are first-line options [487, 488]. In the anxiolytic category used in analyses in this thesis, the two drugs diazepam and clobazam were the predominant benzodiazepines prescribed in 2018, making up over 90% of anxiolytic prescriptions for 0-14-year-olds and 83% for 15-18-year-olds. Diazepam is commonly recommended for seizures in paediatric guidelines [487-491] and clobazam is TGA-approved for epilepsy in children over 3 years of age [492].

One BMJ Best Practice guideline for sleep disorders [319] (discussed in Section 8.6) included three anxiolytics for parasomnias (e.g., sleepwalking, sleep terrors). However, no anxiolytics are TGA-approved for these conditions, and it is unlikely the few non-first-line benzodiazepine recommendations mentioned in the BMJ Best Practice guideline significantly contributed to off-label anxiolytic prescribing.

8.6 Sedatives/hypnotics

Sedatives/hypnotics were the only class of psychotropics to show a significant decreasing trend in prescriptions across the study period of 40.2% and the only class of drugs with no approvals for any mental disorders in children and adolescents. There were also no sedatives/hypnotics in paediatric clinical practice guidelines for sleep disorders[m] (see Appendix 12 for summary), where melatonin was the most commonly recommended drug (discussed further in Section 8.7). Figure 8.6 (presented in Section 8.7) shows the crude proportion of patients prescribed sedatives/hypnotics and melatonin, compared to the crude proportion of patients with recorded sleep disorder diagnoses.

While not approved for any mental disorders, one sedative/hypnotic (midazolam) is TGA-approved for non-psychiatric use in anaesthesia, perioperative sedation, and relief of pre-operative apprehension in children over 7 years of age [493]. Midazolam is also a preferred drug for seizures in children [487-491], although it was not TGA-approved for this indication during the study period[n]. In the 2018 analysis of sedative/hypnotic prescribing, 84.6% of 0-4-year-olds were prescribed midazolam, followed by 82.9% of 5-9-year-olds and 61.7% of 10-14-year-olds, compared to 9.3% of 15-18-year-olds (see Chapter 4, Table 4). Seizures are relatively common in children, with around 8% experiencing them by 15 years of age [488]. Therefore, the pattern of prescribing is consistent with the drug being used primarily to manage perioperative apprehension or seizures in childhood and early adolescence.

Another notable finding was the choice of temazepam as the preferred sedative/hypnotic when prescribing to 15-18-year-olds in 2018. The majority of sedative/hypnotic prescriptions for children and adolescents in all years in the present thesis were for temazepam (see Chapter 4, Supplementary Table S9), which is also the sedative/hypnotic most commonly prescribed to adults with insomnia [495, 496] and recommended in Australian adult insomnia guidelines [176]. Indeed, all sedatives/hypnotics except midazolam are TGA-approved for adults with insomnia [497-501]. This suggests a level of concordance with adult guidelines.

Overall, the pattern of paediatric sedative/hypnotic prescribing suggests guideline-concordant prescribing of midazolam for seizures in under 15-year-olds, despite a lack of

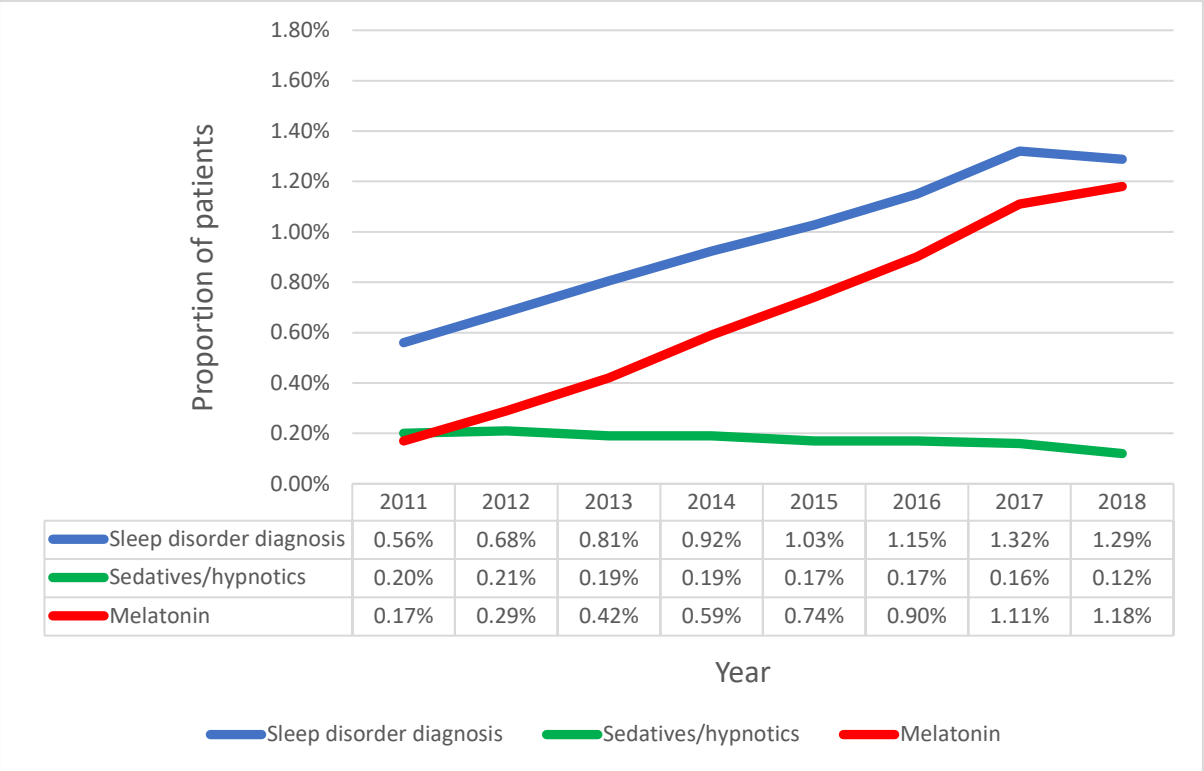
m. Although no sedatives/hypnotics were listed in any guidelines, benzodiazepines classified as anxiolytics were mentioned in options in the BMJ Best Practice child guidelines for parasomnias.
n. Midazolam oromucosal solution (Zyamis) was approved by the TGA in April 2022 for treatment of epilepsy in patients over 6 months of age. [494].

approval for seizures or epilepsy across the study period. In 15-18-year-olds, most prescribing appears off-label and non-guideline-concordant prescribing of temazepam for sleep problems. Of note, prescribing of the sedative/hypnotic class of psychotropics declined across the study period, with temazepam contributing the most to this trend, demonstrating a positive move toward reducing off-label prescribing to children and adolescents.

8.7 Melatonin

Melatonin was not TGA-approved for any paediatric conditions during the study period but was recommended often by CPGs. Almost all guidelines for ASD recommend melatonin in children with ASD and sleep disturbances [289, 290, 295, 296, 299-301] (see Appendix 10 for summary), and several guidelines for paediatric sleep disorders refer to melatonin as a treatment option [318-322, 324] (see Appendix 12 for summary). One paediatric ADHD guideline also recommends melatonin for treating comorbid insomnia [231].
Figure 8.6 compares the crude proportions of patients prescribed sedatives/hypnotics and melatonin and the crude proportions of patients with recorded diagnoses of sleep disorders in the MedicineInsight paediatric dataset from 2011 to 2018. The trend lines show a remarkable similarity between sleep disorders and the prescription of melatonin.

The high levels of prescribing of melatonin observed in this thesis are consistent with the frequent mentions of melatonin in paediatric CPGs. Melatonin prescribing in this thesis was all off-label but appears to be largely guideline-concordant.



	2011	2012	2013	2014	2015	2016	2017	2018
Sleep disorder diagnosis	0.56%	0.68%	0.81%	0.92%	1.03%	1.15%	1.32%	1.29%
Sedatives/hypnotics	0.20%	0.21%	0.19%	0.19%	0.17%	0.17%	0.16%	0.12%
Melatonin	0.17%	0.29%	0.42%	0.59%	0.74%	0.90%	1.11%	1.18%

Figure 8.6 Crude proportions of patients prescribed sedatives/hypnotics and melatonin, and crude proportions of patients with diagnoses of sleep disorders recorded in MedicineInsight from 2011 to 2018. Illustration of trends is not comparable to other figures due to differing percentage ranges. Graph axes have been restricted to 0.0% to 1.8% to aid the visualisation of trends.

8.8 Summary

Off-label paediatric prescribing by general practitioners was present to some degree for all the main classes of psychotropics examined in this thesis and was especially concerning for antipsychotics, antidepressants, and melatonin. Although occurring nearly 100% off-label, melatonin and antidepressant prescribing appeared to be guideline-concordant. Antipsychotic prescribing occurred mostly off-label, with low levels of adherence to metabolic monitoring protocols. Possible explanations for the patterns of off-label prescribing observed in this thesis, as well as implications for health care policy, are discussed further in Chapter 9.

9 Chapter 9 General discussion

9.1 Preface

The aim of this thesis was to examine how psychotropic drugs were being prescribed to children and adolescents in Australian general practice from 2011 to 2018. In this chapter, key findings are summarised and compared to Australian and international studies. Implications for health policies are also examined.

The chapter is divided into six sections (Sections 9.2 to 9.7).

Section 9.2 briefly summarises overall prescribing patterns and trends and compares the findings to other published studies. Section 9.3 follows with an examination of off-label prescribing trends and patterns.

Section 9.4 explores changes in CPGs since the end of the study period to determine whether there have been any major changes in therapeutic recommendations since these analyses were undertaken. This section also discusses a recent controversial FDA drug approval for paediatric anxiety disorders. Section 9.5 continues the discussion of guidelines but critically examines the quality and usefulness of paediatric CPGs using the findings in this thesis to expand on the discussion in Chapter 2.

Section 9.6 examines the patterns of prescribing of psychotropic drugs by social disadvantage. The present thesis found a social gradient in prescribing (see Chapter 4) that was lessened in the study of off-label antipsychotic prescribing using a sample of children and adolescents with mental disorders (Chapter 5). Possible reasons for this observation are discussed in this section, and recommendations for future research are made.

Section 9.7 discusses the implications for health policy, with special attention to antidepressants and antipsychotics.

Section 9.8 discusses the methodological contribution of this thesis, highlighting the benefits and limitations of using EHRs to examine prescribing practices and patient health outcomes.

9.2 Trends in psychotropic prescribing to children and adolescents

The changes in prescribing of psychotropics recorded in the MedicineInsight dataset were similar to those reported by two Australian studies using PBS datasets [12, 502]. An earlier study by Karanges et al. (2014) examining paediatric PBS prescribing from 2009 to 2012 for three classes of psychotropics (antidepressants, antipsychotics, and ADHD drugs) found

similar increases to this thesis: the highest increases occurred in prescriptions for ADHD drugs, followed by antipsychotics and antidepressants [12]. Also, in agreement with our findings, increases observed for antidepressants and antipsychotics were highest in 10-14-year-olds [12]. The patterns of most frequently prescribed antidepressants and antipsychotics were also similar to those found in this thesis: fluoxetine was most commonly prescribed to 3-19-year-olds, risperidone to children under 15 years, and quetiapine to adolescents and young adults (aged 15-24 years) [12]. A more recent study by Wood and colleagues [502] using PBS data from 2013 to 2021 also observed increased prescribing of psychotropics to children and adolescents. Altogether, the similarities in prescribing patterns show a consistent and continuing upward trend in prescribing psychotropics to Australian children and adolescents.

Changes observed in this thesis were also concordant with international studies that found increased prescribing over the last two decades for antipsychotics [3, 4, 503, 504], antidepressants [1, 3, 47, 505-507], ADHD drugs [2, 3, 507, 508], and melatonin [115, 117, 509, 510]. Studies examining anxiolytics and sedatives/hypnotics [3, 6, 115, 117, 127, 503, 509-511] recorded generally low prescription rates that were stable or declining slightly, which are also similar to this thesis. Melatonin prescribing has been rising rapidly in Australian general practice and worldwide [115, 117, 509, 510, 512], despite concerns with a lack of quality paediatric studies [513]. Issues around melatonin prescribing are discussed further in Section 9.3.3.

With respect to sociodemographics and concordant with other Australian and international studies, antidepressants were more frequently prescribed to females [1, 6, 47, 502, 503, 505, 506], and ADHD drugs [2, 3, 507, 508] and antipsychotics [6, 502, 503] were prescribed more frequently to males. This thesis also generally observed a social gradient whereby prescribing was higher in more socio-economically disadvantaged areas. Existing literature examining prescribing and social gradients is inconsistent and is discussed in depth in Section 9.6.

In summary, patterns and trends in psychotropic prescriptions to children and adolescents in Australian general practice are concordant with national and international findings, demonstrating concerning ongoing increases in prescribing. This increase appears to be driven mostly by off-label prescribing, discussed in Section 9.3.

9.3 Summary of off-label prescribing in Australian primary care

High levels of off-label prescribing were observed for antipsychotics, antidepressants, and melatonin. All melatonin and most antidepressant prescribing occurred off-label but was generally in concordance with CPGs. Antipsychotic prescribing occurred mostly off-label and not in concordance with CPGs, with an adjusted rate of 80% of patients in 2017 receiving off-label antipsychotic prescriptions. Such high rates of off-label prescribing are particularly concerning given the adverse event profile of antipsychotics and the lack of adequate monitoring for metabolic complications occurring in primary care. Off-label prescribing is discussed in relation to Australian and international findings for antipsychotics, antidepressants, and melatonin in sections 9.3.1 to 9.3.3.

9.3.1 Off-label antipsychotic prescribing

A notable finding in this thesis was the high number of children and adolescents prescribed antipsychotics off-label for depression and/or anxiety, consistent with several international paediatric studies [31, 456, 514-516] and one Australian study of 12-17-year-olds attending a public mental health clinic in NSW during 2016 [61]. Quetiapine, in particular, was regularly prescribed for depression and/or anxiety [31, 61, 456, 514-516].

High rates of paediatric antipsychotic prescribing for depression and anxiety may occur because clinicians are adapting recommendations from adult guidelines [251, 517, 518]. During the study period, the Australian guidelines for paediatric anxiety were limited[o]. The one eTG Complete guideline for childhood anxiety disorders only mentioned three disorders: OCD, separation anxiety disorder, and generalised anxiety disorder (GAD) [251]. SSRIs were listed as options for treating severe anxiety for these three conditions, but no recommendations included antipsychotics [251]. The eTG Complete paediatric guideline also referred prescribers to adult guidelines for managing GAD [251] but only two adult guidelines summarised in Appendix 7 (2014 BAP [259] and 2018 BMJ Best Practice guidelines [261]) mentioned antipsychotics for treating this condition, and both relegated antipsychotics to third-line drug options after non-pharmacological therapies, SSRIs, and other non-SSRI antidepressants (e.g., duloxetine, venlafaxine) were trialled. Reference to adult guidelines, therefore, appears an unlikely explanation for the high use of antipsychotics in MedicineInsight. Since 2010, however, quetiapine has been TGA-approved

o. Australian guidelines have since been published for anxiety disorders in children and adolescents by the Melbourne Children's Campus Mental Health Strategy Anxiety Guideline Development Group in October 2023 [250].

for both treatment-resistant depression (TRD) and GAD in adults [519], which may partially explain the prescribing patterns observed in this thesis. Supporting this explanation is the finding that quetiapine was the most prescribed antipsychotic for depression and/or anxiety in both 2011 and 2017 in the off-label study in this thesis (Chapter 5, Table 5).

An alternative explanation is that SGAs are perceived as safer than other psychotropics used to treat anxiety or depression [520]. For example, concerns about benzodiazepines that were used extensively to treat adult anxiety from the 1960s to early 1980s [521] may have resulted in clinicians being wary of prescribing this drug class to paediatric patients [520]. Similarly, SSRIs are approved and commonly used to treat adult anxiety [252], but black box warnings regarding drug-induced suicidality in children and adolescents using SSRIs may deter GPs from prescribing these drugs to young patients, instead opting for a perceived "safer" SGA alternative [520].

There are also a number of concerns with the high level of antipsychotic prescribing to children and adolescents with ASD. Comorbidity of ASD with other mental disorders is common [522-524], but only ASD diagnoses with associated records of behavioural disorders (including self-destructive/self-injurious behaviours) or aggression have an approved indication for antipsychotics in Australia [476, see also Chapter 5, Supplementary Table S1] and internationally [478]. A 2018 UK primary care study examined psychotropic prescribing and mental disorder comorbidities in patients with ASD aged 3-65 years (58% children under 18 years) [522]. The researchers found antipsychotics prescribed in 8.3% of patients, but comorbid behavioural problems (conduct disorders [CDs]) were recorded in only 0.4% of patients [522]. Similarly, in a 2017 US study of commercially insured and Medicaid patients aged 3-65 years (58% children under 18 years), the number of patients prescribed antipsychotics exceeded the number with comorbid CDs [523]. In the latter study, researchers found that one-third of patients were prescribed a psychotropic drug with no psychiatric comorbidities [523]. Both studies also suggested that some psychotropic prescribing appeared to be targeted at ASD itself [522, 523], despite the fact that antipsychotics are considered ineffective for the core symptoms of ASD [289, 290, 294, 296]. This points to possible misconceptions about the appropriate use of antipsychotics in patients with ASD. This is concerning as children with ASD can be more sensitive to adverse effects of medications [299, 525]. Drivers of antipsychotic prescriptions in general practice in the apparent absence of behavioural issues therefore require further examination.

9.3.2 Off-label antidepressant prescribing

Antidepressant prescribing in this thesis occurred largely off-label. Despite this, prescribing appears to be mostly guideline concordant. In the analysis of individual psychotropic drugs reported for 2018 (see Chapter 4, Table 4), the SSRI fluoxetine was the most prescribed antidepressant in 5-18-year-olds. Although not approved for any paediatric conditions in Australia, it is approved in the US and Europe for treating child and adolescent depressive disorders [191] and is listed as the preferred pharmacological option in all depression guidelines summarised in Chapter 2, including the Australian NHMRA-approved *beyondblue* guidelines [171][p]. The second most prescribed antidepressant in 5-18-year-olds in 2018 was sertraline, which is also mentioned as a treatment option in most paediatric depression guidelines (Chapter 2, Appendix 2). This prescribing pattern suggests a high level of guideline-concordance.

SSRIs are also considered effective for treating anxiety in children in multiple guidelines [196, 251, 256]. Fluvoxamine, sertraline, and fluoxetine feature prominently in paediatric guidelines and are also recommended by a 2005 article in Australian Prescriber that provided advice on prescribing psychotropics to children in general practice [253]. As a respected open-access journal designed to assist health professionals with pharmacological treatment decisions, Australian Prescriber publications are an influential source of information for prescribers [526]. The presence of these three drug recommendations in the article could have considerable influence on GP prescribing.

The widespread mentions of SSRIs in all paediatric CPGs for depression and anxiety disorders and GP resources, in conjunction with regulatory approvals in Europe and the US, create an impression that the drugs are safe and efficacious [166]. This perception could, in turn, contribute to high levels of off-label prescribing observed in this thesis. Indeed, the three most recommended SSRIs in CPGs were also the three most prescribed SSRIs in the MedicineInsight dataset in 2018.

9.3.3 Off-label melatonin prescribing

One of the most significant findings in this thesis was the rapid increase in melatonin prescribing that occurred across all age groups. A similar increase in children and adolescents was found in both international studies [5, 58, 113-117, 509, 527] and an

p. The *beyondblue* guidelines were NHMRC approved in 2011 and remained current for 5 years until 2016.

Australian study of paediatrician prescribing [111]. In this thesis, it was the only psychotropic drug to increase significantly across the study period in children aged 0-4 years, similar to findings in two Swedish studies [113, 115].

In the majority of countries, melatonin is sold as a prescription-only drug and is not approved for children and adolescents [58, 117, 513, 528], despite being mentioned as a treatment option for sleep problems in several guidelines (see Chapter 2). Although melatonin was recently TGA-approved[q] for sleep disturbances in paediatric patients with ASD or Smith-Magenis syndrome [529], it remains unapproved worldwide for insomnia in typically developing children [513] and was not approved for any paediatric conditions during the period studied in this thesis.

High levels of worldwide off-label melatonin use in children and adolescents may be due to the perception it is a benign drug [513]. Compared to benzodiazepines, melatonin is considered to have less severe adverse effects [530] and no potential for physiological or psychological addiction [531]. It is available as an over-the-counter (OTC) product in some countries [513] and has been down-regulated from prescription-only status in several other countries [528, 532, 533]. For example, in Australia in 2021, melatonin was rescheduled for adults over 55 years from prescription-only to an OTC drug [533]. Melatonin was also down-scheduled to an OTC drug for adults in Sweden in 2020 [532], and in France it became available as an OTC health supplement at doses <2mg in 2011 [528]. Changing status from prescription-only to OTC may have led to the perception that it is well researched, tolerated, and safe. In the US, melatonin has always been marketed as a dietary supplement with poor regulation and safety mechanisms in place [527], resulting in calls for the drug to be up-regulated [534].

The increase in paediatric prescriptions for melatonin is particularly concerning, as evidence for efficacy and safety remains limited [513]. In a recent meta-analysis of sleep-onset insomnia in paediatric patients [535], only seven small studies of low to moderate quality were identified. The analysis found melatonin was effective in advancing sleep onset time by 37 minutes [535]. Safety outcomes were also not significantly different between melatonin and placebo as measured by drop-outs from all causes and dropouts from adverse events, leading researchers to conclude that it was “an effective and tolerable drug in the short-

q. Melatonin was TGA-approved in May 2022 for children and adolescents aged 2-18 years with insomnia and ASD or Smith-Magenis syndrome.

term treatment of sleep-onset insomnia in children and adolescents" [535, p.1]. However, several studies in the analysis recorded adverse events of low to moderate intensity, including headaches, tiredness, and lowered mood, and one study noted possible convulsant effects [535]. Other publications raise concerns about the effect of melatonin on sexual maturation [112, 528, 531] and its function as a modulator of blood pressure, body temperature, cortisol levels, and the immune system [531, 536]. A systematic review of adverse events associated with melatonin in adults found significant effects on endocrine factors and glucose metabolism [537]: insulin sensitivity was impaired, prolactin increased, and reproductive hormones were altered in both males (reduced sperm count and increased androgen/oestrogen ratio) and females (suppressed ovulation). The significant effects on reproductive hormones raise particular concerns about the use of melatonin in developing children [112].

In some countries, children are using melatonin on a continuous basis for years [113-115, 538]. One study of children with ADHD found 64.9% of patients who were prescribed melatonin were still using it daily three years later (mean follow-up 3.7 years), with a further 11.7% continuing use two to three times a week [538]. In another study, 16% of girls and 17% of boys aged 5-9 years were continuously prescribed melatonin eight years after commencing the drug [115]. In this study, long-term use was defined as at least three dispensations of melatonin every year after the incident prescription. The recurrent use of melatonin is concerning, given the lack of evidence on the long-term consequences of using melatonin in paediatric patients [113, 117, 535, 536].

In this thesis, continuous prescribing of melatonin was not analysed. There remains an urgent need for studies examining melatonin use in children and clinician education programs to discourage its widespread and escalating use until long-term safety and efficacy can be reliably established.

9.4 Changes to psychotropic approvals and clinical practice guidelines post 2018

At the time of writing this thesis there was only one NHMRA-approved guideline that provided recommendations for paediatric mental disorders, the *beyondblue* depression guidelines. There were also few TGA-approved drug recommendations for paediatric mental disorders. In this section, significant changes to guidelines and drug approvals that have occurred since 2018 are examined to determine if recommendations for drug prescribing are becoming more cautious or more liberal.

There have been few changes to guidelines since 2018. Only two new guidelines for managing ADHD [539] and anxiety disorders [250] have been produced in Australia, and international guideline organisations have also only produced a few new or updated CPGs for paediatric depression [165, 540] and anxiety [541]. Any changes to living guidelines, such as the eTG Complete and BMJ Best Practice guidelines, were also minor.

There have been no major changes to NICE guidelines for depression in children since 2018 [165]. BMJ Best Practice guidelines (2024) increased the period of active monitoring from four to six weeks and removed two non-SSRI treatment (duloxetine, venlafaxine) options from their treatment algorithm [542]. Melatonin is no longer recommended as an adjunct treatment for childhood depression [542]. The new 2023 AACAP depression guidelines [540] do not make any class 1 recommendations for any drug treatments for depression. Class 1 typically means clinicians can be confident that the benefits of the treatment outweigh the harms. In fact, the three recommendations for drug, non-drug, and combined therapies were classified as 2I, meaning there was insufficient evidence to confidently claim that the benefits outweighed the harms. The claim of insufficient evidence contrasts with the claim in the 2007 guidelines that concluded "the risk/benefit ratio for SSRI use in pediatric depression appears to be favorable with careful monitoring" [188, p.1516]. The new guidelines also specifically contraindicated the drug paroxetine [540]. The guideline changes from 2007 to 2023 represent a positive move towards reducing reliance on drugs for treatment of paediatric depression.

The WHO Essential Medicines List for children (EMLc) also provides guidance on best treatments for diseases and has recently reduced the number of psychotropics considered essential for children [188]. In 2023, following a submission by Papola and colleagues [543], fluoxetine was removed from the EMLc for children aged under 13 years [544]. As of 2023, there are now no psychotropics on the EMLc for children 12 and under. On the other hand, the eTG Complete depression guidelines increased the range of medication options from the three mentioned in its minimalistic 2018 guidelines [191] to now include five SSRIs[r] [545]. The age limit for considering pharmacological treatment also expanded from >7years to >5 years in the 2021 guideline [191, 540]. In all post-2018 depression guidelines, SSRIs have

r. The SSRIs recommended in the earlier guideline (accessed in 2019) were fluoxetine, sertraline, and citalopram. This was expanded to also include fluvoxamine and escitalopram in the later 2021 guidelines.

continued as the mainstay of treatment when non-pharmacological therapies are ineffective, with fluoxetine remaining the recommended first-line drug [165, 540, 542, 545].

Similarly, ADHD guidelines have changed little. The Australian 2022 guidelines [539] were similar to the earlier RACP guidelines [214] and NHMRC practice points [215], but included a newly TGA-approved drug, lisdexamphetamine[s] as a first-line option. The more recent eTG Complete 2021 guidelines also increased the minimum age limit for drug treatments from 4 to 6 years [546].

Eating disorder guidelines generally have few recommended drugs due to the physiological issues associated with the disorders adversely affecting drug metabolism [306]. However, the eTG Complete guidelines have included new drugs for adults with BED – lisdexamphetamine and fluoxetine [547]. No major changes to advice on sleep disturbances have occurred, although the 2021 eTG Complete guidelines for the paediatric population are more extensive and warn against the use of melatonin due to a lack of good quality evidence of its long-term benefit and safety [548].

A new AACAP guideline for anxiety in children and adolescents was published in 2020 that included recommendations for GAD, social anxiety disorder (SAD), separation anxiety disorder, and panic disorder [541]. Following a similar format to the 2023 depression guidelines, the use of SSRIs to treat anxiety in 6-18-year-olds was classified as 1B (confident that benefits outweighed harms, moderate strength of evidence). Recommendations for SSRIs remained as first-line pharmacological options, with non-SSRIs (duloxetine, venlafaxine, and desvenlafaxine) as second-line. TCAs were removed as non-SSRI options. There were, however, no SSRIs approved by the FDA for anxiety disorders in children or adolescents in 2020[t]. This changed in May 2023, when the FDA approved the first SSRI for treating GAD in children 7-17 years, escitalopram [549], discussed further in Section 9.4.1.

The Australian guidelines, published in October 2023, in concert with many other guidelines in Appendix 7, and the new 2020 AACAP anxiety guidelines [541], suggest all SSRIs are equally effective for anxiety disorders. However, when advising about choice of SSRI, 2023 Australian guidelines suggested clinicians consider fluoxetine or escitalopram, as these two SSRIs are FDA-approved for paediatric depression [250, p.63]. This is concerning as the

s. Lisdexamphetamine was TGA-approved for the treatment of ADHD in children and adolescents on October 23, 2013.

t. The selective serotonin noradrenaline reuptake inhibitor (SNRI) duloxetine was FDA-approved for the treatment of GAD in 7-17-year-olds in 2014.

approval for escitalopram in adolescent depression was based on only one controversial trial of 312 participants [550]. In 2011, researchers in Canada had reassessed all evidence for escitalopram use in paediatric depression and implored authorities in Canada not to follow the FDA's decision until sufficient evidence supporting efficacy and safety could be provided [550].

9.4.1 Approval of the first SSRI for treatment of paediatric GAD

The approval of escitalopram for treating children with GAD is controversial [551]. Similar to the studies informing the approval of fluoxetine for treating childhood depression during the early 2000s (see Appendix 1) and evidence informing escitalopram's approval for treating paediatric depression [550] (see previous section), the approval for escitalopram for paediatric GAD was based on inadequate data, lacklustre results, and significant conflicts of interest (COIs).

The FDA approval of escitalopram for GAD was based on one multicentre, double-blind, placebo-controlled trial of 275 participants aged 7-17 years [549]. At 8 weeks, the study found a 1.42-point difference on the 30-point Pediatric Anxiety Rating Scale (PARS) in favour of escitalopram, with no secondary measures for functional improvement and remission reaching significance [552]. Such a small change in the PARS scale is clinically insignificant and represents a small standardised mean difference of 0.27 [551]. Furthermore, 13 trial patients on escitalopram (9.5%) experienced suicidal ideation compared to two patients on placebo (1.5%), and one patient on escitalopram attempted suicide[u] [552]. For the other 15 categories combined, exclusive of suicidal ideation, adverse events were significantly higher in the escitalopram arm [551]. There were also considerable COIs in this study whereby the pharmaceutical company, AbbVie, funded the study, contributed to trial design, and participated in the collection, analysis and interpretation of data. Several authors were employees of Syneos Health, an organisation funded by AbbVie, to write the study protocol. Four authors were employed by pharmaceutical companies (three were employed with AbbVie) [552].

The approval of a drug with such poor results and extensive COIs suggests that the quality of studies on which approvals are based could be putting the health of children and adolescents at risk. Data from a paediatric trial examining paroxetine for treating adolescent depression [553] was reanalysed in 2015 [554] under the Restoring Invisible and Abandoned

u. The researchers classified the attempted suicide as a non-drug-related event.

Trials (RIAT) initiative. RIAT was formed in 2013 by Associate Professor Peter Doshi to encourage researchers to access, analyse, and republish misreported drug trials or abandoned (unpublished) trial data [555]. The authors of the original trial analysis concluded that paroxetine was "well-tolerated and effective for major depression in adolescents" [553, p.762]. The RIAT reanalysis found paroxetine to be no more effective than placebo. Further, the RIAT team found increased harms, including suicidal ideation and behaviour, in trial adolescents taking paroxetine. Subsequently, several paediatric guidelines now specifically contraindicate the use of paroxetine [191, 540, 542, 545, 556].

Another controversial paediatric antidepressant trial that guidelines are based on is undergoing a RIAT reanalysis: the Treatment for Adolescents with Depression Study (TADS) [557]. TADS was a multicentre, four-arm trial examining the effect of fluoxetine, cognitive-behaviour therapy (CBT), combined fluoxetine and CBT, and placebo in adolescents 12-17 years with MDD [558]. Results of the reanalysis of the acute 12-week phase of the TADS trial suggest fluoxetine is neither safe nor efficacious for adolescents [559].

The results from the two RIAT reanalyses discussed in this section point to problems with early paediatric drug trials, such as poor reporting of adverse events [554, 559] and extensive COIs of study authors [558]. Both trials reported the drugs were safe and effective for children and adolescents and were incorporated into paediatric depression guidelines. Problems in the original TADS and paroxetine studies are similar to those identified in the recent study of escitalopram for paediatric GAD that underpinned the recent TGA approval [552]. The study of escitalopram for paediatric GAD [552] also warrants a thorough reappraisal or RIAT re-analysis, to determine if the original trial findings of efficacy and tolerability in children and adolescents are accurately reported.

In summary, guideline changes have been minor, with some guidelines becoming more conservative with respect to psychotropic drug recommendations (e.g., AACAP depression guidelines). The exclusion of paroxetine and melatonin from more recent guidelines is also a positive move, as is the removal of fluoxetine from the WHO EMLc for children. However, there were other guidelines where drug recommendations have become more liberal (e.g., eTG Complete 2021 guidelines reducing minimum age for SSRI treatment).

CPG recommendations influence the level of off-label prescribing that occurs. Many drug recommendations included in guidelines are based on published trials with no regulatory

approvals (e.g., *beyondblue* depression guidelines suggest SSRIs with no TGA approvals). Further, mentioning drugs in guidelines has been shown to increase off-label prescribing [166]. The high levels of off-label prescribing observed in this thesis suggest GPs are prescribing in a guideline-concordant manner, which may not result in best practice. In the following section, guideline-concordant prescribing, regulatory approvals, and the influence on best clinical practice are further examined.

9.5 Clinical guidelines and clinical best practice

Guideline-concordant and best practice prescribing are not necessarily the same. As discussed in the previous section, Chapter 2 and Appendix 1, there are multiple issues with guidelines that limit their usefulness and may compromise the quality and safety of their recommendations. This includes problems with COIs [135], publication bias [152, 560] and the general quality of studies underlying guideline recommendations [153, 561]. According to Ioannidis (2016) [153], despite being a respected tool of evidence-based medicine, randomised trials are mostly funded by the pharmaceutical industry, often ask the "wrong questions", use inappropriate analytical techniques, use the wrong criteria for success (e.g., non-inferiority trials[v]), and draw unfounded inferences [153, p.83].

The Institute of Medicine in the US released a comprehensive report addressing COIs in medicine in 2009 [156], defining COIs as "circumstances that create a risk that professional judgement or actions (…) will be unduly influenced by secondary interests" [156, p.6]. Secondary interests included financial gains as well as the "desire for personal advancement [and] recognition for personal achievement" [156, p.6]. The report also highlighted the importance of unconscious and unintentional cognitive biases and how this can impact clinical guidelines. Other researchers have also flagged the influence of cognitive biases as an important factor to consider in the context of guideline development [156, 158, 562-564].

Health care professionals, researchers, and readers of academic literature are often driven by unconscious biases [156, 158, 563, 564] such as the self-serving bias[w] [158, 566], confirmation bias[x] [563] and blind spot bias[y] [158, 563, 566]. These cognitive biases can

v. A non-inferiority trial seeks to prove a new treatment is not inferior to a currently used treatment.
w. The self-serving bias is a cognitive bias that allows people to process self-relevant information in a distorted way, which preserves a positive self-image and self-esteem. People see themselves as better than average and their opinions and expertise as superior to others [565].
x. Confirmation bias is a tendency to search for information that confirms one's preconceptions [565].
y. The blind spot bias is the tendency to believe one is less susceptible to cognitive biases than other people. [567].

result in individuals with the best of intentions unconsciously favouring a particular outcome or theoretical viewpoint and believing that their conclusions are less biased than others assessing the same information [158, 562]. Cosgrove and Whittaker [562] point out that biases can arise from financial COIs such that individuals may consciously recognise their potential COIs but remain unaware of how it impacts their thought processes and behaviours. They further point out that cognitive biases can be particularly problematic in psychiatry due to the subjective nature of mental disorder diagnoses and the lack of testable biological markers for mental disorders [562].

Cognitive biases also affect every stage of the research process, from choice of trial design through to the production and dissemination of clinical practice guidelines [562], which can subsequently "exert an enormous influence on prescription practices" [562, p.6] and result in worsening health outcomes for patients [568].

Studies have also shown that declarations of COIs in journals can worsen the bias in guidelines through a subconscious phenomenon called "moral licensing" (see Chapter 2, Section 2.2.2.1).

Another notable issue affecting best clinical practice is the discrepancy between TGA approvals and CPG recommendations. The TGA approval process is comprehensive, ensuring the best possible decisions with the available evidence (see Chapter 1). However, the TGA registration process has been criticised as "suboptimal" and not conducive to providing prescribers with the most accurate, up-to-date information [569]. Pharmaceutical companies often do not want to undertake the expensive, cumbersome, and time-consuming processes required to update product information to include new indications, even if there is evidence readily available to support the indication [569]. This can lead to approvals lagging behind the evidence base and prescribers increasing reliance on recommendations in CPGs. This increases the inherent risks associated with off-label prescribing. In this thesis, drugs were approved by the TGA, yet generally not recommended in available guidelines (e.g., TCAs for bedwetting). In other cases, drugs were not TGA-approved yet highly recommended in multiple guidelines (e.g., fluoxetine for depression and melatonin for sleep disturbances). This issue is not uncommon in many jurisdictions. For example, the range of drugs recommended in AACAP guidelines for childhood depression [540] and anxiety [541] exceeds the number of drugs approved by the FDA for the indicated condition.

Concerns about the lag in TGA registration processes have led to the Australian government recently establishing the Medicines Repurposing Program (March 2024) in an attempt to address this problem by introducing a more streamlined approval process for new indications [570].

In summary, both TGA approvals and clinical practice guidelines come with limitations and often do not guide clinicians to provide the best treatment. There are discrepancies between multiple CPG recommendations and TGA drug approvals, leading to high levels of off-label prescribing. This raises further concerns about the impact on health outcomes for children and adolescents prescribed psychotropic drugs in Australian primary care.

9.6 Social determinants of psychotropic prescribing

Social determinants of mental health include a range of individual-level factors such as gender, race, educational attainment, and employment status, as well as more distal social factors such as neighbourhood disadvantage (see Chapter 1 for detailed discussion). Both adult and paediatric studies have found a trend towards higher rates of diagnosis of mental disorders in disadvantaged areas compared to the most advantaged areas [47, 119, 122, 125, 571]. However, trends in the prescription of psychotropic medications with social disadvantage are fewer and results are mixed. Some Australian [129, 131] and international [42, 404, 572-574] studies found no relation between social disadvantage and psychotropic prescribing, whereas other studies for both adults and children have found a gradient whereby greater disadvantage was associated with higher levels of psychotropic prescribing [47, 124, 128, 130, 574-579]. Yet other studies have found a positive gradient, whereby drugs are prescribed more frequently to those in the most advantaged areas [580, 581]. These different findings may relate to the class of drug being studied and to varying definitions of disadvantage used in studies. Accordingly, the relationship between social disadvantage and prescriptions for different drug classes is discussed below.

9.6.1 Antipsychotic prescribing and social disadvantage

There was a clear social gradient in the prescribing of antipsychotics to children and adolescents in Chapter 4. Prescribing increased monotonically with increasing socio-economic disadvantage. However, when examining antipsychotics associated with any mental health diagnosis (Chapter 5), this gradient was lessened. In Chapter 4, examining psychotropic prescribing trends, 2.8% of children and adolescents in the most socially advantaged areas were prescribed an antipsychotic in 2017, monotonically increasing to

6.9% in the least advantaged areas, with all quintiles from two to five significantly higher than the base level of "most advantaged". When examining the subset of patients with a mental health diagnosis (Chapter 5), the gradient ranged from 1.9% of patients in the most advantaged areas to at least 3% in the lower three quintiles, while only the middle quintile (3.7%) was significantly different to those in the most advantaged areas. There was also no social gradient evident in the off-label analysis, but patients in the most disadvantaged areas (lowest quintile) showed a concerning and significant increase in off-label prescribing from 2011 to 2017. There were no significant changes in other quintiles.

These findings are partially supported by the findings of a recent population-level study of children and youth (0-24 years of age) in Ontario, Canada, which has a universal health scheme similar to Medicare in Australia [580]. Antoniou and colleagues (2023) found a strong inverse gradient for antipsychotic prescribing and quintiles of neighbourhood disadvantage, but when examining a subsample of children and youth with diagnoses of psychotic disorders who were prescribed an antipsychotic, the gradient disappeared, suggesting prescribing could be driven by need [580]. However, this only partially explained the observed gradient, as the rates of psychosis diagnoses were similar across quintiles and very low. Antipsychotics were mainly prescribed for non-psychotic conditions, in particular for externalising problems in children, leading the authors to speculate that the observed gradient may still function with diagnoses other than psychosis. Specifically, they suggested health professionals seeing children from low-income families may disproportionately label children's behaviours as problematic, resulting in higher levels of disruptive behaviour disorder prevalence and higher levels of drug prescribing.

Other international studies on antipsychotics have used different definitions of socio-economic disadvantage and reported varying results. While Antoniou et al. [580] found an inverse gradient for prescribing of antipsychotics in Canada, a French study by Verdoux and colleagues (2015) found no evidence of a social gradient [572]. Examining total dispensations in 0-24-year-olds, irrespective of diagnosis, Verdoux et al. found no overall association between antipsychotic prescribing and zone of residence, which was defined using census variables and included unemployment and welfare recipient levels, population density, and psychiatric service density [572]. Another French study examined children aged under 18 years using an individual-level socio-economic variable and found a 10-fold increase in prescribing of antipsychotics to children in low-income families compared to the general population [124]. The lack of consistent definitions of socio-economic disadvantage makes it

difficult to draw conclusions about the relationship between antipsychotic prescribing and social disadvantage from the existing body of research.

9.6.2 Antidepressants, anxiolytics and sedatives/hypnotics

This thesis demonstrated evidence of a clear gradient in prescribing of antidepressants, whereby a greater proportion of children in more disadvantaged areas received these drugs. This agrees with the findings of John and colleagues (2016), who also found a similar gradient for antidepressant prescribing in 6-18-year-olds in Wales using a GP database [47]. The measure of disadvantage used in their study, the Welsh Index of Multiple Deprivation, comprised eight domains inclusive of income, employment, and education, similar to the IRSAD measure used in this thesis.

In the present thesis, there was a less pronounced social gradient for anxiolytic and melatonin prescribing compared to antipsychotics, antidepressants, and ADHD drugs, and no gradient for the prescription of sedatives/hypnotics. This contradicts the findings in a second study by John et al. (2015) that found an inverse social gradient with prescribing of anxiolytics and hypnotics [127]. In the two Welsh studies examining the prescribing of antidepressants [47] and anxiolytics and hypnotics [127], the researchers also examined diagnoses of depression [47] and anxiety disorders [127]. They found a similar social gradient for both diagnoses and prescriptions, so it was not clear whether the increase in prescribing represented a tendency to prescribe more frequently to disadvantaged children or an increased prevalence of disorders diagnosed in disadvantaged children and adolescents. Similarly, the finding in this thesis of a social gradient in prescribing of antidepressants cannot be accurately determined as diagnoses were not associated with prescriptions. The study by Antoniou et al. that examined antipsychotic prescribing in Canada also examined antidepressant and benzodiazepine prescribing and found no evidence of a gradient [580].

9.6.3 ADHD drugs

In the present thesis, there was a noticeable inverse prescribing gradient for ADHD drugs, with more drugs being prescribed for patients in more disadvantaged areas. International studies have found variable evidence for a social gradient in the prescription of ADHD drugs, some showing an inverse gradient [576, 579] and others a positive gradient [580, 581].

Similar to the findings in this thesis, a Swedish study using a national drug register for prescriptions issued in 2006 found increasing prescribing of ADHD drugs to children aged 6-

19 years associated with increasing social welfare assistance and lower maternal education levels [579]. A study of children and young people with ADHD attending secondary care services in the UK also found a clear inverse gradient of increasing prescribing of ADHD drugs with increasing disadvantage [576].

On the other hand, a Canadian study by Antoniou et al. (2023) found a positive association, whereby patients were more likely to be prescribed ADHD drugs in high compared to low-income neighbourhoods in 2018 [580]. The socio-economic level of neighbourhoods was estimated using post-code information and Canadian census data that included household size, education levels, employment, and citizenship status as factors of interest. Density of mental health services in neighbourhoods was an additional factor examined in the study. Stimulant prescribing in this study was inversely associated with the average number of people in the household and proportion of non-Canadian citizens in the neighbourhood, but positively associated with the density of mental health services in the neighbourhood. The researchers speculated that children in low-income families, despite being more likely to meet the diagnostic criteria for ADHD, may be less likely to receive treatment due to the lack of adequate and accessible services [580].

A similar finding of a positive gradient remained after linking the medication to diagnoses in an earlier US population-based study [581]. In the US, children in racial and ethnic minority groups are 2.5 times more likely to receive an ADHD diagnosis than a CD diagnosis, which Fadus et al. (2020) attribute to a tendency of clinicians to over-pathologise their behaviours as more dangerous and disobedient than the behaviours of non-Hispanic white children [582]. Children living in higher-income households are also five times more likely to receive an ADHD diagnosis than children enrolled in Medicaid [582]. The confluence of these factors may explain the positive gradient observed in the US.

ADHD diagnoses have been shown to be higher among more socially disadvantaged children in Australia [15]. Although this thesis did not consider density of mental health services, as was done in the Canadian study by Antoniou et al. [580], the inverse gradient observed in MedicineInsight suggests that children and adolescents may have adequate access to mental health services. The higher rates of stimulant prescribing are consistent with the higher rates of ADHD diagnoses in socially disadvantaged children. However, the higher prescribing rates may also indicate suboptimal access to non-pharmacological treatment for ADHD, as observed by Antoniou et al.

It is also important to consider the role of specialists when examining ADHD diagnosis rates and ADHD drug prescribing in Australia. ADHD drugs are under strict prescribing regulations and in most cases must be initiated by paediatric specialists, after which GPs can apply to be co-prescribers [458]. Therefore, any trends observed are likely attributable to the treatment decisions of specialists. Interestingly, a study of Australian paediatricians found that ADHD medication prescriptions for patients in 2008 were not predicted by child gender or family disadvantage using the Index of Relative Disadvantage (IRSD) [583]. To examine the role of social disadvantage in ADHD drug prescribing, further studies are needed in both primary care and specialist settings.

9.6.4 Social disadvantage, mental disorder prevalence and psychotropic prescribing

In studies where the prevalence of disorders has been used as a covariate, the effects of area-level disadvantage are commonly lessened. For example, after controlling for ADHD symptoms, a 2023 Canadian study found insufficient family income was no longer predictive of ADHD drugs being prescribed for children aged 3-10 years [578]. Similarly, controlling for symptoms of anxiety and depression in an Australian study of antidepressant prescribing to adults reduced the summary measure for social disadvantage from an odds ratio of 2.91 to 1.82 [125]. The summary measure in this study consisted of six variables (educational level, occupational background, rental housing tenure, employment status [unemployed, not in labour force], receipt of government pension/benefit, financial hardship). The number of variables that significantly predicted receiving an antidepressant reduced from six to two after controlling for symptoms. Similarly, a study of 16-85-year-olds by Harris and colleagues (2011) [131] found no association between the use of antidepressants, anxiolytics, or hypnotics after controlling for the presence of different mental and physical diagnoses.

In the present thesis, after accounting for the prevalence of mental disorders, the social gradient for the prescription of antipsychotics to children and adolescents was also lessened. Although detailed analyses were not carried out for the other four psychotropic classes examined in this thesis, it is possible the strong social gradients observed for antidepressants and ADHD drugs would also be lessened after controlling for the prevalence of mental health diagnoses.

9.6.5 Measures of social disadvantage

Another possible explanation for the differing findings between this thesis using MedicineInsight and that of other studies discussed in Sections 9.6.1 to 9.6.4 above is the

use of differing indexes of social disadvantage. For example, in an Australian study by Page et al. (2009) [129], researchers found a positive socio-economic gradient in association with antidepressant prescribing for 0-19-year-olds while observing no gradient for 20-29-year-olds and an inverse gradient for all older ages. However, the authors used the Index of Economic Resources (IER) as a measure of advantage. The IER concentrates on the financial aspects of an area, including variables of income and housing, but excludes education and occupation-related variables [132]. Another point of difference between the MedicineInsight study in this thesis and Page et al. is the use of a PBS dataset that included prescriptions issued by paediatricians and child psychiatrists, as well as GPs. Therefore, when examining PBS data, it is difficult to know whether prescribing by specialists obfuscates trends observed in general practice or other factors are involved. No papers examining socio-economic gradients and specialist psychotropic prescribing in Australia were identified in literature searches, so the cause of the discrepant findings is difficult to determine.

Similar to the IRSAD used in this thesis, many studies have used area-level indexes of social disadvantage that summarise the socio-economic features of defined geographical regions [125, 128, 129, 131, 575, 576, 578]. Some studies, however, suggest individual-level measures may provide a more insightful understanding of the impact of social deprivation on psychotropic prescribing [124, 584-586]. Findings from studies using individual-level indexes are discussed and compared to area-level indexes in the next section.

9.6.6 Area-based versus individual-based measures of social disadvantage

Several studies [124, 584-586] have suggested that individual-level disadvantage measures may capture important information undetected by broad area-level indexes. In an Australian study [131] that found no association between socio-economic disadvantage and antidepressant, anxiolytic, and hypnotic use in a sample of 16-85-year-olds, the researchers suggested that the socio-economic factors associated with an area level may not be important predictors at the individual level [131, p.258].

This explanation is supported by the findings in a 2017 French study by Bonnot et al. [124]. Sociodemographic information was collected from patients affiliated with the Couverture Maladie Universelle Complementaire (CMU-C), a universal public health insurance scheme for low-income persons in France. Patients aged 0-17 years who were prescribed an antipsychotic and affiliated with the CMU-C were compared to the whole population of 0-17-year-olds in the region. The study found a 10-fold increase in prescribing to children in

low-income families. The rates of prescribing to disadvantaged children in their study were higher than that reported in other studies using area-level indexes, leading the researchers to conclude that living in low-income families was the more relevant predictor. Other studies comparing individual-level and area-level disadvantage for adults also found stronger associations between individual-level deprivation measures and mental well-being [585] and premature mortality from any cause [587].

However, this does not reduce the importance of including area-level measures in studies addressing the social determinants of health. Various studies have demonstrated neighbourhood factors remain an important, independent predictor of various health outcomes [126, 584, 585, 587]. For example, a Swedish study examining adult psychotropic prescribing found neighbourhood deprivation was an independent risk factor for prescribing after controlling for individual sociodemographic factors [126]. Therefore, research into social disadvantage and health needs to incorporate both individual-level and area-level measures of disadvantage to develop appropriate health policies that can reduce health inequalities [584, 585].

9.6.7 Future directions for research on social disadvantage and psychotropic prescribing

Given the contradictions across studies reported in sections 9.6.1 to 9.6.6, whether children and adolescents in more disadvantaged areas receive proportionally more psychotropic drugs remains an unanswered question. There is a clear need to examine social gradients in the prescribing of all classes of psychotropics. Ideally, future research will include a wider range of individual-level factors in quantitative studies, complemented by qualitative studies of GPs' reasons for providing pharmacologic and non-pharmacologic treatments.

It is also important to address the possibility of overdiagnosis as a contributing factor to the increased prescribing that occurred in more disadvantaged areas in this thesis. A study by Fadus et al. mentioned in Section 9.6.3 suggested implicit bias may lead clinicians to pathologise behaviours in patients in lower-income families compared to higher-income families, possibly resulting in higher rates of diagnosis of CD or ODD in children from disadvantaged areas [582]. Implicit bias is the tendency to subconsciously perceive others through stereotypes, which can affect attitudes and behaviours toward the individual [588]. In a study examining implicit and explicit biases in clinicians with mental health training, those who exhibited high levels of implicit bias towards patients were more likely to overdiagnose patients [589]. Clinicians' biases were measured using clinical vignettes.

Implicit bias was measured using the Implicit Association Test and explicit bias was measured on a 7-point semantic differential scale where "1" represented an extremely negative view and "7" an extremely positive view of people with mental disorders. The semantic scales measured stereotypes commonly associated with persons with mental illness, including good/bad, blameworthy/innocent, and helpless/competent. A positive implicit bias (i.e., a less stigmatising view of people with mental disorders) predicted a tendency to overdiagnose, while measures of explicit bias had no effect. The findings of these studies suggest that the overdiagnosis that can result from implicit biases may explain higher rates of prescribing in areas of higher disadvantage.

It is also possible, however, that clinicians may be biased towards pharmacological treatments in disadvantaged patients. In an earlier 2000 study of Australian GPs, the authors highlighted that GPs can be influenced by adult patients' socio-economic circumstances [574]. In this study by Comino et al., GPs were three times more likely to prescribe medication for anxiety and depression to unemployed compared to employed patients, perceiving that they did not have the personal, social or financial resources to engage with more active treatments [574].

The area of implicit bias in healthcare is an emerging field of research and holds promise for improving health outcomes for patients experiencing financial and social disadvantage [588]. Further research is needed to examine the extent to which implicit biases influence both overdiagnosis and overprescribing.

9.7 Health policy implications: Strategies to improve the safe and judicious use of psychotropics in children and adolescents

Internationally, there has been a range of programs introduced with the aim of improving quality use of psychotropic drugs in paediatric patients [590, 591], particularly in the US [433, 447, 592].

In 2009, the US government passed the Children's Health Insurance Program Reauthorization Act (CHIPRA) to improve the quality of healthcare for children [593]. Subsequently, new measures (the child core dataset) were added to the Health Effectiveness Data and Information Set (HEDIS) [593, 594]. HEDIS was developed in the early 1990s by the National Committee for Quality Assurance (NCQA), a non-profit organisation tasked with monitoring the quality of healthcare in the US through regular collection and analysis of healthcare data [595]. The initial 2009 child core dataset of 24 measures included only two

measures for mental health: follow-up care of children prescribed ADHD drugs and follow-up of children discharged from hospital following treatment for mental illness [593]. US states were encouraged to voluntarily adopt these measures in Medicaid and foster care programs [593]. From early 2024, it has been mandatory in the US to report all measures of the child core dataset for patients enrolled in Medicaid and Children's Health Insurance Program[z] [594, 596].

Following 2009 CHIPRA legislation and after several federal and state investigations highlighted a problem with all psychotropic drug use in children in foster care, the US federal government mandated psychotropic drug oversight in this group of vulnerable children [592]. Since then, there have been a range of programs introduced with the aim of improving quality use of psychotropic drugs in paediatric patients [590, 591]. The impact of these programs and other international initiatives addressing the quality of antipsychotic and antidepressant prescribing are discussed in Sections 9.7.1 to 9.7.4.

9.7.1 Antipsychotics

Quality improvement programs focussed on antipsychotic prescribing to children and adolescents in the US have led to significant improvements in medication management [433, 590]. Studies examining the effectiveness of programs reported rates of antipsychotic prescribing declined [597-602], dosages were reduced [597], and overall lower cumulative exposures to antipsychotics were recorded [591]. There was also no evidence of substitution with other psychotropic medications [601]. The programs used a variety of strategies, including drug utilisation reviews and prior authorization (PA) policies, requiring physicians to obtain pre-approval from appropriate state authorities before prescribing antipsychotics to children or adolescents [433]. Other strategies included improved access to consults with paediatric psychiatrists [596, 597], prescriber education and feedback [596], and mandatory medication reviews, triggered when antipsychotics were prescribed to very young children or at higher than recommended doses [597].

In 2015, three new measures related to antipsychotic use in children and adolescents were added to the US national HEDIS child core dataset: "monitoring the concurrent use of multiple antipsychotics", "provision of psychosocial therapies as first-line treatments in patients without a primary indication", and "metabolic monitoring of glucose and lipids for

z. The Children's Health Insurance Program (CHIP) provides health coverage for children from low-income families that do not qualify for Medicaid. (https://www.healthcare.gov/medicaid-chip/childrens-health-insurance-program/).

children prescribed antipsychotics" [596]. These three measures broadly correspond to monitoring polypharmacy, guideline-concordant prescribing (adherence to non-pharmaceutical recommendations as first-line treatment options), and metabolic parameters for paediatric patients using antipsychotics. Similar measures have been reported to be problematic in this thesis (co-prescribing (Chapter 5), guideline-concordance for psychotropic prescribing (Chapters 5 and 8), and cardiometabolic monitoring for antipsychotic users (Chapter 6). Currently, these measures are not being adequately monitored in Australian healthcare programs for paediatric patients.

In Australia, the Drug Utilisation Sub-Committee (DUSC) of the PBS has undertaken three antipsychotic reviews in the last decade [64, 603, 604], including one of the paediatric population [64]. The first study examined adult prescribing in 20-59-year-olds [604], with its results triggering major changes to the supply and prescription of quetiapine [604]. A second DUSC report commissioned in 2016 found these supply changes had resulted in the desired reduction in quetiapine use [603]. The same dataset was used to examine antipsychotic prescribing in 0-19-year-olds in a third report [64]. Report findings raised concerns about high increases in prescriptions of antipsychotics to children and adolescents from 2008 to 2011 (138% increase in quetiapine; 46% increase in risperidone) and highlighted concerns with adverse metabolic effects in adolescents. The report also called for further investigations to determine whether antipsychotics are being prescribed safely to children and adolescents [64] but did not recommend changes to supply or prescription for paediatric patients.

Along with changes following the 2013 DUSC report on antipsychotic prescribing in adults, programs have been implemented to improve antipsychotic prescribing in the elderly in Australia. The Australian federal government introduced the RedUSe program in Residential Aged Care Facilities (RACFs) in 2008/2009 [605]. The program entailed staff education, audit and feedback, and interdisciplinary case reviews [605]. Pilot testing of the program in 2008 across 25 RACFs provided promising results, reducing antipsychotic prescribing by 8% and benzodiazepine prescribing by 15% [606]. In 2013, the Australian government provided funding to expand the program to 150 RACFs, and further assessment found a 13% reduction in the proportion of residents prescribed an antipsychotic and a 21% reduction for benzodiazepines [605]. The positive results from international studies and the Australian RedUSe project suggest similar programs could be introduced to monitor psychotropic prescribing in children and adolescents.

9.7.2 Strategies to improve metabolic monitoring in children and adolescents using antipsychotics

While it is desirable to reduce overall antipsychotic prescribing to children and adolescents, monitoring of health outcomes for patients already prescribed antipsychotics needs improvement. The results from this thesis indicate rates of monitoring of metabolic adverse effects in children and adolescents in Australian primary care is inadequate.

As mentioned in Chapter 6, although guidelines have been developed for metabolic monitoring, the uptake of their recommendations has been poor. This points to the need for improved education and training, adequate resourcing and improved communication between GPs and other mental health care practitioners [437]. Several of the international programs mentioned in the previous section that aimed to improve the quality use of antipsychotics, demonstrated positive effects on metabolic monitoring as well [596, 602, 607]. Monitoring of glucose and lipids for paediatric patients using antipsychotics has also been included in the US HEDIS dataset since 2015 [594, 596]. Equivalent initiatives do not currently exist in Australia but could significantly improve health outcomes for Australian children.

9.7.3 Antidepressants

High levels of antidepressant prescribing to children and adolescents also need to be addressed with new healthcare initiatives. Findings in this thesis highlighted that one in 10 adolescents aged 15-18 years received antidepressant prescriptions in 2018, rising progressively from 7.2% in 2011. The annual average increase for 10-14-year-olds was 6.5%, culminating in 2.6% of children in this age group receiving antidepressants in 2018. In 2019, Australia had the fourth highest rate of antidepressant prescribing of 29 OECD countries [608], and results from this thesis suggest the high levels of prescribing are also observed in children and adolescents. The poor quality of evidence for the antidepressant fluoxetine in paediatric trials (Appendix 1), the removal of all antidepressants from the WHO EMLc for children aged under 13 years, and the poor efficacy found in recent meta-analyses of all paediatric antidepressant studies [609] provide further impetus to reduce antidepressant prescribing to children and adolescents. Various programs have been shown to be effective in reducing antidepressant use [591, 610], several of which are briefly discussed in the following paragraphs.

A recent study by Wallis and colleagues (2024) compared antidepressant dispensing in all age groups across Australia and the Netherlands, two countries with very similar social profiles and health care systems [610]. The authors reported rates of dispensing were twice as high in Australia as the Netherlands in 2013 and increased to 2.4 times as high in 2021. The rate of antidepressant dispensing for 5-24-year-olds was closer to 4-fold higher in Australia. In the Netherlands, there have been substantial efforts over the past 15 years to reduce antidepressant use, resulting in a system where 80% of general practices have well-trained mental health nurses, who can provide diagnostic assessments and psychological therapies at no cost to patients [610]. Although Australia introduced the Better Access initiative in 2006 [461], the cost to patients can be up to $90 AUD per session, and access to therapists is often difficult [610]. The Netherlands initiative also includes prescriber education programs and much tighter regulation of pharmaceutical company marketing than currently found in Australia [610].

The Australian federal government recently introduced the Nurse Practitioner Primary Care Pilot program [611]. Similar to the Netherlands' nurse practitioner program, nurse practitioners (NPs) will be able to diagnose and treat patients, prescribe medications, and refer to other health practitioners at no cost to the patient as part of a GP-led multidisciplinary team [612]. Although NPs have been an expanding part of the healthcare landscape for some 20 years, the pilot will significantly extend the scope of services that NPs can provide [613]. However, the pilot is primarily aimed at reducing pressure on hospital emergency departments and overstretched GP services, so it is not clear if it will include recruitment of specialist mental health NPs.

There are also other initiatives that are beginning to address the problem in the Australian adult population, where there is a recognised problem with high and rapidly increasing use of antidepressants [614, 615]. The WiserAD trial was an NHMRC-funded project that recruited a small 13-participant sample of patients from general practice and examined the effects of using a web-based support tool to assist patients and GPs to taper and deprescribe antidepressants [614, 616]. Three patients reduced their dosage by half after three months, and two patients commenced tapering but returned to full dose [616]. Another trial addressing overuse of antidepressants, the RELEASE trial (REdressing Long-tErm Antidepressant uSE), is currently being undertaken in general practices in Queensland [615] with results expected in 2026 (https://medical-school.uq.edu.au/release). Horowitz and Taylor published the first edition of the Maudsley antidepressant deprescribing guidelines in

February 2024 [617], addressing the long-recognised need to reduce antidepressant use in adult populations worldwide. While these deprescribing programs are positive, there remains an additional need to reduce the initiation of antidepressants, especially in children and adolescents [618].

9.7.4 All psychotropics

The rates of psychotropic prescribing to children and adolescents in Australian primary care have risen substantially from 2011 to 2018, especially antipsychotics, antidepressants, and melatonin. While programs to improve safe prescribing have been examined for adults using antipsychotics (RedUSe) and antidepressants (wiserAD, RELEASE), no equivalent programs have been created for paediatric psychotropic users to date.

There is an urgent need for state and federal governments to address the issue of the safe and judicious use of these drugs in paediatric populations. This could include the introduction of "hard stop" initiatives, similar to prior authorisation Medicaid programs in the US [619]. Alternatively, "soft-stop" programs that encourage education, consultation, and a sense of collegiality between prescribers, paediatric specialists, and government agencies may be useful [619]. For example, the A-KIDS (Antipsychotics – Keeping It Documented for Safety) web-based prescription register adopted in North Carolina is a "soft stop" program that guides clinicians through the decision to prescribe antipsychotics and provides pharmacy automated alerts for prescriptions for unusually high dosages of antipsychotics and possible drug interactions [599]. Preliminary evidence shows the A-KIDS program effectively reduces the prevalence of antipsychotic prescribing and increases metabolic monitoring in antipsychotic users [602]. Other programs mentioned in Sections 9.7.1 to 9.7.3 also provide examples of successful initiatives, elements of which could be used within the Australian context to create paediatric psychotropic monitoring programs.

9.8 Contribution to research methodology

9.8.1 Strengths

This thesis adds to a growing body of research demonstrating the feasibility of using EHRs to answer a range of questions in health research [474, 620]. Although administrative datasets such as the PBS are valuable for examining drug prescribing practices [38], primary care datasets using EHRs such as MedicineInsight complement data on prescriptions with extensive information on physical observations, laboratory measurements, diagnoses, and comorbid health conditions [621]. Importantly, the use of EHRs in primary care provides an

accurate snapshot of real-world prescribing practices [621]. Health surveys and longitudinal datasets such as the CAMHW survey and the Longitudinal Study of Australian Children provide detailed information of patient diagnoses, socio-economic factors, and drug use but may be biased. Specifically, there is a risk of patient self-reporting bias, including recall bias and social desirability bias, or a tendency to respond with information perceived to be socially appropriate [622]. Real-world EHR datasets remove these biases as the information is captured at the time of GP visit and retained in longitudinal records [622].

The diagnostic algorithms for mental disorders in children and adolescents were developed specifically for this thesis, complementing algorithms used for adult mental health diagnoses [360], which, at the commencement of this thesis, were also in development. The algorithm was created using the full dataset in consultation with a child psychiatrist and medical professionals, including GPs. These algorithms can be used in future studies using MedicineInsight or similar primary care databases.

The use of a primary care database also provided valuable information on previously unexamined GP paediatric prescribing practices. A 2016/2017 survey found Australian GPs experienced difficulties managing paediatric patients with complex mental disorders and frequently refer to specialist services [623], where the majority of psychotropic prescriptions are initiated [438]. This thesis provides valuable insight into the treatment practices specific to primary care.

This thesis also demonstrated how a relatively new statistical technique, Augmented Inverse Probability Weighting (AIPW), can be used to emulate randomised controlled trials using EHR datasets [391], expanding the analyses in this thesis beyond purely descriptive analyses. The availability of rich clinical data and diagnoses, as well as a range of sociodemographics, allowed for a broad range of covariates to be included in the analyses, thereby improving the accuracy of estimates in the study on metabolic monitoring (Chapter 6).

9.8.2 Limitations

The use of EHRs also has limitations. EHRs collected in databases such as MedicineInsight are designed for patient management, not research purposes [357, 474]. Although great care was taken in the development of the diagnostic algorithms, the comparability to diagnoses made by specialists using DSM or ICD classifications and using validated symptom scales would be limited. Further, relevant information may not be transferred from secondary care, and information in GPs' progress notes would be excluded. This could be particularly

problematic when establishing off-label status of prescribing, as diagnoses may be underreported.

Although a strength of using EHRs is the removal of recall biases, EHRs are limited in other ways. MedicineInsight recorded prescriptions written, which may not have been dispensed or consumed by patients, resulting in an overestimate of the prevalence of psychotropic use.

Similarly, use of target trial methodology was a strength but requires a comprehensive set of covariates to enable accurate estimates of treatment effects. Although use of a doubly robust AIPW technique can reduce bias, there would still be some residual confounding.

Finally, although a large dataset, some analyses were restricted by small sample sizes. Detailed analyses of sociodemographic patterns were not possible in the off-label antipsychotic prescribing study (Chapter 5), and the impact of overweight/obesity on cardiometabolic monitoring was not reliable in AIPW analyses (Chapter 6). These analyses need to be examined with larger datasets.

10 Conclusion and recommendations

This thesis is the first to examine paediatric psychotropic drug prescribing in Australian primary care settings, giving a unique insight into GP prescribing practices. In this section, key findings are summarised, and directions for future research and public health policy initiatives are suggested.

10.1 Summary of findings

Findings from this thesis highlight problematic prescribing of psychotropic drugs to children and adolescents in Australian general practice. There were marked increases in prescriptions across the study period for antidepressants, antipsychotics, ADHD drugs, and melatonin (Chapter 4). The highest prevalence recorded was 10% for antidepressant prescriptions in 2018 in the 15-18-year age group. With the exception of melatonin that increased by 534% in 0-4-year-olds over the study period, very young children received few psychotropic prescriptions. Off-label prescribing also increased across the study period for antidepressants, antipsychotics, and melatonin.

This thesis also examined whether prescribing was guideline-concordant and found a large discrepancy between two sources of information that provide guidance on appropriate medication use for children and adolescents: TGA approvals (used to define off-label prescribing in this thesis) and clinical practice guidelines (CPGs). Most prescribing was not in agreement with TGA approvals but generally concordant with Australian and international CPGs, especially for antidepressant and melatonin prescribing. A focus on antipsychotic prescribing patterns in Chapter 5 indicated the most common off-label use was for depression and/or anxiety. For those patients prescribed antipsychotics, monitoring for adverse cardiometabolic outcomes was low (chapter 6).

10.2 Implications and future research

While these findings highlight a concerning increase in psychotropic prescribing, they provide little information as to the reasons behind the increase. There may be an increasing prevalence of mental disorders, although the CAMHW and other international surveys have not found any marked increases in diagnoses over the last few decades (see Chapter 7). However, the last CAMHW survey was undertaken in 2013/2014 and measured a small sample of mental disorders. Trends may have changed. As discussed in Chapter 7, there is a

need for improvement in the monitoring of paediatric mental disorder prevalences in order to highlight areas of clinical need [14] and assess treatment effectiveness [608]. Alternatively, there may be an increasing trend to treat childhood mental disorders with pharmacological rather than non-pharmacological options. This is not concordant with CPG recommendations that predominantly emphasise non-pharmacological treatments for children and adolescents. Increasing reliance on drug treatments raises concerns that children may be unnecessarily receiving psychotropic drugs that could be putting their health at risk. There are also concerns about clinicians' apparent reliance on CPGs. In the majority of CPGs summarised in Chapter 2 and Appendices 2 to13 drug recommendations exceeded those approved by regulatory authorities worldwide, including the Australian TGA. CPGs can be compromised by COIs and the quality of the evidence base that underpins the recommendations. Relying on CPG drug recommendations may do more harm than good.

Analyses examining social disadvantage and psychotropic prescribing were fraught with inconsistencies, providing little explanation as to what caused the increased prescribing with increasing disadvantage found in Chapter 4 or why this trend was attenuated for antipsychotic prescribing in Chapter 5. Literature reviews of international studies suggest that increased prescribing to patients in socially disadvantaged areas could be driven by both overdiagnosis and over-medication of mental disorders. Future research needs to disentangle these factors by examining the social determinants of health (SDH) in greater depth.

Key to explaining all the prescribing patterns observed in this thesis, however, is a deeper understanding of GP perspectives. A measure of GP attitudes to prescribing psychotropics is not available in EHR datasets, pointing to the need for mixed methods research studies that can complement the rich quantitative data available in EHRs with qualitative research findings. Qualitative research could explore reasons why GPs are choosing pharmacologic treatments and engaging in such low levels of cardiometabolic monitoring. GP surveys could also examine the resources that GPs use and trust to guide treatment decisions. While there have been recent Australian surveys assessing GP knowledge, attitudes, and beliefs about prescribing medicinal cannabis (2022) [624], opioids (2021) [625], and non-drug interventions for a variety of health conditions (2024) [626], there are no recent studies examining beliefs and attitudes towards prescribing psychotropics in Australian general practice. There is a need for updated perspectives on GP attitudes towards diagnosing and treating mental disorders for all age groups, including children and adolescents.

10.3 Public health initiatives

Increasing paediatric prescribing of psychotropic drugs is occurring worldwide, and initiatives to reduce prescribing are already in place in the US. As discussed in Section 9.7, many states in the US have been monitoring antipsychotic use in children in the foster care system and Medicaid-enrolled children since 2009. These programs have resulted in decreased prescribing of antipsychotics and increased levels of monitoring for adverse health outcomes in children receiving these drugs. Some elements of the programs have been mandatory since early 2024. The programs implement a range of strategies, including prescriber education, prior authorisation programs, and facilitated access to specialist advice.

In Australia [605, 615, 616], the UK [617], and the Netherlands [610], programs designed to promote safe and judicious psychotropic prescribing in adults have been initiated over the last 15 years. In Australia, these initiatives include the RedUSe and WiserAD projects that address deprescribing for antipsychotics and antidepressants, respectively. Both programs have demonstrated positive outcomes. There is also a need for initiatives to encourage deprescribing of all psychotropics to children and adolescents in Australia across all sectors of healthcare, including GPs and specialists.

In 2013, the PBAC advisory committee undertook an analysis of antipsychotic utilisation in children and adolescents [64]. The report found concerningly high rates of prescribing for the same three antipsychotics as recorded in this thesis. GPs, not paediatric psychiatrists or specialists, were the most likely to initiate quetiapine and olanzapine during a three-month period from December 2011 to March 2012. The authors of the report expressed concerns that use did not appear to be in accordance with TGA or PBS approvals and called for further investigation into the utilisation of all psychotropics to determine if the drugs are being prescribed safely [64, p.18]. This thesis, examining prescribing of all the main classes of psychotropics, contributes to a deeper understanding of paediatric prescribing practices and partially addresses the call for further investigations recommended by the PBAC report. The results from this thesis provide evidence that psychotropics, particularly antipsychotics, are still increasingly being prescribed to children and adolescents and highlight that this is most frequently inappropriate, off-label prescribing.

There remains a need for public health initiatives to address the concerning increases in paediatric psychotropic prescribing in Australian general practice.

11 Appendices

11.1 Appendix 1. Quality of evidence for the pharmacological treatment of child and adolescent mental health – an example

The evidence base recommending pharmacological treatment for child and adolescent mental disorders guidelines is poor [33]. Trials related to pharmacological interventions are sparse [33], so recommendations have been made based on small numbers. In some cases, cited publications do not unequivocally support the recommendation. For example, the 2005 (updated 2015) NICE guidelines for depression in children and adolescents [197] recommended fluoxetine as the only antidepressant that has clinically proven effects in young people. The recommendation for fluoxetine remains in the new 2019 NICE guidelines for depression in children and adolescents [165]. This was based on four trials totalling 393 participants who received the active drug fluoxetine [199]. Table 1 summarises all paediatric trials examining fluoxetine as a treatment for depression, and entries 1 to 4 list the four trials underpinning the guideline recommendation.

There are issues with the quality of evidence for all four studies. One study that underpins NICE recommendations for fluoxetine was conducted by Simeon et al. (1990) and included only 40 participants (20 on fluoxetine and 20 on placebo) aged 13 to 18 years [627]. Only 15 participants in each group completed the trial. Further, there was no significant difference between drug and placebo at trial end (following 8 weeks' treatment) or long-term follow-up (average: 24 months, range: 8-46 months). Although fluoxetine was superior to placebo on all measures but one, there were no statistically significant differences.

A subsequent trial by Emslie et al. (1997) [628] included 48 participants on fluoxetine who demonstrated a significant difference on two outcome measures but not on the protocol-defined primary outcome (a score <29 on the CDRS-R scale, $p = 0.339$) [629]. Another trial by Emslie et al. (2002) included 109 participants on fluoxetine [630]; in this trial, the primary outcome measure was predefined as an improvement of at least 30% on the CDRS-R outcome measure. The primary outcome measure was similarly not significant ($p = 0.093$), even though fluoxetine was superior to placebo at week 9 (at the end of the acute trial phase). Post-hoc, the authors critiqued their choice of cut-off measurement and calculation method for the pre-defined primary outcome. In post-hoc analyses, they calculated the change in CDRS-R scores by adjusting for the scale having a non-zero minimum, after which the result was significant ($p = 0.006$). Changing protocol-specified primary outcome

measures in such a manner is recognised as a threat to the validity of study findings [631] and a source of biased reporting [632, 633].

The fourth trial informing NICE guidelines was the Treatment for Adolescents with Depression Study (TADS) [558], a highly cited and influential trial comparing fluoxetine to cognitive behavioural therapy (CBT) alone or combined with fluoxetine. This trial included 216 participants who received fluoxetine but was not adequately blinded and is currently undergoing reanalysis under the Restoring Invisible and Abandoned Trial (RIAT) program [557].

In summary, only one trial published in 1997 of 48 participants on fluoxetine [628] provides reasonable support for NICE recommendations but would still be considered poor evidence. The primary author of the 1997 publication also listed conflicts of interest (COIs) with the pharmaceutical industry in the 2002 publication [630]. However, COIs were not required to be reported in 1997, so the status of COI at time of publication is unknown.

Table 11.1 A summary of all studies examining fluoxetine in children and adolescents with depression[a]

Study	Participants	Participants receiving fluoxetine	Age group	Length of trial	Results	Comments	COIs	Included as reference in review of fluoxetine or SSRIs
Simeon 1990[1]	40	20 (15 completed acute phase)	13-18 years	Acute – 8 week Follow-up – average 24 months (range 8-46 months)	Fluoxetine was superior to placebo on all measures except sleep disorder, but difference was not significant. Both groups showed further improvement at follow-up but there were no significant group differences.		None recorded	NCCMH/NICE 2005[11] Sharp & Hellings 2006[12] Hetrick et al. 2012[13] Hetrick et al. 20211[14] Wallace et al. 2006[b,15]
Emslie et al. 1997[2]	96	48	7-17 years	8 weeks	Clinical improvement (CGI scale rated much or very much improved): 56% on fluoxetine improved, compared to 33% on placebo (p=0.02) Rating on CDRS scale – fluoxetine significantly superior to placebo after week 5	Exclusion: Responders to 1 week single blind placebo run-in	NIMH funded No COI recorded	Whittington et al. 2004[16] NCCMH/NICE 2005[11] Sharp & Hellings 2006[12] Wallace et al. 2006[15] Hetrick et al. 2012[13] Hetrick et al. 2021[14] Bridge et al. 2009[17]

Study	Participants	Participants receiving fluoxetine	Age group	Length of trial	Results	Comments	COIs	Included as reference in review of fluoxetine or SSRIs
Emslie et al. 2002[3]	219	109	8-18 years	9 week acute phase of 51 week multicentre, controlled clinical trial	Primary outcome response criterion (>= 30% decrease in CDRS-R score, not significant (p=0.093) Fluoxetine was associated with greater mean improvement in CDRS-R score than placebo after week 1(p<.05) and throughout study	Exclusions: • Responders to placebo during 1 week placebo lead-in • those who previously did not respond to fluoxetine	Study funded by Eli Lilly 8 authors: 4 authors from Eli Lilly 2 primary authors (Emslie and Wagner) paid consultants on study by Eli Lilly	Whittington et al. 2004[16] NCCMH/NICE 2005[11] Sharp & Hellings 2006[12] Wallace et al. 2006[15] Hetrick et al. 2012[13] Hetrick et al. 2021[14] Vartiainen 2019[18] Bridge et al. 2009[17]
March et al. 2004[4]	439	216	12-17 years	Acute: 12 weeks Follow-up: 36 weeks	Fluoxetine significantly better than placebo on CDRS-R and CGI-I scales	No placebo group for the patients allocated to the fluoxetine plus CBT group (COMB)	Funded by NIMH No COIs listed Lilly provided drug and placebo but had no role in design, implementation or authorship of study	NCCMH/NICE 2005[11] Sharp & Hellings 2006[12] Wallace et al. 2006 Hetrick et al. 2012[13] Hetrick et al. 2021[14] Vartiainen 2019[18] Bridge et al. 2009[17]

Study	Participants	Participants receiving fluoxetine	Age group	Length of trial	Results	Comments	COIs	Included as reference in review of fluoxetine or SSRIs
Emslie et al. 2004[5]	40	20 (10 completed)	8-18 years	32 week relapse prevention phase of 51 week multicentre, controlled clinical trial	Mean time to relapse was significantly longer in the group that remained on fluoxetine, compared to the group that switched from fluoxetine to placebo (p=.046) Relapse occurred in an estimated 34% of those remaining on drug and 60% of those switched to placebo	Abstract did not mention that on measures of depression and functioning, changes on symptoms and functioning were not significantly different between the 2 groups on CDRS-R (total), CGI-S, MADRS, CDI, BDI, GAF, HAMA. Only 2 subscales of CDRS-R were significant- Mood[c] and Subjective[d]	Supported by Eli Lilly 8 authors, 3 current and 1 former employee of Eli Lilly – all minor stockholders	Vartiainen 2019[18]

Study	Participants	Participants receiving fluoxetine	Age group	Length of trial	Results	Comments	COIs	Included as reference in review of fluoxetine or SSRIs
Emslie et al. 2014[6]	463	117 (84 completed acute phase)	7-17 years	Acute: 10 week	Neither fluoxetine not duloxetine significantly different to placebo on CDRS-R total score.	Uses same data as Atkinson et al 2014 Study examined adverse event profile of duloxetine, using fluoxetine as an active control.	Sponsored by Eli Lilly 6 authors: Emslie received research support from 5 drug companies, and consults for 10 drug companies and 1 non-drug medical company March has been consultant for 3 drug companies and 1 non-drug medical company – he has not engaged in promotional work for over 15 years 4 authors are Eli Lilly employees and hold stock in the company	Vartiainen 2019[18] Hetrick et al. 2021[14] Cipriani et al. 2016[e,19]
Nilsson et al. 2004[7]	96	49	9-17 years	Acute: 9 weeks Continuation: up to 19 weeks	Examined safety of fluoxetine, not efficacy Patients taking fluoxetine had significantly lower alkaline phosphatase and higher cholesterol at week 19, and had gained less weight and height Concluded that fluoxetine was safe and well tolerated in this study	This data is taken from Emslie et al 2002 study	Supported by Eli Lilly 5 authors; no COIs listed	Vartiainen 2019[18]

Study	Participants	Participants receiving fluoxetine	Age group	Length of trial	Results	Comments	COIs	Included as reference in review of fluoxetine or SSRIs
Atkinson et al. 2014[8]	337	117 – (91 completed acute phase)	7-17 years	Acute: 10 week Follow-up: at 36 weeks	Study of duloxetine (flexible dose) using fluoxetine as an active control: neither drug superior to placebo on CDRS-R	Uses same data as Emslie et al 2014	Sponsored by Eli Lilly 7 authors: Atkinson has research grant affiliations with 17 drug companies (4 past) Emslie received research support from 5 drug companies, and consults for 10 drug companies and 1 non-drug medical company March has been consultant for 3 drug companies and 1 non-drug medical company – he has not engaged in promotional work for over 15 years 4 authors are Eli Lilly employees and hold stock in the company	Vartiainen 2019[18] Hetrick et al. 2021[14]
Almeida-Montes 2005[9]	43	23	8-14 years	6 weeks	No significant difference between fluoxetine and placebo for patients with depression		Eli Lilly (Mexico) provided the fluoxetine and placebo pills but did not contribute in any other way	Hetrick et al. 2012[13] Hetrick et al. 2021[14] Cipriani et al. 2016[e,19]

Study	Participants	Participants receiving fluoxetine	Age group	Length of trial	Results	Comments	COIs	Included as reference in review of fluoxetine or SSRIs
Findling et al. 2009[10]	34	18	12-17 years	8 weeks	No significant difference between fluoxetine and placebo	Pilot study: Participants with depression comorbid substance use disorder	Clinical research grant from Lilly	Cipriani et al. 2016[e,19]

Abbreviations: BDI, Beck Depression Inventory; CDRS-R, Children's Depression Rating Scale-Revised; CDI, Children's Depression Inventory; CGI-I, Clinical Global Impressions-Improvement; CGI-S, Clinical Global Impressions-Severity; COI, conflicts of interest; HAMA, Hamilton Anxiety Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; NCCMH, National Collaborating Centre for Mental Health; NICE, National Institute for Health and Care Excellence; NIMH, National Institute of Mental Health.

Notes:

a. Studies included only those where there was a comparison between fluoxetine and placebo as part of the study.

b. Simeon et al 1990 was included in the descriptive analysis but not the meta-analysis in Wallace et al 2006, due to inadequacy of the data.

c. The CDRS Mood subscale includes irritability, depressed feeling, weeping, depressed affect.

d. The CDRS Subjective subscale includes guilt, self-esteem, morbid ideation, suicidal ideation.

e. One 1986 study included in the Cipriani analysis was obtained from Eli Lilly has not been listed in this table. The study of 40 participants (21 on fluoxetine), included inpatient and outpatients, and was not published in a peer reviewed journal.

References included in this table: [199, 558, 609, 627, 628, 630, 634-646]

1. Simeon JG, Dinicola VF, Ferguson HB, et al. (1990) Adolescent depression: a placebo-controlled fluoxetine treatment study and follow-up. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 14(5): 791-795.

2. Emslie GJ, Rush AJ, Weinberg WA, et al. (1997) A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. *Archives of General Psychiatry* 54(11): 1031-1037.

3. Emslie GJ, Heiligenstein JH, Wagner KD, et al. (2002) Fluoxetine for acute treatment of depression in children and adolescents: a placebo-controlled, randomized clinical trial. *Journal of the American Academy of Child and Adolescent Psychiatry* 41(10): 1205-1215.

4. March J, Silva S, Petrycki S, et al. (2004) Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *JAMA* 292(7): 807-820.

5. Emslie GJ, Heiligenstein JH, Hoog SL, et al. (2004) Fluoxetine treatment for prevention of relapse of depression in children and adolescents: a double-blind, placebo-controlled study. *Journal of the American Academy of Child and Adolescent Psychiatry* 43(11): 1397-1405.

6. Emslie GJ, Prakash A, Zhang Q, et al. (2014) A double-blind efficacy and safety study of duloxetine fixed doses in children and adolescents with major depressive disorder. *Journal of Child and Adolescent Psychopharmacology* 24(4): 170-179.

7. Nilsson M, Joliat MJ, Miner CM, et al. (2004) Safety of subchronic treatment with fluoxetine for major depressive disorder in children and adolescents. *Journal of Child and Adolescent Psychopharmacology* 14(3): 412-417.

8. Atkinson SD, Prakash A, Zhang Q, et al. (2014) A double-blind efficacy and safety study of duloxetine flexible dosing in children and adolescents with major depressive disorder. *Journal of Child and Adolescent Psychopharmacology* 24(4): 180-189.

9. Almeida-Montes L, Friederichsen A. Treatment of major depressive disorder with fluoxetine in children and adolescents. A double-blind, Placebo-controlled study. *Psiquiatria Biologica*. 2005;12:198-205.
10. Findling RL, Pagano ME, McNamara NK, et al. (2009) The short-term safety and efficacy of fluoxetine in depressed adolescents with alcohol and cannabis use disorders: a pilot randomized placebo-controlled trial. *Child Adolesc Psychiatry Ment Health* 3(1): 11.
11. National Collaborating Centre for Mental Health (2005) Depression in Children and Young People: Identification and management in primary, community and secondary care. Full guideline - cg28. Leicester, UK: British Psychological Society & The Royal College of Psychiatrists. (Report commissioned by NICE).
12. Sharp SC and Hellings JA (2006) Efficacy and safety of selective serotonin reuptake inhibitors in the treatment of depression in children and adolescents: practitioner review. *Clinical Drug Investigation* 26(5): 247-255.
13. Hetrick SE, McKenzie JE, Cox GR, et al. (2012) Newer generation antidepressants for depressive disorders in children and adolescents. *Cochrane Database Systematic Reviews* 11: Cd004851.
14. Hetrick SE, McKenzie JE, Bailey AP, et al. (2021) New generation antidepressants for depression in children and adolescents: A network meta-analysis. *Cochrane Database Systematic Reviews* 5: CD013674.
15. Wallace AE, Neily J, Weeks WB, et al. (2006) A cumulative meta-analysis of selective serotonin reuptake inhibitors in pediatric depression: did unpublished studies influence the efficacy/safety debate? *Journal of Child and Adolescent Psychopharmacology* 16(1-2): 37-58.
16. Whittington CJ, Kendall T, Fonagy P, et al. (2004) Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. *Lancet* 363(9418): 1341-1345.
17. Bridge JA, Birmaher B, Iyengar S, et al. (2009) Placebo response in randomized controlled trials of antidepressants for pediatric major depressive disorder. *American Journal of Psychiatry* 166(1): 42-49.
18. Vartiainen JS (2019) *Pharmacotherapy in depressed children and adolescents*. Masters, University of Eastern Finland.
19. Cipriani A, Zhou X, Del Giovane C, et al. (2016) Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis. *The Lancet* 388(10047): 881-890.

For added context, Table 11.1 also includes more recent studies that included a comparison between fluoxetine and placebo in children and adolescents with depression (rows 5 to 9). These studies also failed to find a significant difference between fluoxetine and placebo on paediatric depressive symptoms. Therefore, there remains no evidence of sufficient quality for any approval for fluoxetine or any other antidepressant to treat depression in children and adolescents.

The paucity of evidence in support of the recommendation for fluoxetine led McArdle (2007) to conclude "that a gross discrepancy exists between the scale of data available to biomedicine and to mental health, and particularly child and adolescent mental health" [647, p.66]. More recent reviews of evidence for fluoxetine treatment in children and adolescents with depression [609, 641, 644], however, still reference the same studies as providing evidence of efficacy (Table 11.1).

A recent network meta-analysis of 34 trials [637] and 5,260 patients examined the efficacy and tolerability of 14 different antidepressants in the treatment of children and adolescents with major depressive disorder. Three of the four studies presented as supporting evidence for NICE guidelines were also included in this meta-analysis. The authors concluded the "drugs do not seem to offer a clear advantage for children and adolescents" [637, p.881] and noted fluoxetine was "probably" the best option if drug treatment is considered necessary.

Despite such poor evidence, fluoxetine remains recommended or suggested as first-line pharmacological treatment for children and adolescents with depression in all guidelines listed in the section on "Depressive disorders" in Chapter 2 (Section 2.3.1).

11.2 Appendix 2. Depressive disorders guideline summaries by severity of disorder

Guideline	Sub-syndromal	Mild	Moderate	Severe	Psychotic	Comorbid, complicated
beyondblue 2011 [a] (13-18 years)	Psycho-education, active listening, lifestyle advice OR CBT for short-term reduction of symptoms OR Group CBT/IPT	**1st line**: CBT or IPT: SSRIs are not recommended for mild depression.	**1st line**: CBT or IPT: SSRIs are not recommended unless psychotherapy is not effective, unavailable or refused. **2nd line**: After assessing that poor response is not due to incorrect diagnosis, poor therapeutic relationship, poor adherence or undetected comorbidity: • after 6-10 session CBT/IPT and/or 8 weeks FLX up to max 40gm/day), consider change of therapy (p.65) • Based on expert opinion only, 2nd line switching antidepressants are SERT, CIT, MIRT, or augmentation with MS	**1st line**: CBT or IPT: SSRIs are not recommended unless psychotherapy is not effective, unavailable or refused. **2nd line**: After assessing that poor response is not due to incorrect diagnosis, poor therapeutic relationship, poor adherence or undetected comorbidity: • after 6-10 session CBT/IPT and/or 8 weeks FLX up to max 40gm/day), consider change of therapy (p.65) • Based on expert opinion only, 2nd line switching antidepressants are SERT, CIT, MIRT, or augmentation with MS	ECT may be considered where other approaches have been unsuccessful. If psychosis is part of bipolar, consider adding LITH, anticonvulsants, or atypical antipsychotics (SGAs). (Refer to bipolar guideline summary)	No specific recommendation: suggestion that CBT may help with comorbid conduct disorder
eTG Complete (current as at April 2019) (child and adolescent)		**1st line**: CBT or IPT	**1st line**: CBT or IPT **2nd line**: Management of moderate-to-severe depression in adolescents should be assertive and prompt, typically including a combination of psychological and pharmacological interventions. • if SSRIs are used treatment trials (FLX>=8 years) should last for 3 to 4 weeks before considering a dose increase, and 8 to 12 weeks before considering a change of therapy • **3rd line**: SERT and CIT are potential 2nd line drugs. • PAR and VEN should not be used. • TCAs should not be used in children under 16 years. • MIRT may cause problems due to sedation and weight gain.	**1st line**: CBT or IPT **2nd line**: Management of moderate-to-severe depression in adolescents should be assertive and prompt, typically including a combination of psychological and pharmacological interventions. • if SSRIs are used treatment trials (FLX>=8 years) should last for 3 to 4 weeks before considering a dose increase, and 8 to 12 weeks before considering a change of therapy • **3rd line**: SERT and CIT are potential 2nd line drugs. • PAR and VEN should not be used. • TCAs should not be used in children under 16 years. MIRT may cause problems due to sedation and weight gain.		

Guideline	Sub-syndromal	Mild	Moderate	Severe	Psychotic	Comorbid, complicated
Royal Australian and New Zealand College of Psychiatrists (RANZCP) mood disorders guideline (2015) (Child an adolescent section pp1168-1169)		**1st line:** CBT or IPT **2nd line**: potentially add FLX when psychotherapy trialled and found ineffective	**1st line**: CBT or IPT **2nd line**: potentially add FLX when depression is moderate or severe or when psychotherapy trialled and found ineffective. **3rd line**: Clinicians with child/ adolescent expertise can consider non-FLX medications (SERT, CIT, and if necessary antipsychotic augmentation) for recurrent, unresponsive depression.	**1st line**: CBT or IPT **2nd line**: potentially add FLX when depression is moderate or severe, or when psychotherapy trialled and found ineffective. **3rd line**: Clinicians with child/ adolescent expertise can consider non-FLX medications (SERT, CIT, and if necessary antipsychotic augmentation) for recurrent, unresponsive depression.	Clinicians with child/ adolescent expertise can consider non-FLX medications (SERT, CIT, and if necessary antipsychotic augmentation) for recurrent, unresponsive or psychotic depression.	
National Institute for Health and Care Excellence (NICE) (2005) (children and young people)		**1st line**: watchful waiting up to 4 weeks **2nd line:** non-directive supportive therapy or group CBT for 2 to 3 months **3rd line**: persisting unresponsive depression should follow guidelines for moderate to severe depression	**1st line:** offer a specific psychological therapy (individual CBT, IPT, family therapy or psychodynamic psychotherapy) for at least 3 months. **2nd line**: if unresponsive after 4-6 weeks offer combined FLX and psychological therapy for moderate to severe depression for 12–18-year-olds (Offer cautiously for 5–11-year-olds as effectiveness is not established.) **3rd line**: if unresponsive to combined therapy after further 6 sessions, or refused FLX, trial short-term family therapy for at least 3 months, or systemic family therapy for at least 15 fortnightly sessions, or alternate individual child psychotherapy for approximately 30 weekly sessions. **4th line**: if FLX is not tolerated or ineffective, 2nd line medications are SERT or CIT. • PAR, VEN and TCAs are not to be used in children and young people.	**1st line**: offer a specific psychological therapy (individual CBT, IPT, family therapy or psychodynamic psychotherapy) for at least 3 months. **2nd line**: if unresponsive after 4-6 weeks offer combined FLX and psychological therapy for moderate to severe depression for 12–18-year-olds (Offer cautiously for 5–11-year-olds as effectiveness is not established.) **3rd line**: if unresponsive to combined therapy after further 6 sessions, or refused FLX, trial short-term family therapy for at least 3 months, or systemic family therapy for at least 15 fortnightly sessions, or alternate individual child psychotherapy for approximately 30 weekly sessions. **4th line**: if FLX is not tolerated or ineffective, 2nd line medications are SERT or CIT. • PAR, VEN and TCAs are not to be used in children and young people.	Consider augmenting current treatment plan with an atypical antipsychotic (SGA), although optimum dose and duration is unknown.	If not responding to psychological therapy due to comorbid conditions or persisting psychosocial risk or presence of parental mental ill-health, consider alternative psychological therapy for patient or additional therapy for parent.

Guideline	Sub-syndromal	Mild	Moderate	Severe	Psychotic	Comorbid, complicated
AACAP (American Academy of Child and Adolescent Psychiatry) (2007)		**1st line**: Education, support and case management appear to be sufficient. **2nd line**: trial with specific psychotherapies	**1st line**: Education, support and case management (not usually adequate) **2nd line**: trial with specific psychotherapies and/ or antidepressants (FLX is first choice if medication selected) **3rd line**: Combination of psychotherapy and antidepressants if fail to respond to prior monotherapy • TCAs not first-line	**1st line:** Education, support and case management (not usually adequate – generally require AD) **2nd line**: trial with specific psychotherapies and/ or antidepressants (FLX is first choice if medication selected) **3rd line**: Combination of psychotherapy and antidepressants if fail to respond to prior monotherapy • TCAs not first-line	Clinical consensus recommends adding an atypical antipsychotic (SGA) to antidepressant. ECT may be used based on effectiveness demonstrated in non-controlled studies, but high-quality evidence in children and adolescents does not exist.	Clinician should determine which condition is causing the greatest distress and treat that first: if comorbid substance abuse treat both disorders.

Guideline	Sub-syndromal	Mild	Moderate	Severe	Psychotic	Comorbid, complicated
GLAD-PC (Guidelines for Adolescent Depression in Primary Care) (2007)		**1st line**: consider a period of active support and monitoring (6-8 weeks, biweekly) before starting evidence-based treatment.	**1st line**: no period of active monitoring is recommended. Initiate treatment immediately •Offer antidepressants or proven psychotherapy (e.g., CBT, IPT) or combination therapy. •When indicated, and there is a family preference, an SSRI should be used. •Only FLX has been approved for depression in children and adolescents. •ESCIT is approved (US) for aged 12 and older. **2nd line**: • if partial improvement after 6-8 weeks maximum dose of SSRI, consider adding evidence-based psychotherapy if not already initiated, an increase in dose above FDA approved range, addition of another medication, or switch to another medication. • If partial improvement after trial of CBT or IPT, consider adding SSRI: • FLX for children and adolescents • ESCIT only evidence for over 11 years • Alternative SSRIs include CIT, FLUV, SERT, PAR.	**1st line**: no period of active monitoring is recommended. Initiate treatment immediately •Offer antidepressants or proven psychotherapy (e.g., CBT, IPT) or combination therapy. •When indicated, and there is a family preference, an SSRI should be used. •Only FLX has been approved for depression in children and adolescents. •ESCIT is approved (US) for aged 12 and older. **2nd line**: • if partial improvement after 6-8 weeks maximum dose of SSRI, consider adding evidence-based psychotherapy if not already initiated, an increase in dose above FDA approved range, addition of another medication, or switch to another medication. • If partial improvement after trial of CBT or IPT, consider adding SSRI: • FLX for children and adolescents • ESCIT only evidence for over 11 years • Alternative SSRIs include CIT, FLUV, SERT, PAR.	Consider consultation with a mental health specialist.	Consider consultation with a mental health specialist.

Guideline	Sub-syndromal	Mild	Moderate	Severe	Psychotic	Comorbid, complicated
BMJ Best Practice (2018) (children and adolescents)		**1st line**: active monitoring and supportive care for up to 4 weeks •Typically, adjunctive medications (melatonin, antihistamines) or psychosocial interventions are instituted to manage symptoms associated with depression (e.g., insomnia and agitation) for all levels. **2nd line**: if there is inadequate improvement add a course of specific evidence-based psychotherapy, such as CBT IPT, if available and appropriate. **3rd line**: switch to or add SSRI + continue supportive care (FLX, ESCIT, SERT, CIT) **4th line**: if inadequate improvement after 8 weeks of SSRI at adequate dose, either as monotherapy or combined, or there is only a partial response, switch to another SSRI (FLX, SERT, CIT, ESCIT [adolescents only]), or add CBT if not initiated already. **5th line**: usually not required for mild depression.	**1st line**: active monitoring and supportive care for up to 4 weeks •Typically, adjunctive medications (melatonin, antihistamines) or psychosocial interventions are instituted to manage symptoms associated with depression (e.g., insomnia and agitation) for all levels. **2nd line**: SSRI (FLX, ESCIT, SERT, CIT) + continued supportive care and adjunct psychotherapy, such as CBT IPT, if available and appropriate. **3rd line**: switch to different SSRI (FLX, ESCIT, SERT, CIT) + supportive care **4th line**: Switch to non-SSRI (VEN, DUL, MIRT, BUP) + supportive care **4th line**: augment 2nd SSRI with psychotherapy or another medication + supportive care (BUP, QUE, ARIP, ZIP, RIS, OLAN, LAM, LITH) [consult with specialist on dose] **5th line**: if inadequate response in 1st to 4th line options, consider novel alternative approaches + supportive care. This should be commenced by specialists (TCA, MAOI, ECT)	**1st line**: active monitoring and supportive care for up to 4 weeks •Typically, adjunctive medications (melatonin, antihistamines) or psychosocial interventions are instituted to manage symptoms associated with depression (e.g., insomnia and agitation) for all levels. **2nd line**: SSRI (FLX, ESCIT, SERT, CIT) + continued supportive care and adjunct psychotherapy, such as CBT IPT, if available and appropriate. **3rd line**: switch to different SSRI (FLX, ESCIT, SERT, CIT) + supportive care **4th line**: Switch to non-SSRI (VEN, DUL, MIRT, BUP) + supportive care **4th line**: augment 2nd SSRI with psychotherapy or another medication + supportive care (BUP, QUE, ARIP, ZIP, RIS, OLAN, LAM, LITH) [consult with specialist on dose] **5th line**: if inadequate response in 1st to 4th line options, consider novel alternative approaches + supportive care. This should be commenced by specialists (TCA, MAOI, ECT)	If antidepressant is not adequately controlling psychotic symptoms, add an atypical antipsychotic (SGA).	Psychotherapy for an anxiety disorder may be started concomitantly with antidepressant treatment. Not recommended to start two medications together. Treat disorder causing the most impairment of function first. A stimulant may be started sequentially with an antidepressant.

Guideline	Sub-syndromal	Mild	Moderate	Severe	Psychotic	Comorbid, complicated
British Association of Psychopharmacology (BAP) (2015)[b] (all ages) (child or adolescent in red ink)		**1st line**: structured supportive treatment **2nd line** CBT or IPT if no response • combining drugs with non-drug treatments not routinely recommended as this stage. **3rd line**: consider drugs if partial or no response to other treatments •Drugs: generally use SSRIs •only FLX shown effective for both children and adolescents • TCAs may be effective for older adolescents •In children < 13 years TCA effectiveness is not proven	**1st line**: structured supportive treatment **2nd line**: CBT or IPT if no response •combining drugs with non-drug treatments not recommended as first line. **3rd line**: consider drugs if partial or no response to other treatments •Drugs: choose drug to suit individual patient. Most evidence for SSRIs, which together with newer antidepressants are first-line choices •Reserve TCAs and MAOIs for 2nd line •only FLX shown effective for both children and adolescents •TCAs may be effective for older adolescents •In children < 13 years TCA effectiveness is not proven **4th line: (There is limited evidence for next step treatments in children and adolescents – refer adult guidelines).** If inadequate response: •increase dose (no evidence that effective) or •switch to alternative antidepressant of same or other class or •augment (best evidence for QUE, ARIP, RIS or LITH)	**1st line**: structured supportive treatment **2nd line:** CBT or IPT if no response •combining drugs with non-drug treatments not recommended as first line. **3rd line:** consider drugs if partial or no response to other treatments •Drugs: choose drug to suit individual patient. Most evidence for SSRIs, which together with newer antidepressants are first-line choices •Reserve TCAs and MAOIs for 2nd line •In more severely ill consider (CLOM, VEN, ESCIT, SERT, AMIT, MIRT) in preference to other ADs •only FLX shown effective for both children and adolescents • TCAs may be effective for older adolescents •In children < 13 years TCA effectiveness is not proven •Adult studies for severe depression consider clomipramine, VEN, ESCIT, SERT, amitriptyline, MIRT **4th line: (There is limited evidence for next step treatments – refer adult guidelines**). If inadequate response: •increase dose (no evidence that effective) or •switch to alternative antidepressant of same or other class •if adolescent, switch should have CBT/IPT added as well. •augment (best evidence for QUE, ARIP, RIS or LITH)	• Use of antidepressant and antipsychotic combination is preferable to antidepressant or antipsychotic monotherapy (adult) •ECT is superior to antidepressant for psychotic depression (adult)	**Anxiety**: •most evidence for SSRIs **OCD:** •There is no evidence that one antidepressant is any better than others for comorbid conditions, except for one study that showed SERT more effective than desipramine for comorbid OCD

Guideline	Sub-syndromal	Mild	Moderate	Severe	Psychotic	Comorbid, complicated
Texas Medication Algorithm Project (TMAP) (2007)[c] (child and adolescent)		**1st line**: Watchful waiting for few weeks, including psychoeducation, lifestyle management. **2nd line**: specific therapies (e.g. CBT, IPT) are as effective as medication. If medication commenced use SSRI monotherapy – first preference FLX, SERT, CIT. **3rd line**: switch to alternate SSRI monotherapy	**1st line**: Watchful waiting for few weeks, including psychoeducation, lifestyle management. **2nd line**: specific therapies (e.g. CBT, IPT) are as effective as medication. If medication commenced use SSRI monotherapy – first preference FLX, SERT, CIT. **3rd line**: if inadequate response, switch to alternate SSRI monotherapy or augment with MIRT, BUP, LITH (augmentation usually for partial response or no remission). **4th line:** if inadequate response after 2 SSRI trials, reassess child's situation and consider switch to non-SSRI.	**1st line**: Watchful waiting for few weeks, including psychoeducation, lifestyle management. **2nd line**: specific therapies (e.g. CBT, IPT) are as effective as medication. If medication commenced use SSRI monotherapy – first preference FLX, SERT, CIT. **3rd line**: if inadequate response, switch to alternate SSRI monotherapy or augment with MIRT, BUP, LITH (augmentation usually for partial response or no remission). **4th line:** if inadequate response after 2 SSRI trials, reassess child's situation and consider switch to non-SSRI.	**Note: if it can be done safely first engage in watchful waiting, especially for pre-adolescents** **1st line:** • The treatment of MDD with psychotic features same as for nonpsychotic MDD but add clinician's choice of antipsychotic medication. • Newer atypical antipsychotics (SGAs) preferred. • May first use antipsychotic monotherapy and add antidepressant if necessary.	**Anxiety:** • no algorithm- consider CBT first **PTSD:** • consider trauma focussed CBT first • Adult studies support SSRI. **ADHD:** • Treat MDD first with SSRI only if MDD more severe than ADHD. • consider adding stimulant later if depression improves & ADHD symptoms remain. • Treat ADHD first where possible & add SSRI if ADHD successful treatment. • if not successful ADHD treatment, discontinue stimulant and treat with MDD algorithm. **DBD**: • If SSRI not successful, consider bipolar possibility. • If bipolar diagnosed, use bipolar algorithm. **Aggression/irritability:** • Follow guidelines for mood disorders with co-occurring aggression. • Guide recommends atypical antipsychotics (SGAs).

Guideline	Sub-syndromal	Mild	Moderate	Severe	Psychotic	Comorbid, complicated
British Columbia GPAC (2010)		1st line: active monitoring	**1st line**: active monitoring **2nd line**: CBT/IPT **3rd line**: medication (FLX) **4th line**: SERT or FLUV	**1st line**: active monitoring **2nd line**: CBT/IPT **3rd line**: medication (FLX) **4th line**: SERT or FLUV		If FLX not effective, consider SERT if there is bipolar vulnerability, or SERT or FLUV if there is comorbid anxiety

Abbreviations organisations/institutions: AACAP, American Academy of Child and Adolescent Psychiatry; BAP, British Association of Psychopharmacology; GPAC, Guidelines and Protocols Advisory Committee; eTG Complete, Electronic Therapeutic Guidelines Complete; GLAD-PC, Guidelines for Adolescent Depression in Primary Care**;** NICE, National Institute for Health and Care Excellence; RANZCP, Royal Australian and New Zealand College of Psychiatrists; TMAP, Texas Medication Algorithm Project.
Abbreviations disorders: ADHD, attention deficit hyperactivity disorder; DBD, disruptive behaviour disorders; MDD, major depressive disorder; OCD, obsessive compulsive disorder; PTSD, post-traumatic stress disorder.
Abbreviations treatments: AD, antidepressant; AMIT, amitriptyline; ARIP, aripiprazole; BUP, bupropion; CBT, cognitive behaviour therapy; CIT, citalopram; CLOM, clomipramine; ECT, electroconvulsive therapy; ESCIT, escitalopram; FLX, fluoxetine; FLUV, fluvoxamine; IPT, interpersonal therapy; LAM, lamotrigine; LITH, lithium; MAOI, monoamine oxidase inhibitor; MIRT, mirtazapine; OLAN, olanzapine; PAR, paroxetine; QUE, quetiapine; RIS, risperidone; SERT, sertraline; SGA, second-generation antipsychotic; SNRI, selective serotonin and noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; VEN, venlafaxine; ZIP, ziprasidone.
Notes:
a. *beyondblue* guidelines are currently out of date (published in 2011) but were applicable from 2011 to 2016.
b. The British Association for Psychopharmacology (BAP) guidelines cover all age groups, with most evidence presented for adults. Except where specific reference is made to children or adolescents, all recommendations are derived from adult studies. Child-related recommendations are marked in red ink.
c. The Texas algorithm is currently being updated. This algorithm provides information on medication decisions only but does provide general advice on initial non-medication stages.

11.3 Appendix 3. Depression disorder guideline summaries: continuation, maintenance and treatment resistant depression

Guideline	Continuation	Maintenance	Recurrent	Treatment Resistant Depression
beyondblue 2011 [a] (13-18 years)	Continue 6 months post-remission.	• No studies provide evidence for maintenance period in children and adolescents. • While maintenance treatment in adults may involve continuing pharmacological treatment, this is usually not appropriate in young people, as major depressive disorder may not continue to be a problem in adulthood (p.67). • Follow the management plan, even when mood starts to improve — for example, take medication for the period advised by the doctor and keep attending psychological therapy sessions.	Intensive psychological intervention plus FLX if necessary to be administered by psychiatrists or specialists in mental health (p.49).	Non-response after 6–10 sessions of individual or group CBT/IPT and/or 8 weeks of FLX (up to a maximum dose of 40mg/day), indicates possible TRD/ chronic depression. **1st line**: • Review the following factors: i. Accuracy of diagnosis. ii. Quality of therapeutic relationship/ patient's motivation to change. iii. Adherence to treatment. iv. Unrecognised comorbid disorders or life circumstances. • Obtain specialist advice before changing therapy. **2nd line**: • Establish relationships with local specialists with expertise in child and adolescent mental health. • Under specialist guidance consider 2nd line antidepressant if no response to FLX: i. Consider a second SSRI (e.g. SERT or CIT) or ii. change to a newer antidepressant (e.g. MIRT, or iii. augmentation with a mood stabiliser. **3rd line**: ECT may be used in severe cases where other approaches have not been successful.
RANZCP (Royal Australian and New Zealand College of Psychiatrists) Mood Disorders Guidelines (2015)			Clinicians with child/adolescent expertise can consider non-FLX medications (SERT, CIT, and if necessary antipsychotic augmentation) for recurrent, unresponsive or psychotic depression.	Clinicians with child/ adolescent expertise can consider non-FLX medications (SERT, CIT, and if necessary antipsychotic augmentation) for recurrent, unresponsive or psychotic depression.

Guideline	Continuation	Maintenance	Recurrent	Treatment Resistant Depression
National Institute for Health and Care Excellence (NICE) (2005) (children and young people) AND NCCMH (2005) full guideline for NICE cg28	• continue 6 months post-remission (defined as no symptoms and full function for at least 8 weeks) • Child or young person in remission should be regularly reviewed for 12 months by CAMHS professional. • No compelling evidence on treatment strategies for either continuation (how long to continue treatment after a positive response) or maintenance (how to prevent recurrence). (p.123, full guideline)	No compelling evidence on treatment strategies for either continuation (how long to continue treatment after a positive response) or maintenance (how to prevent recurrence). (p.123, full guideline).	If high likelihood of recurrence or high risk (at least 2 prior episodes), provide follow-up psychological therapy. When in remission they should be reviewed regularly for 2 years by CAMHS professional.	• If moderate or severe depression has necessitated treatment with FLX and been ineffective, after review consider SERT or CIT as 2nd line medications. • Do NOT use PAR, VEN or TCAs. • ECT should only be considered if severe and not responded to other treatments.
GLAD-PC (Guidelines for Adolescent Depression in Primary Care) – 2007	Medication continuation of possibly 1 year may be necessary for relapse prevention.	If the depressive episode is a recurrence, clinicians are encouraged to monitor patients for up to 2 years (derived from adult literature).	If the depressive episode is a recurrence, clinicians are encouraged to monitor patients for up to 2 years (derived from adult literature).	• Review the following factors: i. Accuracy of diagnosis. ii. Adherence to treatment. iii. Unrecognised comorbid disorders or life circumstances. • If failed to improve on CBT/IPT, add SSRI. • If patient has been treated with a SSRI (maximum tolerated dosage) and has shown only partial improvement: i. add evidence-based psychotherapy if not previously initiated. ii. increase dose above FDA approved range. iii. switch to other SSRI for which recent positive trials exist (CIT, SERT). iv. switch to other SSRIs (e.g., FLUV, PAR [adolescents only], ESCIT). v. switch to another medication (as suggested by TORDIA – e.g., VEN).

Guideline	Continuation	Maintenance	Recurrent	Treatment Resistant Depression
AACAP (American Academy of Child and Adolescent Psychiatry) - 2007[b]	To consolidate the response to the acute treatment and avoid relapses, treatment should always be continued for 6 to 12 Months. Usually seen monthly.	• Once the child has been asymptomatic for approximately 6 to 12 months, the clinician must decide whether maintenance therapy is indicated and the type and duration of therapy. • This phase may last 1 year or longer and is typically conducted with visits at a frequency of monthly to quarterly. • Rule of thumb: longer recovery time and higher number of recurrences, the longer the maintenance period • Those with double depression (depression with comorbid DD) who have been depressed for 'as long as they can remember' may need treatment indefinitely (p.1518).	• Those patients with at least two episodes of depression or one severe episode or chronic episodes of depression should have maintenance treatment for longer than 1 year.	If not responding to psychological or medication treatment, reassess. Consider: i. Accuracy of diagnosis. ii. Unrecognised comorbid disorders. iii. Inadequate dose, length of treatments. iv. Adherence. v. Chronic or severe life events. vi. Quality of therapeutic relationship or skill of therapists. vii. Cultural or personal identity issues. After assessment, consider: • extending the initial medication trial and/or adjust the dose. • adding CBT or IPT. • switching to another agent in the same or other class (usually when no response or medication not tolerated). • augmentation (usually when partial response) with triiodothyronine (T3), LITH. • intravenous clomipramine. • ECT.
BMJ Best Practice – 2018 (child and adolescent)	• 6-12 months • Recommendation is 6 months for first episode, 12 months for recurrent episode.	Following the period of continuation therapy, 1 to 2 years of maintenance treatment may be needed for children who are at risk of having recurrent depression (multiple episodes, chronic depression, comorbid disorders).	• Once remission is achieved, whether it is after the first medication or psychotherapy treatment or after multiple treatment trials, treatment is continued for 6 to 12 months to avoid relapse, at the same dose used for acute treatment. • Recommendation is 6 months for first episode, 12 months for recurrent episode. (p.57) • Following the period of continuation therapy, 1 to 2 years of maintenance treatment may be needed for children who are at risk of having recurrent depression (multiple episodes, chronic depression, comorbid disorders).	• If inadequate response reassess diagnosis - consider: i. Accuracy of diagnosis. ii. Comorbid disorders. iii. Inadequate psychosocial intervention. iv. Unresolved stress or new trauma. After re-assessment consider: • switch to another SSRI (FLX, ESCIT, SERT, CIT, PAR (adolescent) or a different class of medications (VEN, DUL, MIRT, BUP, NEFAZ[c] [with extreme caution due to hepatotoxicity]). • augment (e.g., LITH, triiodothyronine (T3), atypical antipsychotics (SGAs), BUP, LAM, CBT/IPT. • consider novel alternative approaches if response remains poor (e.g. TCAs, MAOIs), light therapy, ECT, transdermal selegiline patch.

Guideline	Continuation	Maintenance	Recurrent	Treatment Resistant Depression
TMAP (Texas Medication Algorithm Project) - 2007 [c] (child and adolescent)	6-12 months	Patients with 2nd or 3rd depressive episode should be considered for maintenance treatment: • Duration depends on severity index episode, history, residual symptoms, patient and family preference. • From 3 years to lifetime. • Continue with same regimen associated with previous remission.	If previous depressive episodes have occurred, then the patient should be evaluated for maintenance treatment: • Duration depends on severity index episode, history, residual symptoms, patient and family preference. • From 3 years to lifetime. • Continue with same regimen associated with previous remission.	• Augment with MIRT, BUP. LITH for partial response or • Switch to non-SSRI • If the depression is severe and nonresponsive, then ECT should be considered at some point.
BAP (British Association for Psychopharmacology) – 2016[d]	Recommendation based on adult studies: 6-9 months after full remission if low risk of relapse (adult guideline) Increased risk of relapse – • 12 months treatment recommended More than 5 lifetime episodes and/or at least 2 in last few years – • 2 years treatment recommended	Recommendation based on adult studies: 6-9 months after full remission if low risk of relapse (adult guideline) Increased risk of relapse – 12 months More than 5 lifetime episodes or at least 2 in last few years – 2 years	Antidepressants are not first line treatment for major depression in children and adolescents but should be considered when there is a history of moderate to severe recurrent depression.	Antidepressants are not first line treatment for major depression in children and adolescents but should be considered when there has been a partial or no response to other treatment, where the depression is severe or there is a history of moderate to severe recurrent depression. • Lack of evidence for increase in dose • Only switching strategies that have evidence is from an SSRI to VEN or from SSRI/SNRI to VOR • Augmentation – best evidence is for QUE, ARIP
British Columbia GPAC (2010)	6-12 months			• FLX • SERT or FLUV if comorbid with anxiety

Abbreviations: CAMHS, Child and Adolescent Mental Health Service; FDA; Food and Drug Administration; TORDIA, Treatment of Resistant Depression in Adolescents.
Abbreviations organisations/institutions: AACAP, American Academy of Child and Adolescent Psychiatry; BAP, British Association of Psychopharmacology; GPAC, Guidelines and Protocols Advisory Committee; eTG Complete, Electronic Therapeutic Guidelines Complete; GLAD-PC, Guidelines for Adolescent Depression in Primary Care**;** NCCMH, National Collaborating Centre for Mental Health; NICE, National Institute for Health and Care Excellence; RANZCP, Royal Australian and New Zealand College of Psychiatrists; TMAP, Texas Medication Algorithm Project.
Abbreviations disorders: DD, dysthymic disorder; TRD, Treatment Resistant Depression.
Abbreviations treatments: ARIP, aripiprazole; BUP, bupropion; CBT, cognitive behaviour therapy; CIT, citalopram; DUL, duloxetine; ECT, electroconvulsive therapy; ESCIT, escitalopram; FLX, fluoxetine; FLUV, fluvoxamine; IPT, interpersonal therapy; LAM, lamotrigine; LITH, lithium; MAOI, monoamine oxidase inhibitors; MIRT, mirtazapine; NEFAZ, nefazodone; PAR, paroxetine; QUE, quetiapine; SERT, sertraline; SGA, second-generation antipsychotic; SNRI, selective serotonin and noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; VEN, venlafaxine; VOR, vortioxetine.
Notes:
a. *beyondblue* guidelines are currently out of date (published in 2011).
b. The Texas algorithm is currently being updated. This algorithm provides information on medication decisions only but does provide general advice on initial non-medication stages.
c. Nefazodone was withdrawn from most international markets in 2004. It is currently available only in the US.
d. The British Association for Psychopharmacology (BAP) guidelines cover all age groups, with most evidence presented for adults. Except where specific reference is made to children or adolescents, all BAP recommendations are derived from adult studies.

11.4 Appendix 4. Bipolar disorder guideline summaries

Guideline	Acute manic/mixed episode	Acute depressed episode	Maintenance
beyondblue 2011 [a]	**1st line:** LITH, VAL, SGAs.	**1st line**: LITH, LAM, QUE monotherapy.	**1st line**: LITH, LAM, OLAN.
eTG Complete – child recommendations (accessed April 2019)	**1st line:** SGAs **2nd line:** i. LITH + SGA ii. antiepileptic (CAR, VAL) + SGA		
eTG Complete – adult guidelines (accessed April 2019)	**Mixed or rapid cycling episodes** may respond better to VAL or CAR than LITH, but evidence is very limited. **For manic episodes**: **1st line**: i. OLAN, RIS. ii. combination of LITH or VAL with any AP if severe manic episode. **2nd line**: i. HAL, ARIP, ASEN, PAL, QUE, ZIP. ii. LITH. iii. sodium VAL. iv. CAR. **3rd line:** i. increase to maximum tolerable dose ii. switch to different drug (e.g., SGA to LITH). iii. combine drugs (e.g., SGA + LITH). **4th line**: ECT.	**1st line**: i. AD + drug used for maintenance. ii. QUE. **2nd line**: i. Change to different AD or different maintenance drug. ii. Augment with psychological treatment (e.g., psychoeducation, CBT). **3rd line**: ECT.	If 2 or more prior manic or depressive episodes, or if 1st manic episode severe, continue acute treatment for 12 months. **1st line:** i. Mania prominent: LITH (most evidence), ARIP, ASEN, PAL, ZIP, RIS (depot only effective). ii. Both mania and depression: OLAN, QUE. iii. Depression prominent: LAM. iv. For some patients, augmentation with psychotherapies is effective and preferred (e.g., CBT, IPSRT, psychoeducation). **2nd line:** i. CAR, VAL (neither currently approved by TGA for adults or children) **3rd line:** i. Ensure adequate dose. ii. Check for treatment concordance. iii. Check for substance abuse (e.g., cannabis). iv. Implement adequate treatment for comorbid anxiety disorder. v. Combine maintenance treatments (e.g., LITH with either VAL, LAM or OLAN).
RANZCP (Royal Australian and New Zealand College of Psychiatrists) Mood Disorder Guidelines (2015) – (child and adolescent) (pp.1169-1171)	**Step 0**: • Adolescents with BP1 should be offered psychosocial intervention with family involvement, and pharmacotherapy carefully considered. **Step 1**: • OLAN, QUE, ZIP, RIS or ARIP as monotherapy • VAL + QUE	**Step 0**: • Adolescents with BP1 should be offered psychosocial intervention with family involvement, and pharmacotherapy carefully considered. **Step 1:** • Consider evidence-based psychotherapies recommended for depression (e.g., CBT, psychoeducation, FFT, IPRST). **Step 2:** • LAM.	**Note:** Currently, there are few well-controlled studies examining the efficacy of pharmacological treatments for prophylaxis in adolescents with bipolar disorder. **1st line:** SGAs. **2nd line**: LITH or VAL. **2nd line**: LITH + (ARIP or RIS). **3rd line**: ECT.

Guideline	Acute manic/mixed episode	Acute depressed episode	Maintenance
RANZCP (Royal Australian and New Zealand College of Psychiatrists) - Mood Disorder Guidelines (2015) – (adult)	**Note:** Psychological interventions are potentially useful, but only as an adjunct to pharmacotherapy. **Step 0**: • Taper and cease mood elevating agents (e.g., ADs and stimulants). • Reduce environmental stimulation, restore sleep. • Maintain structured routine. **Step 1**: • Monotherapy or combined: ARIP, ASEN, HAL, LITH, OLAN, QUE, RIS, VAL. • ZIP (mono only). • Short-term use of adjunct BZ or AP may be required for acute behavioural disturbance (2 AP not recommended). • AP may be used as adjunct for acute psychosis (if not used already as antimanic). • SGA preferred to AP. **Step 2:** • LITH + VAL. • LITH or VAL + SGA (not CLOZ). • PAL. • CAR. • ECT. **Step 3:** • LITH + CAR. • VAL + CAR. • CLOZ. • Consider augmentation with TAM/ medroxyprogesterone.	**Note:** Psychological interventions are potentially useful, but only as an adjunct to pharmacotherapy. **Step 1**: • Monotherapy of QUE, LUR, OLAN, LITH, VAL or LAM. **Step 2**: combination options: • QUE +/- (LITH or VAL or LAM) +/- adjunct AD. • LUR +/- (LITH or VAL) +/- adjunct AD. • OLAN +/- FLX. • LITH +/- (LAM or VAL) +/-adjunct AD. • VAL +/- LITH +/- adjunct AD. • LAM +/- LITH. **Step 3**: ECT. **Step 4**: • Transcranial Magnetic Stimulation. • Adjunctive treatments (e.g., MOD, PRAM, thyroxine).	**Note:** Long-term treatment needs both psychotherapy and drugs. **Step 1**: **continuation 6 months:** • Depressive dominant – LAM. • Equal polarity – QUE. • Manic dominant – LITH or OLAN. • Combination - LITH or VAL, with adjunctive LAM, QUE or ARIP. **Step 2**: • Step 1 +OLAN. **Step 3:** • LITH + VAL. • Well tolerated options from Step 1 and Step 2 **Step 4:** • CLOZ + antiC or LITH (not with an AP). **Step 4**: **Maintenance -after 6 months continuation:** • Consider successful acute treatment regime, and taper if possible. **1st line**: LITH mono, LITH + VAL, SGAs. **2nd line**: VAL mono. **3rd line**: LAM mono. **4th line**: CAR mono or with LITH. • NOT GABA or TOP.

Guideline	Acute manic/mixed episode	Acute depressed episode	Maintenance
RANZCP (Royal Australian and New Zealand College of Psychiatrists) (2004) – (adult)	**Note:** psychological treatments should be considered in conjunction with medications (e.g., CBT, IPRST, family therapy) **1st line**: • LITH, VAL, CAR • OLAN (do not use in combination with another AP). **2nd line:** Augment with BZ +/- AP to sedate until MS takes effect (Approx 1week). • BZ -DIAZ, CLONAZ, LOR. • APs- RIS, CHLOR, THIOR, HAL, OLAN. • If oral not possible use IM – MID, DIAZ, HAL, DROP, ZUC. **3rd line**: - if 1st and 2nd line treatments ineffective: • optimise dose of current MS. • switch MS. • augment MS with AP (OLAN, RIS, HAL). • combine MS. **4th line**: ECT.	**Note:** psychological treatments should be considered in conjunction with medications (e.g., CBT, IPRST, family therapy) **Depression de novo** **1st line:** LITH. **2nd line**: LAM. **3rd line**: OLAN + FLX. **4th line**: VAL, CAR. **5th line**: MS + AD. **Depression – already on long-term medication for bipolar** **1st line:** optimise dose MS. **2nd line**: • add AD or 2nd MS. • 1st line choice of AD is SSRI, followed by venlafaxine, MAOI or TCA in order. • Do not use antidepressant as monotherapy. • 1st choice of MS – LITH, LAM, OLAN +FLX. **3rd line**: • optimise dose of medications. • switch MS or AD. • add another MS – switch pairs and add AD. **4th line**: ECT (recommended after failed AD trial).	**Note:** psychological treatments should be considered in conjunction with medications (e.g., CBT, IPRST, family therapy) **Manic episodes** **1st line:** LITH. **2nd line**: CAR, VAL. • If fail to respond – check for non-compliance and treat any comorbid substance misuse **3rd line**: add another MS (preferably LITH, VAL). **Depressive episodes** **1st line:** LAM. • If fail to respond – check for non-compliance and treat any comorbid substance misuse. **Rapid-cycling** **1st line**: VAL, LAM. **2nd line**: CAR, LITH. • If fail to respond – check for non-compliance and treat any comorbid substance misuse. **3rd line**: add another MS.
Australian Family Practice article (2013) – (adult)	**Note: Psychological treatments** developed for bipolar disorder (e.g., CBT, IPSRT, psychoeducation, FFT) should NOT be considered as an alternative to medications – only use as adjunct. **1st line**: APs- preferred options RIS, OLAN, HAL **2nd line**: LITH, VAL, CAR	**Note: Psychological treatments** developed for bipolar disorder (e.g., CBT, IPSRT, psychoeducation, FFT) should NOT be considered as an alternative to medications – only use as adjunct. **1st line**: QUE monotherapy **2nd line**: OLAN + FLX **3rd line**: ADs in conjunction with MS (e.g., LITH, VAL, AP)	**Note: Psychological treatments** developed for bipolar disorder (e.g., CBT, IPSRT, psychoeducation, FFT) should NOT be considered as an alternative to medications – only use as adjunct. **Prevention manic episodes** **1st line**: LITH **2nd line**: any SGAs Prevention depressive episodes **1st line**: LAM **2nd line**: QUE, OLAN

Guideline	Acute manic/mixed episode	Acute depressed episode	Maintenance
CANMAT-ISBD: guidelines for the management of patients with bipolar disorder (2013)[b] (Recommendations for specific child & adolescent population)	**1st line**: family-focussed CBT, DBT, IPSRT **2nd line**: QUE, possibly RIS, ARIP, LAM **3rd line**: OLAN, ZIP	**1st line**: family-focussed CBT, DBT, IPSRT **2nd line**: possibly LAM	
CANMAT-ISBD: guidelines for the management of patients with bipolar disorder (2013)[b] (adult)	**1st line**: • LITH, VAL, OLAN, RIS, ARIP, ASEN, QUE, ZIP, PAL. • (LITH or VAL) + (RIS, QUE, OLAN, ARIP, ASEN) **2nd line**: • CAR, HAL, ECT • LITH + VAL **3rd line**: • CHLOR, CLOZ, OXCAR, CARIP, TAM. • LITH + HAL, VAL + HAL, LITH + CAR **Not recommended**: • GABA, TOP, LAM, verapamil, TIAG. • RIS + CAR, OLAN + CAR.	**1st line**: • LITH, LAM, QUE. • (LITH or VAL) + SSRI, LITH + VAL, (LITH or VAL) + BUP, OLAN + SSRI. **2nd line**: • VAL, LUR. • (QUE + SSRI) +/-MOD, (LITH or VAL) + LAM, (LITH or VAL) + LUR. **3rd line**: • CAR, OLAN, ECT, • LITH + CAR, LITH + PRAM, (LITH or VAL) + VEN, LITH + MAOI, (LITH or VAL or SGA) + TCA, (LITH or VAL or CAR) + SSRI, QUE + LAM. **Not recommended**: • GABA, ARIP, ZIP • adjunctive ZIP or levetiracetam. **Note**: SSRI does not include paroxetine as option.	**1st line**: • LITH, LAM, VAL, OLAN, QUE, RIS, ARIP. • (LITH or VAL) + (QUE, RIS, ARIP, ZIP). **2nd line**: • CAR, PAL. • LITH + VAL, LITH + CAR, (LITH or VAL) + OLAN, LITH + RIS, LITH + LAM, OLAN + FLX. **3rd line**: • ASEN. • adjunct (phenytoin, CLOZ, ECT, TOP, OXCAR, GABA, ASEN) **Not recommended**: • GABA, TOP, antidepressants. • adjunct FLUP.

Guideline	Acute manic/mixed episode	Acute depressed episode	Maintenance
CANMAT-ISBD guidelines for the management of patients with bipolar disorder (2018) (Recommendations for specific child & adolescent population) (pp.133-135)	**1st line**: • LITH, RIS, ARIP, ASEN, QUE • RIS preferred to LITH with non-obese youth and comorbid ADHD **2nd line**: • OLAN, ZIP • QUE adjunct **3rd line**: • VAL **Not recommended**: • OXCAR	**1st line**: LUR **2nd line**: LITH, LAM **3rd line**: OLAN + FLX, QUE (mono) **4th line**: combine MS with AD **Not recommended**: • OXCAR	**1st line**: • ARIP, LITH, VAL. • LITH + VAL better than each mono. • RIS + (LITH or VAL). • LITH + (VAL or CAR). • adjunctive LAM for 13 years and older. **2nd line**: no treatments with sufficient evidence to recommend. **3rd line**: • ASEN (mania dominant). • QUE, RIS, ZIP. **Comorbid conditions**: • **ADHD** – use adjunctive amphetamines or methylphenidate. (ATOM NOT currently recommended). • **SUD** – treat concurrently, a. LITH may be useful b. also consider FFT • cannabis use – N-acetylcysteine • **anxiety**: use QUE as monotherapy
CANMAT-ISBD guidelines for the management of patients with bipolar disorder (2018) – (adult)	**1st line:** • LITH, QUE, VAL, ASEN, ARIP, PAL, RIS, CARIP. • (LITH or VAL) + (QUE, ARIP, RIS, ASEN). **2nd line:** • OLAN, CAR, ZIP, HAL • (LITH or VAL) + OLAN, LITH + VAL • ECT **3rd line:** • CHLOR, CLONAZ, CLOZ, TAM. • (LITH or VAL) + (CAR, OXCAR, HAL, TAM). **Not recommended:** • allopurinol, GABA, LAM, TOP, eslicarbazepine, licarbazepine, valnoctamide, zonisamide.	**1st line:** • QUE, LITH, LAM, LUR. • (LITH or VAL) + (LUR. ASEN). • adjunct LAM. **2nd line:** • VAL, CARIP. • OLAN + FLX • adjunct SSRIs, BUP. • ECT **3rd line:** • CAR, OLAN. • adjunct ARIP, ASEN, ARMOD, MOD, ketamine, levothyroxine, *N*-acetylcysteine, PRAM, SNRI, MAOI. **Not recommended:** • ARIP, antidepressant monotherapy, LAM + folic acid, mifepristone.	**1st line:** • QUE, LITH, VAL, LAM, ASEN, ARIP. • (LITH or VAL) + (QUE, ARIP). • adjunct LAM. **2nd line:** • OLAN, RIS, PAL, CAR. • (LITH or VAL) + (LUR, ZIP). • adjunct RIS. **3rd line:** • ARIP + LAM. • OLAN + FLX. • adjunct CLOZ, GABA. **Not recommended:** • perphenazine, TCAs.

Guideline	Acute manic/mixed episode	Acute depressed episode	Maintenance
Practice Parameter for the Assessment and Treatment of Children and adolescents with Bipolar Disorder (American Academy of Child and Adolescent Psychiatry [AACAP]) 2007	**Note**: Adjunctive psychosocial therapies are almost always indicated. **1st line**: • LITH for age 12 and over (only drug approved by FDA for youths). • monotherapy ARIP, VAL, OLAN, RIS, QUE, ZIP. • CHLOR –approved for adult, not generally used in children and adolescents. • trial 6-8 weeks before adding or substituting drugs. **2nd line**: • CAR. • RIS + (LITH or VAL). • QUE + VAL. • TOP as adjunct (TOP not recommended in adults). **3rd line**: CLOZ. **4th line**: ECT. **Not recommended**: • GABA.	**Note:** Adjunctive psychosocial therapies are almost always indicated. **1st line**: • OLAN + FLX. • SSRI + at least one MS. **2nd line**: LAM. **3rd line**: ECT.	**Note**: Adjunctive psychosocial therapies are almost always indicated. **1st line**: • LITH for age 12 and over. • LAM, OLAN. • LITH + VAL better than either mono. • maintain regimen successful in stabilising acute mania 12-24 months, possibly lifelong.

Guideline	Acute manic/mixed episode	Acute depressed episode	Maintenance
Child and Adolescent Bipolar Foundation (CABF) guidelines (2005)	**NON-PSYCHOTIC** **Stage 1**: • monotherapy with LITH, VAL, CAR, OLAN, QUE or RIS **Stage 1A**: partial response to monotherapy • LITH + VAL • (LITH, VAL, CAR) + (OLAN, QUE, RIS) • (do not combine 2 SGAs) **Stage 2**: alternate monotherapy -switch to agent not used in Stage 1 or 1A **Stage 2A**: partial response – augment Stage 2 drug with alternate monotherapy (do not combine 2 SGAs) **Stage 3A**: No or partial response switch to alternate monotherapy not used Stage 1 or 2. **Stage 3B**: - No or partial response Stage 3A, try new combination MS and SGA (do not combine 2 SGAs). **Stage 4**: No or partial response to Stage 3A & 3B, combine 2 MS +SGA. • (LITH + VAL) + (OLAN, QUE or RIS). • (LITH + carbamazapine) + (OLAN, QUE or RIS). **Stage 5**: alternate monotherapy • OXCAR, ZIP, ARIP, (not GABA) **Stage 6 & 6A:** • ECT (adolescents), CLOZ. **WITH PSYCHOSIS** **Stage 1:** – (LITH, VAL, or CAR) + SGA. **Stage1A – partial response Stage 1** • LITH + (VAL or CAR) +SGA. **Stage 2: -** try combination (LITH, VAL, or CAR) + SGA not tried in Stage 1. **Stage 2A: partial response Stage 2** • LITH + (VAL or CAR) +SGA. **Stage 3**: try alternate combination not tried in Stage 1 or stage 2 (LITH, VAL, or CAR) + alternate SGA. **Stage 4: partial or no response** – • LITH + (VAL or CAR) + SGA. **Stage 5:** – • OXCAR, ZIP, ARIP, (OXCAR +SGA). **Stage 6 & 6A:** • ECT (adolescents), CLOZ.	Insufficient studies to develop algorithm. Based on adult studies only: **1st line**: LITH **2nd line**: • after stabilisation with an MS, consider adjunct SSRI or BUP. • continue adjunct AD at least 8 weeks after symptom remission **3rd line**: • LAM (despite black box warning for under 16-year-olds) • VAL **4th line**: ECT for severe resistant bipolar depression	Consider continuing agents that resulted in remission, or **1st line**: • LITH, VAL, CAR. • LITH + VAL. **2nd line**: current research in adults also supports: • LAM, OLAN. • continue treatment 12-24 months, or possible lifelong, after remission

Guideline	Acute manic/mixed episode	Acute depressed episode	Maintenance
	Comorbid Disorders: Always treat with psychosocial therapies if possible and stabilise bipolar symptoms before adding drugs. • **ADHD**: add stimulants with caution (methylphenidate, amphetamines) • **ODD and CD**: add with caution, if not already used, LITH, VAL, AP, or SGA. Consider parent behaviour management. • **Substance Use**: treat simultaneously without delay. Consider adjunct family therapy. • **Anxiety**: consider in order, a. CBT b. SSRI c. BZ for short-term agitation		

Guideline	Acute manic/mixed episode	Acute depressed episode	Maintenance
National Institute for Health and Care Excellence (NICE) (2014) [c] (child and adolescent)	**1st line**: • If bipolar is suspected in child under 14 years in primary care – refer to a specialist. • When offering treatment take into account cognitive ability, emotional maturity, developmental level, and severity. **2nd line:** • ARIP is recommended for moderate to severe manic episodes in BP1 for children 13 years and over for up to 12 weeks. **Do not offer:** • VAL to girls. • Do not routinely continue AP treatment more than 12 weeks.	**1st line:** • structured psychological intervention at least 3 months (e.g., CBT, IPT) • intervention must have published evidence-based manual describing how to deliver therapy **2nd line:** • if after 4-6 weeks, there is no or partial response, carry out multidisciplinary review, and consider alternative individual or family psychological intervention. • if there is risk of suicide or self-harm, develop a risk management plan. **3rd line**: **if after review, there are comorbid conditions, risk factors, parental mental ill-health** consider: • alternative psychological intervention for young person, parent or other family member. • an additional psychological therapy for comorbid conditions. **4th line**: **If moderate or severe, consider**: • adding drug to psychological intervention. • Do not routinely continue AP for more than 12 weeks. • At 12 weeks carry out multidisciplinary review.	**1st line:** • Consider structured individual or family psychological intervention for managing bipolar disorder in young people.

Guideline	Acute manic/mixed episode	Acute depressed episode	Maintenance
NICE (National Institute for Health and Care Excellence) (2014) [C] – (adult)	**1st line:** • ensure access to a calming environment. • if taking AD consider stopping and offer AP regardless. **If not taking prophylactic MS or AP** **2nd line:** offer HAL, OLAN, QUE, RIS. **3rd line**: if 1st AP not tolerated or ineffective, offer alternative AP from 2nd line list above. **4th line**: if 2nd AP not effective at maximum dose, consider adding LITH (1st choice), or VAL (2nd choice) • if taking AD + MS, consider stopping AD. • if taking MS consider adding HAL, OLAN, QUE or RIS. **If taking prophylactic MS** **2nd line:** • if on LITH or VAL, consider adding HAL, OLAN, QUE, RIS. • do not offer LAM for mania. **3rd line**: • ECT if severe and not responding to treatment. **Do not offer** GABA or TOP. **Review treatment** within 4 weeks. After review, offer treatment for further 3-6 months and review again.	**1st line:** • offer psychological intervention developed specifically for bipolar which has a published evidence-based manual describing how to implement therapy. • therapists should have training and experience working with bipolar. • offer high-intensity psychological intervention (CBT, IPT, couples therapy) in line with NICE clinical guideline on depression. **2nd line**: **If moderate or severe and not taking drug for bipolar:** • offer FLX + OLAN. • QUE, OLAN, LAM monotherapy. **If taking LITH or VAL and inadequate response:** • increase dose. • add FLX + OLAN or QUE. • add OLAN (without FLX) or LAM if patient prefers. **3rd line**: **If moderate or severe and not taking drug for bipolar:** • consider LAM monotherapy **If taking LITH or VAL and inadequate response:** • stop added 2nd line treatment and consider adding LAM. **Review treatment** within 4 weeks If person continues – offer for further 3-6 months and review.	First discuss course of disorder, risk of relapse, benefits and risks of treatments. **1st line**: • offer family intervention for people living with families. • offer structured psychological intervention (individual, group or family) designed for bipolar and has published evidence-based manual describing how to implement. **2nd line**: • offer LITH. **3rd line**: if LITH ineffective: • consider adding VAL. • consider OLAN or QUE. **Continue monitoring** symptoms for 2 years if medication is stopped.
BAP (British Association for Psychopharmacology) (2016) – (child and adolescent section, pp.12, 44)	**1st line**: ARIP (adolescents over 13 years) **2nd line**: OLAN, QUE, RIS in adolescents	Consider medicines and psychological treatments largely from extrapolation from data in adults. • Poor quality evidence for LITH, LAM	The need for long-term treatment should be considered in young people because of the potentially disruptive effect of relapse and mood instability on cognitive and emotional development.

Guideline	Acute manic/mixed episode	Acute depressed episode	Maintenance
British Association of Psychopharmacology (BAP) (2016) (adult)	**1st line**: • HAL, OLAN, RIS, QUE. **2nd line**: • ARIP, ASEN, CARIP, PAL, ZIP. **3rd line**: • (LITH or VAL) + SGA. **4th line**: • CLOZ if more refractory. • ECT if preferred or pregnant. **To promote sleep**: adjunctive BZs.	Consider psychoeducation, FFT, or CBT therapy as adjunct treatment when available – very little evidence as monotherapy. **1st line**: • QUE **2nd line**: • OLAN + FLX • LUR i. Other ADs can be used in combination with a drug for mania (e.g., dopamine antagonists, LITH, VAL) if patients have history of mania **3rd line**: • AD approved for unipolar depression +SGA • LAM **4th line**: • LITH, VAL, CAR. **5th line**: • ECT	**If mania predominant:** **1st line**: LITH, best evidence **2nd line**: If LITH not effective, consider • VAL, OLAN, QUE, RIS. **3rd line**: • (LITH or VAL) + SGA **4th line**: • ECT **If predominant depressive:** **1st line**: • LITH, LAM. **2nd line**: • LITH + (LAM, QUE, LUR). **3rd line**: ECT • Naturalistic data on hospital readmissions suggest choice of long-term treatment in order of best to least effective (p.38): LITH>VAL>OLAN>LAM>QUE o Reduced manic episodes – LITH, VAL, LAM, CAR, OLAN, QUE o Reduced depressive episodes – LITH, VAL, LAM, QUE, OLAN. o Reduced mixed episodes – LITH. • When a patient has accepted treatment for several years and remains well, they should be advised to continue indefinitely, because the risk of relapse remains high. (p.10) • **Comorbid disorders**: Consider treatment along the lines suggested by BAP guidelines for the treatment of anxiety disorders, attention deficit hyperactivity disorder and substance use disorders. Care in the use of Ads is required.
WFSBP (World Federation of Societies of Biological Psychiatry) Mixed states (2017) – child and adolescent	**1st line**: ARIP **2nd line**: CAR (p.23); RIS (p.36); TOP adjunct (p.42) No evidence for OLAN (p.32)		

Guideline	Acute manic/mixed episode	Acute depressed episode	Maintenance
WFSBP (World Federation of Societies of Biological Psychiatry) Mixed states (2017) – adult	Guideline for MIXED STATES ONLY: "States of substantial mood dysregulation and instability rather than just characterised by either the simultaneous or sequential presence of various combinations of depressive and manic/hypomanic symptoms" (p.13) **1st line**: OLAN, OLAN + VAL **2nd line**: • (LITH or VAL) + (ARIP, PAL, QUE). **3rd line**: • (LITH or VAL) + (ASEN, CAR, CARIP, GABA) • OXCAR +LITH • RIS, • FGAs, VAL, ZIP • ECT + TAU. **4th line**: TOP + TAU	Guideline for MIXED STATES ONLY: "States of substantial mood dysregulation and instability rather than just characterised by either the simultaneous or sequential presence of various combinations of depressive and manic/hypomanic symptoms" (p.13) **1st line**: • ZIP + TAU **2nd line**: • OLAN, CAR, LUR **3rd line**: • ECT + TAU	Guideline for MIXED STATES ONLY: "States of substantial mood dysregulation and instability rather than just characterised by either the simultaneous or sequential presence of various combinations of depressive and manic/hypomanic symptoms" (p.13) **Prevention mania** **1st line:** QUE + (LITH or VAL) **2nd line**: LITH, QUE **3rd line**: ZIP **Prevention depression** **1st line**: QUE + (LITH or VAL) **2nd line**: QUE **3rd line**: ARIP + LAM **Prevention any** **1st line**: QUE + (LITH or VAL) **2nd line**: LITH, OLAN, QUE + (LITH or VAL) **3rd line**: RIS **4th line**: ECT + TAU

Abbreviations organisations/institutions: AACAP, American Academy of Child and Adolescent Psychiatry; BAP, British Association of Psychopharmacology; CABF, Child and Adolescent Bipolar Foundation; CANMAT, Canadian Network for Mood and Anxiety Treatments; eTG Complete, Electronic Therapeutic Guidelines Complete; ISBD, International Society for Bipolar Disorders; NICE, National Institute for Health and Care Excellence; RANZCP, Royal Australian and New Zealand College of Psychiatrists; WFSBP, World Federation of Societies of Biological Psychiatry.

Abbreviations disorders: ADHD, attention deficit hyperactivity disorder; BP1, bipolar 1 disorder; SUD, substance use disorder; CD, conduct disorder; ODD, Oppositional Defiant Disorder.

Abbreviations treatments: AD, antidepressant; antiC, anticonvulsant; AP, antipsychotic; ARIP, aripiprazole; ARMOD, armodafinil; ASEN, asenapine; ATOM, atomoxetine; BZ, benzodiazepine; BUP, bupropion; CAR, carbamazepine; CARIP, cariprazine; CBT, Cognitive Behavioural Therapy; CHLOR, chlorpromazine; CLONAZ, clonazepam; CLOZ, clozapine; DBT, Dialectal Behaviour Therapy; DIAZ, diazepam; DROP, droperidol; ECT, Electroconvulsive Therapy; FFT, Family Focussed Therapy; FLX, fluoxetine; FLUP, flupenthixol; GABA, gabapentin; HAL, haloperidol; IPRST, Interpersonal and Social Rhythms Therapy; IPT, Interpersonal Therapy; LAM, lamotrigine; LITH, lithium; LOR, lorazepam; LUR, lurasidone; MAOI, Monoamine Oxidase Inhibitor; MID, midazolam; MOD, modafinil; MS, mood stabiliser; OLAN, olanzapine; OXCAR, oxcarbazepine; PAL, paliperidone; PRAM, pramipexole; QUE, quetiapine; RIS, risperidone; SGA, second-generation antipsychotic; SSRI, Selective Serotonin Reuptake Inhibitor; TAM, tamoxifen; TAU, treatment as usual, THIOR, thiorizadine; TIAG, tiagabine; TOP, topiramate; VAL, valproate; VEN, venlafaxine; ZIP, ziprasidone; ZUC, zuclopenthixol.

Notes:

a. Recommendations taken from Canadian Network for Mood and Anxiety Treatments and International Society for Bipolar Disorders (CANMAT-ISBD) 2009 guidelines.

b. The 2013 CANMAT guidelines did not have a detailed section on child and adolescent bipolar disorder. Readers were referred to the AACAP 2007 guidelines for clinical advice.

c. The wording of recommendations reflects different standards of evidence. For example, the word 'offer' is used to reflect a strong recommendation, usually where there is clear evidence of benefit. The word 'consider' is used to reflect a recommendation for which the evidence of benefit is less certain and where there are a number of equally effective alternatives.

11.5 Appendix 5. ADHD guideline summaries

Guideline	Pre-school	School age	Adolescents
NHMRC (2012) Clinical Practice Points on the diagnosis, assessment and management of attention deficit hyperactivity disorder in children and adolescents.	**<7 years** **1st line**: psychological (less effective in young), environmental or family interventions **2nd line**: MPH or DEX, preferably with psychosocial intervention	**6-12 years** **1st line**: psychological therapies with demonstrated effectiveness (e.g., family therapy, CBT, behaviour modification) **2nd line**: MPH or DEX (alone or in combination with psychosocial interventions) **3rd line**: after 1 month with inadequate improvement, try alternate stimulant of MPH/ DEX	**13-18 years** **1st line**: psychological therapies with demonstrated effectiveness (e.g., family therapy, CBT, behaviour modification) (less effective for adolescents) **2nd line**: MPH or DEX (alone or in combination with psychosocial interventions) **3rd line**: after 1 month with inadequate improvement, try alternate stimulant of MPH/ DEX

Guideline	Pre-school	School age	Adolescents
Royal Australian College of Physicians (RACP) (2009)	**Preschool 3-5 years** **Note: MSA may be useful for all age groups, but is not available in Australia** **1st line:** BT or psychosocial therapy **2nd line:** MPH-IR + BT	**School Age – 6-12 years** **Note: MSA may be useful for all age groups, but is not available in Australia** **1st line (severe):** MPH (start IR to titrate, switch to LA), DEX **2nd line:** ATOM (>6 years) **3rd line**: CLON +/- STIM (MPH, DEX) **4th line**: GUAN (not available in Australia in 2009) **COMORBID (Psychosocial interventions[a] should be considered for individuals with ADHD and comorbidities)** **Anxiety** **1st line**: STIM (MPH, DEX), ATOM **2nd line**: ADHD med +/- SSRI + psychotherapy **MDD** – (if on STIM (MPH, DEX) consider if cause of MDD and trial off drugs) **1st line**: non-pharmacological **2nd line**: ATOM **3rd line**: STIM (MPH, DEX) **Bipolar disorder**: refer to specialist **SUD** **1st line:** ATOM **TICS** **1st line:** STIM (MPH, DEX), ATOM **2nd line**: CLON **ODD/CD** **1st line:** psychosocial **2nd line: (**MPH, ATOM) +/- psychosocial **3rd line:** MPH + (CLON, RIS) +/- psychosocial **LD** **1st line: (**STIM [MPH, DEX]), ATOM) + management LD **Intellectual disability** **1st line: (**STIM [MPH, DEX]) + management of disability **Autism** **1st line: (**STIM [MPH, DEX]), ATOM	**Adolescent – 13-17 years** **Note: MSA may be useful for all age groups, but is not available in Australia** **1st line (severe):** MPH (start IR to titrate, switch to LA), DEX **2nd line:** ATOM (>6 years) **3rd line**: CLON +/- STIM (MPH, DEX) **4th line**: GUAN (not available in Australia in 2009) **COMORBID (Psychosocial interventions[a] should be considered for individuals with ADHD and comorbidities)** **Anxiety** **1st line**: STIM (MPH, DEX), ATOM **2nd line**: ADHD med +/- SSRI + psychotherapy **MDD** – (if on STIM (MPH, DEX) consider if cause of MDD and trial off drugs) **1st line**: non-pharmacological **2nd line**: ATOM **3rd line**: STIM (MPH, DEX) **Bipolar disorder**: refer to specialist **SUD** **1st line:** ATOM **TICS** **1st line:** STIM (MPH, DEX), ATOM **2nd line**: CLON **ODD/CD** **1st line:** psychosocial **2nd line: (**MPH, ATOM) +/- psychosocial **3rd line:** MPH + (CLON, RIS) +/- psychosocial **LD** **1st line: (**STIM [MPH, DEX]), ATOM) + management LD **Intellectual disability** **1st line: (**STIM [MPH, DEX]) + management of disability **Autism** **1st line: (**STIM [MPH, DEX]), ATOM

Guideline	Pre-school	School age	Adolescents
eTG Complete (2019)	**Note: With rare exceptions, do not use stimulants in children under 4 years** **<4 years** **1st line**: parent training/ education and/or behavioural intervention **2nd line**: if using stimulants, see algorithm for children aged 4-12 years	**4- 12 years** **1st line**: >3 years -MPH-IR (suggested to trial first), DEX-IR **2nd line**: MPH (or DEX), once stabilised on 2 daily doses, switch to LA (8hr) (>5 years) **2nd line**: MPH (or DEX), once stabilised on 3 daily doses, switch to LA (12hr) (>5 years) **3rd line**: ATOM[d] (>5 years) **4th line**: CLON (>4 years) **5th line**: TCA[b] **COMORBID** **Anxiety** **1st line:** ATOM[c] **TICS** **1st line**: STIM (MPH, DEX) **2nd line**: ATOM[c] **3rd line**: CLON **SUD** **1st line**: ATOM[c] **Aggression** **1st line**: CLON **Sleep** **1st line**: STIM (MPH, DEX) **2nd line**: CLON	**13-18 years** **1st line**: MPH-IR (suggested to trial first), DEX-IR **2nd line**: MPH (or DEX), once stabilised on 2 daily doses, switch to LA (8hr) **2nd line**: MPH (or DEX), once stabilised on 3 daily doses, switch to LA (12hr) **3rd line**: ATOM[d] **4th line**: CLON **5th line**: TCA[b] **COMORBID** **Anxiety** **1st line:** ATOM[c] **TICS** **1st line**: STIM (MPH, DEX) **2nd line**: ATOM[c] **3rd line**: CLON **SUD** **1st line**: ATOM[c] **Aggression** **1st line**: CLON **Sleep** **1st line**: STIM (MPH, DEX) **2nd line**: CLON

Guideline	Pre-school	School age	Adolescents
American Academy Child and Adolescent Psychiatry (AACAP) (2007)	**Notes**: • Behaviour therapy may be recommended as an initial treatment if the patient's ADHD symptoms are mild with minimal impairment, parents reject medication treatment • It seems established that a pharmacological intervention for ADHD is more effective than a behavioural treatment alone. • No evidence supports CBT or dietary modification. • If less than optimal response to medication, has a comorbid disorder, or experiences stressors in family life, then psychosocial treatment in conjunction with medication treatment Is often beneficial [REC 11, p.912]. **3-5 years** **1st line**: MPH-IR **2nd line**: DEX-IR **3rd line**: MPH-LA or DEX-LA **4th line**: ATOM[c] **5th line**: BUP, TCA[b] (not DESIP), α-agonist (GUAN, CLON), with or without BT **6th line**: DESIP **COMORBID** **Anxiety** **1st line**: ATOM[c] **TICS** **1st line**: ATOM[c] **2nd line**: STIM+CLON	**Notes**: • Behaviour therapy may be recommended as an initial treatment if the patient's ADHD symptoms are mild with minimal impairment, the diagnosis of ADHD is uncertain, parents reject medication treatment, or there is marked disagreement about the diagnosis between parents or between parents and teachers. • It seems established that a pharmacological intervention for ADHD is more effective than a behavioural treatment alone. • No evidence supports CBT or dietary modification. • If a patient with ADHD has a less-than-optimal response to medication, has a comorbid disorder, or experiences stressors in family life, then psychosocial treatment in conjunction with medication treatment Is often beneficial [REC 11, p.912]. **6-12 years** **1st line**: MPH or DEX (IR or LA), MSA, LISDEX **2nd line**: alternate stimulant of MPH or DEX (IR or LA), MSA, LISDEX **3rd line**: ATOM[c] **4th line**: May recommend trial of BT before prescribing non-approved FDA drugs: BUP[d], TCA[b] (IMIP, NOR, not DESIP), α-agonist (GUAN, CLON), with/ without BT **5th line**: DESIP[e] **COMORBID** **Anxiety** **1st line**: ATOM[c] **SUD** **1st line**: ATOM[c] **Aggression:** **1st line: CLON, GUAN** **TICS** **1st line**: ATOM[c] **2nd line**: STIM+CLON **Insomnia** **1st line**: CLON **2nd line**: MEL, TRAZ, AHIST **Depression**	**Notes**: • Behaviour therapy may be recommended as an initial treatment if the patient's ADHD symptoms are mild with minimal impairment, the diagnosis of ADHD is uncertain, parents reject medication treatment, or there is marked disagreement about the diagnosis between parents or between parents and teachers. • It seems established that a pharmacological intervention for ADHD is more effective than a behavioural treatment alone. • No evidence supports CBT or dietary modification. • If a patient with ADHD has a less-than-optimal response to medication, has a comorbid disorder, or experiences stressors in family life, then psychosocial treatment in conjunction with medication treatment Is often beneficial [REC 11, p.912]. **13-17 years** **1st line**: MPH or DEX (IR or LA), MSA, LISDEX **2nd line**: alternate stimulant of MPH or DEX (IR or LA), MSA, LISDEX **3rd line**: ATOM[c] **4th line**: May recommend trial of BT before prescribing non-approved FDA drugs: BUP[d], TCA[b] (IMIP, NOR, not DESIP), α-agonist (GUAN, CLON), with/ without BT **5th line**: DESIP[e] **COMORBID** **Anxiety** **1st line** ATOM[c] **SUD** **1st line**: ATOM[c] **Aggression:** **1st line: CLON, GUAN** **TICS** **1st line**: ATOM[c] **2nd line**: STIM+CLON **Insomnia** **1st line**: CLON **2nd line**: MEL, TRAZ, AHIST **Depression**

Guideline	Pre-school	School age	Adolescents
	DBD (CD, ODD) (not usually diagnosed in pre-schoolers) Consider adding psychosocial therapy **Insomnia** **1st line**: CLON **2nd line**: MEL, TRAZ, AHIST **Depression** Choose to treat most severe condition first: if necessary, add SSRI.	Choose to treat most severe condition first: if necessary, add SSRI.	Choose to treat most severe condition first: if necessary, add SSRI.
National Institute for Health and Care Excellence (NICE) - ng72 (2009)	**Pre-school** **1st line:** offer parents/carers education or training program. • Drug treatment is not recommended	**School age and young people – >4 years** **1st line:** • Watchful waiting up to 10 weeks: offer parents/carers education or training program +CBT social skills for child • offer drug treatment if symptoms severe, or symptoms moderate and refuse training, education, CBT **2nd line**: drug treatment, • started by specialist • MPH (>6 years) + parent/carer training **3rd line**: ATOM (>6 years) + parent/carer training **4th line**: Increase dose up to maximum **5th line**: DEX (>3 years), after referral to tertiary services **6th line**: BUP, CLON, MOD, IMIP **COMORBID** **Anxiety** **1st line**: lower dose STIM (MPH, DEX) **2nd line**: add AD, or switch to ATOM[c] **Psychosis** **1st line**: withdraw drug if MPH, DEX and reassess diagnosis **2nd line**: consider ATOM[c] **Seizures (de novo, or exacerbation)** **1st line:** withdraw immediately if MPH, ATOM[c] **2nd line:** consider DEX **TICS** **1st line**: reduce dose if caused by MPH, DEX **2nd line**: withdraw drug or consider ATOM[c]	**School age and young people – >4 years** **1st line:** • Watchful waiting up to 10 weeks: offer parents/carers education or training program +CBT social skills for child • offer drug treatment if symptoms severe, or symptoms moderate and refuse training, education, CBT **2nd line**: drug treatment, • started by specialist • MPH (>6 years) + parent/carer training **3rd line**: ATOM (>6 years) + parent/carer training **4th line**: Increase dose up to maximum **5th line**: DEX (>3 years), after referral to tertiary services **6th line**: BUP, CLON, MOD, IMIP **COMORBID** **Anxiety** **1st line**: lower dose STIM (MPH, DEX) **2nd line**: add AD, or switch to ATOM[c] **Psychosis** **1st line**: withdraw drug if MPH, DEX and reassess diagnosis **2nd line**: consider ATOM[c] **Seizures (de novo, or exacerbation)** **1st line:** withdraw immediately if MPH, ATOM[c] **2nd line:** consider DEX **TICS** **1st line**: reduce dose if caused by MPH, DEX **2nd line**: withdraw drug or consider ATOM[c]

Guideline	Pre-school	School age	Adolescents
National Institute for Health and Care Excellence (NICE) - ng87 (2018)	**<5 years (HCP only treat if expertise in ADHD – PHC should not make initial diagnosis or initiate medication)** **1st line: mild –** watchful waiting up to 10 weeks and offer ADHD-focused group parent training **2nd line**: modify environment **3rd line**: STIM	**>4 years** **1st line – mild:** watchful waiting up to 10 weeks and offer ADHD-focused group parent support **2nd line**: psychoeducation on ADHD and individual or group CBT, skills training, environmental modification **3rd line**: MPH (IR or LA) - consider adding CBT if benefiting from STIM but still significant impairment **4th line**: consider switch to LISDEX[f] after 6 weeks trial MPH at adequate dose **5th line**: consider DEX[g] **6th line**: ATOM[c] or GUAN (after separate 6-week trial of MPH and LISDEX[f]) **7th line**: CLON, SGAs+ (MPH, DEX[g], LISDEX[f]) (only after advice from tertiary ADHD service) **COMORBID** **Anxiety** **1st line:** offer same medication choices as for ADHD **CD/ ODD** Offer parents and carers a parent-training programme – refer NICE cg158 – Antisocial behaviour and conduct disorders in children and young people. **TICS** **1st line:** offer same medication choices as for ADHD **2nd line**: consider change to GUAN, ATOM[c], CLON **Autism** **1st line:** offer same medication choices as for ADHD **Psychosis** Stop ADHD medication – start same or new ADHD medication after resolved **Aggression/ rages** **1st line:** offer same medication choices as for ADHD **2nd line**: • CLON (only after advice from tertiary ADHD service) • STIM (MPH, LISDEX[f], DEX[g]) + SGA (only after advice from tertiary ADHD service) **Sleep** **1st line:** offer same medication choices as for ADHD **2nd line**: CLON (only after advice from tertiary ADHD service)	**>4 years** **1st line – mild:** watchful waiting up to 10 weeks and offer ADHD-focused group parent support **2nd line**: psychoeducation on ADHD and individual or group CBT, skills training, environmental modification **3rd line**: MPH (IR or LA) - consider adding CBT if benefiting from STIM but still significant impairment **4th line**: consider switch to LISDEX[f] after 6 weeks trial MPH at adequate dose **5th line**: consider DEX[g] **6th line**: ATOM[c] or GUAN (after separate 6-week trial of MPH and LISDEX[f]) **7th line**: CLON, SGAs+ (MPH, DEX[g], LISDEX[f]) (only after advice from tertiary ADHD service) **COMORBID** **Anxiety** **1st line:** offer same medication choices as for ADHD **CD/ ODD** Offer parents and carers a parent-training programme – refer NICE cg158 – Antisocial behaviour and conduct disorders in children and young people. **TICS** **1st line:** offer same medication choices as for ADHD **2nd line**: consider change to GUAN, ATOM[c], CLON **Autism** **1st line:** offer same medication choices as for ADHD **Psychosis** Stop ADHD medication – start same or new ADHD medication after resolved **Aggression/ rages** **1st line:** offer same medication choices as for ADHD **2nd line**: • CLON (only after advice from tertiary ADHD service) • STIM (MPH, LISDEX[f], DEX[g]) + SGA (only after advice from tertiary ADHD service) **Sleep** **1st line:** offer same medication choices as for ADHD **2nd line**: CLON (only after advice from tertiary ADHD service)

Guideline	Pre-school	School age	Adolescents
Scottish Intercollegiate Guidelines Network (SIGN) (2009)	**Preschool** **1st line**: behavioural parent training by trained facilitators **2nd line**: MPH, DEX	**Note:** • Where symptoms are mild, first consider behavioural approaches • For severe cases, some children can benefit from very intensive behavioural interventions alone, but the benefit is less than with medication alone. • For school aged children with severe ADHD, medication is recommended. **Pre-adolescent - <12 years** **1st line**: MPH, DEX[g] **2nd line**: alternate of MPH, DEX[g] trialled in 2nd line **3rd line**: ATOM[c] **4th line**: LISDEX[f] (aged 6 and over) **5th line**: CLON +/- MPH **6th line**: TCA[b] (mainly for behavioural symptoms) **7th line**: MOD **COMORBID** **Anxiety** Combine medication and BT **SUD** **1st line**: MPH-LA or DEX-LA **2nd line**: ATOM[c] **ODD** Combine medication and BT **Aggression** Combine medication and BT	**Note:** • Where symptoms are mild, first consider behavioural approaches • For severe cases, some children can benefit from very intensive behavioural interventions alone, but the benefit is less than with medication alone. • For school aged children with severe ADHD, medication is recommended. **Adolescents – >11 years** **1st line**: MPH, DEX[g] **2nd line**: alternate of MPH, DEX[g] trialled in 2nd line **3rd line**: ATOM[c] **4th line**: LISDEX[f] (aged 6 and over) **5th line**: CLON +/- MPH **6th line**: TCA[b] (mainly for behavioural symptoms) **7th line**: MOD **COMORBID** **Anxiety** Combine medication and BT **SUD** **1st line**: MPH-LA or DEX-LA **2nd line**: ATOM[c] **ODD** Combine medication and BT **Aggression** Combine medication and BT

Guideline	Pre-school	School age	Adolescents
BMJ Best Practice (2018)	**3-5 years** **Note:** • **Adjunctive behavioural therapy:** Behavioural therapy in conjunction with medication is often beneficial if a patient with ADHD has a less-than-optimal response to medication, has a comorbid disorder, or experiences family stress. • The MTA study determined that medications were clearly superior to behavioural treatment alone in all ADHD domains. However, combined medication and behavioural therapy did yield improvement in key areas (including parent and teacher ratings of inattention, parent rating of hyperactivity-impulsivity, parent rating of oppositional/ aggressive behaviours, and internalising symptoms of anxiety and depression) at a lower dose of medication. **1st line**: psychoeducation **2nd line**: AMP-IR, DEX-IR **3rd line**: GUAN **COMORBID** **Anxiety** **1st line**: ATOM **2nd line**: TCA (IMIP, NOR) **TICS** **1st line**: ATOM	**6-12 years** **Note:** • **Adjunctive behavioural therapy:** Behavioural therapy in conjunction with medication is often beneficial if a patient with ADHD has a less-than-optimal response to medication, has a comorbid disorder, or experiences family stress. • The MTA study determined that medications were clearly superior to behavioural treatment alone in all ADHD domains. However, combined medication and behavioural therapy did yield improvement in key areas (including parent and teacher ratings of inattention, parent rating of hyperactivity-impulsivity, parent rating of oppositional/aggressive behaviours, and internalising symptoms of anxiety and depression) at a lower dose of medication. **1st line**: psychoeducation **2nd line**: (MPH, AMP, DEX, DEXMETH, LISDEX) +psychoeducation **3rd line**: alternate STIM from 2nd line options **4th line**: ATOM[c] **5th line**: GUAN, CLON (best for hyperactive-impulsive symptoms) **6th line**: TCA[b] (IMIP, NOR) **7th line**: BUP **COMORBID** **Anxiety** **1st line:** psychoeducation **2nd line**: (MPH-LA, ATOM[c], GUAN, CLON, LISDEX) +psychoeducation **3rd line**: TCA[b] (IMIP, NOR) + psychoeducation **4th line**: BUP + psychoeducation **TICS – TIC disorder or stimulant induced** **1st line:** psychoeducation **2nd line**: (ATOM[c], GUAN, CLON) + psychoeducation **SUD/ stimulant abuse** **1st line:** psychoeducation **2nd line**: ATOM[c] +psychoeducation **3rd line**: (GUAN, CLON) + psychoeducation **4th line**: TCA[b] + psychoeducation **5th line**: BUP + psychoeducation **Aggression**	**13-18 years** **Note:** • **Adjunctive behavioural therapy:** Behavioural therapy in conjunction with medication is often beneficial if a patient with ADHD has a less-than-optimal response to medication, has a comorbid disorder, or experiences family stress. • The MTA study determined that medications were clearly superior to behavioural treatment alone in all ADHD domains. However, combined medication and behavioural therapy did yield improvement in key areas (including parent and teacher ratings of inattention, parent rating of hyperactivity-impulsivity, parent rating of oppositional/aggressive behaviours, and internalising symptoms of anxiety and depression) at a lower dose of medication. **1st line**: psychoeducation **2nd line**: (MPH, AMP, DEX, DEXMETH, LISDEX) +psychoeducation **3rd line**: alternate STIM from 2nd line options **4th line**: ATOM[c] **5th line**: GUAN, CLON (best for hyperactive-impulsive symptoms) **6th line**: TCA[b] (IMIP, NOR) **7th line**: BUP **COMORBID** **Anxiety** **1st line:** psychoeducation **2nd line**: (MPH-LA, ATOM[c], GUAN, CLON, LISDEX) + psychoeducation **3rd line**: TCA[b] (IMIP, NOR) + psychoeducation **4th line**: BUP + psychoeducation **TICS – TIC disorder or stimulant induced** **1st line:** psychoeducation **2nd line**: (ATOM[c], GUAN, CLON) + psychoeducation **SUD/ stimulant abuse** **1st line:** psychoeducation **2nd line**: ATOM[c] +psychoeducation **3rd line**: (GUAN, CLON) + psychoeducation **4th line**: TCA[b] + psychoeducation **5th line**: BUP + psychoeducation

Guideline	Pre-school	School age	Adolescents
		1st line: psychoeducation **2nd line**: GUAN, CLON SGA commonly used off-label **Sleep** **1st line:** psychoeducation **2nd line**: GUAN, CLON **CD** **1st line:** psychoeducation **2nd line**: (GUAN, CLON) +/-STIM (MPH, AMP, DEX, DEXMETH, LISDEX)	**Aggression** **1st line:** psychoeducation **2nd line**: GUAN, CLON SGA commonly used off-label **Sleep** **1st line:** psychoeducation **2nd line**: GUAN, CLON **CD** **1st line:** psychoeducation **2nd line**: (GUAN, CLON) +/-STIM (MPH, AMP, DEX, DEXMETH, LISDEX)
Canadian Paediatric Society (CPS) (2018)	**<6 years** **1st line:** parent behaviour training	**>5 years** **1st line:** psychoeducation **2nd line**: MPH-LA, DEX-LA **3rd line**: alternate STIM from options listed 2nd line **4th line**: non-stimulant (ATOM, GUAN) **5th line**: CLON **COMORBID** **Anxiety** **1st line**: ATOM[c] **TIC** **1st line**: ATOM[c] **ODD** **1st line:** GUAN	**>5 years** **1st line:** psychoeducation **2nd line**: MPH-LA, DEX-LA **3rd line**: alternate STIM from options listed 2nd line **4th line**: non-stimulant (ATOM, GUAN) **5th line**: CLON **COMORBID** **Anxiety** **1st line**: ATOM[c] **TIC** **1st line**: ATOM[c] **ODD** **1st line:** GUAN

Guideline	Pre-school	School age	Adolescents
American Academy of Pediatrics (AAP) (2011)	**4-5 years**[m] **1st line**: evidence-based parent and/or teacher administered behaviour therapy (PTBM) **2nd line**: MPH if moderate/severe and PTBM ineffective	**6-11 years** **1st line:** FDA approved STIM[i] (MPH, DEX, LISDEX, DEXMETH, MSA) and/or BT **2nd line**: ATOM[c] **3rd line**: GUAN-LA **4th line**: CLON-LA **COMORBID** Children with ADHD and coexisting anxiety disorders might find that ADHD medications decrease anxiety symptoms as well as ADHD behaviours. In the cases of severe learning disorders or oppositional defiant disorder, a trial of treatment for ADHD might indicate whether the apparent coexisting condition can be modulated with treatment of the ADHD. Other patients might require additional therapeutic treatments, such as cognitive behavioural therapy or a different or additional medication, to adequately treat the ADHD and coexisting condition.	**12-18 years** **1st line:** • FDA approved (STIM[i] (MPH, DEX[g], LISDEX, DEXMETH, MSA), ATOM[c], GUAN-LA, CLON-LA) and/or BT **COMORBID** Children with ADHD and coexisting anxiety disorders might find that ADHD medications decrease anxiety symptoms as well as ADHD behaviours. In the cases of severe learning disorders or oppositional defiant disorder, a trial of treatment for ADHD might indicate whether the apparent coexisting condition can be modulated with treatment of the ADHD. Other patients might require additional therapeutic treatments, such as cognitive behavioural therapy or a different or additional medication, to adequately treat the ADHD and coexisting condition. Consider non-STIM if there is a risk of diversion
Kutcher (2004) – referred to in BMJ Best Practice (2018)	**<6 years** **1st line**: parent training **2nd line**: in insufficient response after 8-10 weeks, refer to specialist, review diagnosis and environment. Consider adding medication.	**>5 years** **1st line**: MPH (IR or LA), DEX (IR or LA) +/- psychosocial interventions[a] parent training, classroom intervention, individualised BT. **1st line- parent refuses medication**: 8-10 weeks psychosocial interventions, then strongly advise adding medication **2nd line**: insufficient response after 2-4 weeks – increase dose **3rd line**: alternate MPH, AMP to that used 1st line **COMORBID** **CD** **1st line**: (MPH, DEX) + psychosocial therapy **2nd line**: (MPH, DEX) + RIS + psychosocial therapy **3rd line**: hospitalise	**6 years- adolescent** **1st line**: MPH (IR or LA), DEX (IR or LA) +/- psychosocial interventions[a] parent training, classroom intervention, individualised BT. **1st line- parent refuses medication**: 8-10 weeks psychosocial interventions, then strongly advise adding medication **2nd line**: insufficient response after 2-4 weeks – increase dose **3rd line**: alternate MPH, AMP to that used 1st line **COMORBID** **CD** **1st line**: (MPH, DEX) + psychosocial therapy **2nd line**: (MPH, DEX) + RIS + psychosocial therapy **3rd line**: hospitalise

Guideline	Pre-school	School age	Adolescents
Texas Children's Medication Algorithm Project (TMAP) (2006)	**No lower age limit mentioned** Short-acting stimulants are often used as initial treatment in small children (weight <16 kg) for whom no long-acting dosage form is available in a sufficiently low dose, or in children whom the physician feels are vulnerable to side effects.	**Stage 0: Assessment and family consultation** non-medication alternatives **Stage 1:** STIM (MPH, AMP, MSA, DEX) **Stage 1A**: partial response (if [MSA, DEX] used in Stage 1) AMP formulation not used Stage 1 **Stage 2:** alternate STIM (MPH, AMP, MSA, DEX) not used stage 1 **Stage 2A**: partial response (if [MSA, DEX] used in Stage 2) - AMP formulation not used Stage 2 **Stage 3:** ATOM[c] **Stage 3A –** if partial response STIM or ATOM[c] - combine ATOM[c] + STIM **Stage 4:** BUP (except if seizures), TCA[b] (IMIP, NOR) **Stage 5:** alternate AD not used Stage 4 **Stage 6:** GUAN, CLON **COMORBID** **Anxiety** **1st line:** • ATOM[c] • STIM (MPH, AMP, MSA, DEX) + SSRI **SUD** **1st line**: ATOM[c] **TICS** **1st line**: MPH, AMP **2nd line**: STIM + (GUAN, CLON) **3rd line**: STIM + SGA **4th line**: STIM +FGA **Aggression:** **1st line**: STIM (MPH, AMP, MSA, DEX) **2nd line**: STIM (MPH, AMP, MSA, DEX) + behavioural intervention **3rd line**: STIM (MPH, AMP, MSA, DEX) +SGA **4th line**: STIM (MPH, AMP, MSA, DEX) + (LI or VAL) **5th line:** STIM (MPH, AMP, MSA, DEX) + agent not used 4th line **MDD- strong consensus that** **1st line**- • ADHD most severe: MPH, AMP (preferably LA) • MDD most severe: try STIM (MPH, AMP, MSA, DEX), but consider SSRI first	**Stage 0: Assessment and family consultation** non-medication alternatives **Stage 1:** STIM (MPH, AMP, MSA, DEX) **Stage 1A**: partial response (if [MSA, DEX] used in Stage 1) AMP formulation not used Stage 1 **Stage 2:** alternate STIM (MPH, AMP, MSA, DEX) not used stage 1 **Stage 2A**: partial response (if [MSA, DEX] used in Stage 2) - AMP formulation not used Stage 2 **Stage 3:** ATOM[c] **Stage 3A –** if partial response STIM or ATOM[c] - combine ATOM[c] + STIM **Stage 4:** BUP (except if seizures), TCA[b] (IMIP, NOR) **Stage 5:** alternate AD not used Stage 4 **Stage 6:** GUAN, CLON **COMORBID** **Anxiety** **1st line:** • ATOM[c] • STIM (MPH, AMP, MSA, DEX) + SSRI **SUD** **1st line**: ATOM[c] **TICS** **1st line**: MPH, AMP **2nd line**: STIM + (GUAN, CLON) **3rd line**: STIM + SGA **4th line**: STIM +FGA **Aggression:** **1st line**: STIM (MPH, AMP, MSA, DEX) **2nd line**: STIM (MPH, AMP, MSA, DEX) + behavioural intervention **3rd line**: STIM (MPH, AMP, MSA, DEX) +SGA **4th line**: STIM (MPH, AMP, MSA, DEX) + (LI or VAL) **5th line:** STIM (MPH, AMP, MSA, DEX) + agent not used 4th line **MDD- strong consensus that** **1st line**- • ADHD most severe: MPH, AMP (preferably LA) • MDD most severe: try STIM (MPH, AMP, MSA, DEX), but consider SSRI first

Guideline	Pre-school	School age	Adolescents
British Association for Psychopharmacology (BAP) (2014)	**No lower age limit mentioned** Parent training programmes may appeal to families as a good alternative to medication, particularly in relation to younger children or in the initial stages of treatment.	**Children** **1st line-** • **mild/moderate ADHD**: psychological treatments[j] • **severe ADHD**: STIM (AMP, DEX, LISDEX) **2nd line**- • **moderate ADHD not responding to psychological treatments[j]**: STIM (AMP, DEX, LISDEX) • **severe ADHD**: consider referral to tertiary centres for high dose STIM or alternatives (CLON, BUP) **COMORBID** **Stimulant abuse risk (for child or adult carer)** **1st line:** ATOM[c] **Autism** **1st line:** MPH **2nd line**: ATOM[c], RIS **3rd line**: CAR, CLON **4th line**: VEN, BUS, TCA[b], LAM (anecdotal only) **CD** **1st line**: RIS (widely used, but off-label) **LD** **1st line**: AMP, MPH, RIS **2nd line**: ATOM[c], ARIP, OLAN, QUE, CLON **TICS** **1st line**: MPH-LA **2nd line**: • ATOM[c] • STIM (AMP, DEX, LISDEX) +/- (GUAN, CLON)	**Adolescents** **1st line-** • **mild/moderate ADHD**: psychological treatments[j] • **severe ADHD**: STIM (AMP, DEX, LISDEX) **2nd line**- • **moderate ADHD not responding to psychological treatments[j]**: STIM (AMP, DEX, LISDEX) • **severe ADHD**: consider referral to tertiary centres for high dose STIM or alternatives (CLON, BUP) **COMORBID** **SUD** **1st line**: ATOM[c] + psychoeducation + CBT **2nd line**: MPH-LA, LISDEX-LA **3rd line**: BUP **Autism** **1st line:** MPH **2nd line**: ATOM[c], RIS **3rd line**: CAR, CLON **4th line**: VEN, BUS, TCA[b], LAM (anecdotal only) **CD** **1st line**: RIS (widely used, but off-label) **LD** **1st line**: AMP, MPH, RIS **2nd line**: ATOM[c], ARIP, OLAN, QUE, CLON **TICS** **1st line**: MPH-LA **2nd line**: • ATOM[c] • STIM (AMP, DEX, LISDEX) +/- (GUAN, CLON)

Guideline	Pre-school	School age	Adolescents
Canadian ADHD Resource Alliance (CADDRA) (2011)	**0-5 years** Psychoeducation/ parent training, psychosocial interventions[a], behaviour management	**School Age – 6-12 years** **Notes:** • **Use a comprehensive, collaborative and multimodal approach** **1st line**: MPH-LA, AMP-LA, MSA-LA[h], LISDEX-LA **2nd line**: alternate STIM[j] not used from 1st line options **3rd line**: • switch release mechanism (MPH-SA/IA, AMP-SA/IA, MSA-SA[h] /IA, LISDEX-SA/IA) • switch to DEX • switch to ATOM[c], GUAN, • augment STIM with ATOM[c], GUAN **4th line**: BUP, CLON, MOD, IMIP **COMORBID –** with the exception of bipolar disorder**,** treat most impairing condition first	**Adolescents 13-17 years** **Notes:** • **Use a comprehensive, collaborative and multimodal approach** **1st line**: MPH-LA, AMP-LA, MSA-LA[h], LISDEX-LA **2nd line**: alternate STIM[j] not used from 1st line options **3rd line**: • switch release mechanism (MPH-SA/IA, AMP-SA/IA, MSA-SA[h] /IA, LISDEX-SA/IA) • switch to DEX • switch to ATOM[c], GUAN, • augment STIM with ATOM[c], GUAN **4th line**: BUP, CLON, MOD, IMIP **COMORBID –** with the exception of bipolar disorder**,** treat most impairing condition first
Canadian ADHD Resource Alliance (CADDRA) (2018)	**Pre-School 3-5 years** **Notes:** • Treatment before the age of 6 should be within the context of specialised care **1st line**: non-pharmacological treatment (parent management training)	**School Age – 6-12 years** **Notes**: • Use a comprehensive, collaborative and multimodal approach • Medications are an important aspect of treatment and assist the facilitation of changes by improving focus and self-regulation and reducing impulsivity, thus allowing the individual to use the psychosocial strategies[a] more effectively. **1st line**: MPH-LA, AMP-LA, MSA-LA[h], LISDEX-LA **2nd line**: alternate STIM[j] not used from 1st line options **3rd line**: • switch release mechanism (MPH-SA/IA, AMP-SA/IA, MSA-SA/IA[h] /IA, LISDEX-SA/IA) • switch to DEX • switch to ATOM[c], GUAN, • augment STIM with ATOM[c], GUAN **4th line**: BUP, CLON, MOD, IMIP **COMORBID** Treat most impairing condition first, except for psychosis, severe mood disorders, substance use disorder or bipolar disorder. These conditions must be treated prior to initiating ADHD treatments.	**Adolescents 13-17 years** **Notes**: • Use a comprehensive, collaborative and multimodal approach • Medications are an important aspect of treatment and assist the facilitation of changes by improving focus and self-regulation and reducing impulsivity, thus allowing the individual to use the psychosocial strategies[a] more effectively. **1st line**: MPH-LA, AMP-LA, MSA-LA[h], LISDEX-LA **2nd line**: alternate STIM[j] not used from 1st line options **3rd line**: • switch release mechanism (MPH-SA/IA, AMP-SA/IA, MSA-SA/IA[h], LISDEX-SA/IA) • switch to DEX • switch to ATOM[c], GUAN, • augment STIM with ATOM[c], GUAN **4th line**: BUP, CLON, MOD, IMIP **COMORBID** Treat most impairing condition first, except for psychosis, severe mood disorders, substance use disorder or bipolar disorder. These conditions must be treated prior to initiating ADHD treatments.

Abbreviations organisations/institutions: AACAP, American Academy Child and Adolescent Psychiatry; AAP, American Academy of Pediatrics; BAP, British Association for Psychopharmacology; CADDRA, Canadian ADHD resource alliance; CPA, Canadian Paediatric Society; eTG Complete, Electronic Therapeutic Guidelines Complete; NHMRC, National Health and Medical Research Council; NICE, National Institute for Health and Care Excellence; RACP, Royal Australian College of Physicians; RANZCP, Royal Australian and New Zealand College of Psychiatrists; SIGN, Scottish Intercollegiate Guidelines Network; TMAP, Texas Medication Algorithm Project.

Abbreviations disorders: ADHD, attention deficit hyperactivity disorder; CD, conduct disorder; LD, learning disorder; ODD, oppositional defiant disorder; DBD, disruptive behaviour disorder; DMDD, disruptive mood dysregulation disorder; MDD, major depressive disorder; OCD, obsessive compulsive disorder; MTA, Multimodal Treatment Study of Children with ADHD.

Abbreviations treatments: AHIST, antihistamines; AD, antidepressant; AMP, amphetamine; ARIP, aripiprazole; ATOM, atomoxetine; BT, behaviour therapy; BUP, bupropion; BUS, buspirone; CAR, carbamazepine; CBIT, comprehensive behaviour intervention for Tics; CBT, cognitive behaviour therapy; CLON, clonidine; CPS, collaborative and proactive solutions; DESIP, desipramine; DESMO, desmopressin; DEX, dexamphetamine/ dextroamphetamine; DEXMETH, dexmethylphenidate; GUAN, guanfacine; HAL, haloperidol; HRT, habit reversal therapy; IMIP, imipramine; IR, immediate release/ short-acting; LA, long-acting/ extended release; LAM, lamotrigine; LISDEX, lisdexamphetamine; MEL, melatonin; MOD, modafinil; MPH, methylphenidate; MSA, mixed salts amphetamines; MS, mood stabiliser; MTA, Multimodal Treatment of Attention Deficit Hyperactivity Disorder; NOR, nortriptyline; OLAN, OLAN; PMT, parent management training; PSST, problem solving skills training; PTBM, parent training in behavioural management; QUE, quetiapine; RIS, risperidone; SGA, second-generation antipsychotic; SSRI, selective serotonin reuptake inhibitor; STIM, stimulant; TCA, tricyclic antidepressant; TRAZ, trazodone; VEN, venlafaxine.

Notes:

a. Psychosocial interventions include parent training, classroom interventions, family therapy, social skills therapy.

b. TCAs are not approved in Australia for the treatment of ADHD, and there is limited evidence of effectiveness in ADHD.

c. A black box warning was added to Atomoxetine on 17 December 2004, due to reported severe liver disease. Nevertheless, routine monitoring for liver function has not been recommended when prescribing Atomoxetine. A black box warning for suicidal thinking in children and adolescents was added in September 2005.

d. Bupropion should not be used if comorbid seizure disorder.

e. Desipramine has been associated with sudden death in children and adolescents.

f. Lisdexamphetamine did not have a UK marketing authorisation for this indication in children aged 5 years (as at March 2018). The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented.

g At the time of publication (March 2018), dexamphetamine was only licensed for the treatment of ADHD in children and adolescents aged 6 to 17 years when response to previous methylphenidate treatment is considered clinically inadequate. Dexamphetamine is not licensed for the treatment of ADHD in children and adolescents aged 5 to 17 years who have responded to but are intolerant to lisdexamphetamine.

h. Mixed salts amphetamines (MSA) are not approved for ADHD in Australia.

i As at 2011, FDA approved medications were mixed AMP salts (Adderall), DEX, LISDEX, MPH, DEXMETH, as well as non-stimulants (ATOM, GUAN-LA, CLON-LA).

j. Psychological treatments include family education, creative therapies, family therapy, sensory integration, positive behavioural support, behavioural therapy, anger management.

11.6 Appendix 6. Disruptive behaviours guideline summaries

Guideline	Uncomplicated	With comorbidity
eTG Complete (2019) -DBDs	• careful assessment and treatment of comorbid conditions is essential • limited role for pharmacological treatment • drug treatment should only be undertaken by specialists **1st line**: non-pharmacological **2nd line**: LITH if very severe	**ADHD** STIM + CLON for aggression +(CD or ODD) – based on 1 study only **Intellectual disability** RIS
AFP (2008) -ODD	• little research on drug treatment • medication may assist until the child and the systems around him develop the skills to cope **1st line**: family psychosocial interventions	**ADHD** **1st line**: non-pharmacological **2nd line**: STIM **3rd line**: ATOM, CLON
NICE (2013) – CDs and associated antisocial behaviours -cg158	• Do not offer pharmacological interventions for the routine management of behavioural problems in children and young people with ODD or CD. **3-11 years with ODD, CD (or at risk of ODD, CD),** or in contact with criminal justice system **1st line**: group parent/carer training **2nd line**: RIS (short-term management severe aggression with CD, >4 years for maximum 6 weeks) **3rd line**: CAR, VAL, LI (1 trial each) **3rd line**: MPH, MSA[a] **9-14 years with ODD, CD** (or at risk of ODD, CD)**,** or in contact with criminal justice system **1st line**: parent training + group social and cognitive problem-solving programmes **2nd line**: RIS (short-term management severe aggression with CD) **3rd line**: CAR, VAL, LI (1 trial each) **3rd line**: MPH, MSA[a] **11-17 years – with CD** **1st line**: multi-systemic therapy[b] **2nd line**: RIS (short-term management severe aggression with CD) **3rd line**: CAR, VAL, LI (1 trial each) **3rd line**: MPH, MSA	**ADHD (see also 2018 ADHD guidelines – ng87)** **1st line**: non-pharmacological **2nd line**: MPH, ATOM
AACAP (1997) CD	• In all cases pharmacological treatment alone will be insufficient to manage and treat CD. • Drugs may be part of treatment, primarily for comorbid conditions • Medications are recommended only on the basis of clinical experience and demonstrated efficacy in some patients **1st line**: psychosocial interventions: parent training, family therapy, individual or group child psychotherapy, peer intervention **2nd line**: LI, CAR, PROP, AD	**ADHD** **1st line**: psychosocial +/-STIM **MOOD/ANXIETY** **1st line**: psychosocial +/- AD **Paranoid ideation/ Aggression** **1st line**: psychosocial +/- low dose major tranquilisers **Seizures** **1st line**: psychosocial +/- anticonvulsant
AACAP (2007) ODD	• Medications for ODD are mostly considered adjunctive, palliative and non-curative at this time • Medication should not be the sole intervention with ODD may be considered adjunctive to treatment packages, for symptomatic treatment, and to treat comorbid conditions	**ADHD** **1st line**: psychosocial treatment plan **2nd line**: STIM, ATOM **PDD, mental retardation** **1st line**: psychosocial interventions **2nd line**: SGA **3rd line**: switch to alternate SGA or MS

Guideline	Uncomplicated	With comorbidity
	• Regardless of diagnosis, SGA seem to be the most commonly prescribed medications for treatment of acute and chronic maladaptive aggression **1st line**: individualised psychosocial treatment plan combining psychotherapy, family therapy, parent training, and ecological strategies **If drugs used for ODD:** **1st line**: SGA, STIM, ATOM **If drugs used for CD –** targeting aggression **1st line**: SGA, AP, VAL, LI, STIM	**Mood disorders (e.g., MDD, anxiety)** **1st line**: psychosocial interventions **2nd line**: SSRI (1 trial)
CPS (2017) -DBDs (Charach et al 2017)	**1st line**: evidence-based parent training, individual or group **2nd line**: evidence-based behavioural intervention **3rd line**: medication (exceptional, severe cases)	
Canadian guidelines on medication for aggression associated with DBD, CD, ADHD, ODD (2015) (Gorman et al 2015)	**ODD or CD (average or sub-average IQ)** **1st line**: psychosocial therapy **2nd line**: RIS **3rd line**: VAL (for aggression)	**ADHD+(disruptive behaviour or aggression)** **1st line:** psychosocial therapy **2nd line**: STIM **3rd line**: ATOM, CLON, GUAN **4th line**: RIS +/- STIM **ADHD +(CD or ODD)** with aggression **1st line:** psychosocial therapy **2nd line**: MPH, AMP **3rd line**: alternate STIM to 1st line **4th line**: ATOM, GUAN, CLON, RIS +/- STIM **5th line**: VAL (for aggression)
T-MAY (2012) Part I: aggression (Knapp et al 2012)	• Use of medication on a stat or p.r.n. basis should not be considered a standard treatment for youth manifesting aggressive and disruptive behaviours **1st line**: • engage patient and family in initial evaluation • do thorough diagnostic workup, investigate comorbidities • provide psychoeducation for patient and family • continuously track and reassess aggression problems using standardised measures • if using SGAs, maintain therapy for at least 2 weeks at therapeutic dose before determining efficacy **2nd line**: Consider referral to psychiatrist or ED and refer to T-MAY Part II recommendations	
T-MAY (2012) Part II: aggression (Scott Rosato et al 2012)	**<8 years (aggression)** **1st line**: psychosocial (group parent training, social skills training parent/child) **2nd line**: psychosocial +AP **3rd line**: **no response** - alternate AP **3rd line**: **partial response** + MS **8-18 years (aggression)** **1st line**: family therapy, multisystemic therapy[b], CBT for 10–16-year-olds **2nd line**: psychosocial +AP **3rd line**: no response - alternate SGA **3rd line**: partial response + MS	• Medication treatment should target the underlying disorder unless there is an emergency, when may need to add an anti-aggression medication • Avoid 2 psychotropic medications simultaneously unless all other alternatives exhausted **1st line**: Follow evidence-based guidelines for primary disorder where available **2nd line**: +AP **3rd line –** no response: + alternate AP **3rd line:** partial response: +LI

Guideline	Uncomplicated	With comorbidity
T-MAY (2010) Center for Education and Research on Mental Health Therapeutics (2010)	**1st line**: psychosocial interventions – child/parent social skills training **2nd line**: medication for primary disorder **3rd line**: medication for primary disorder + AP **4th line**: medication for primary disorder + (alternate AP or MS)	**ADHD + aggression** **1st line:** psychosocial + STIM **2nd line:** +LI or VAL **3rd line:** + alternate agent from 3rd line **Depression/ anxiety** **1st line**: CBT &/or SSRI **2nd line**: SSRI + (LI or VAL) **3rd line**: SSRI + AP **4th line**: alternate class of AD (VEN, BUP, MIRT, DUL) **5th line**: alternate agent not used in 4th line
Pappadopolous (2011) -aggression--survey of experts used to inform T_MAY project	Use of SGA initiated mainly for psychosis (most often), followed by suspicious thinking, odd behaviour, previous response to medication and aggression **1st line**: behavioural intervention **2nd line**: SGA **3rd line:** no response: alternate SGA, MS, antiC **3rd line:** part response: +MS **4th line**: SGA + (AD, α-agonist, β-blocker, other SGA, AP, BZ)[c]	• Monotherapy is preferred to polypharmacy except for bipolar disorder **ADHD +** severe aggression **1st line**: behavioural intervention parent and child **2nd line**: STIM **3rd line**: SGA, MS, antiC **ODD/CD+** disruptive psychopathology **1st line**: parent training+ BT **2nd line**: STIM

Abbreviations organisations/institutions: AACAP, American Academy of Child and Adolescent Psychiatry; AAP, American Academy of Pediatrics; AFP, Australian Family Practice; CPS, Canadian Paediatric Society; eTG, eTherapeutic Guidelines; NICE, National Institute for Health and Care Excellence; T_MAY, Treatment of Maladaptive Aggression in Youth.
Abbreviations disorders: ADHD, attention deficit hyperactivity disorder; CD, conduct disorder; DBD, disruptive behaviour disorder; MDD, major depressive disorder; ODD, oppositional defiant disorder, PDD, pervasive developmental disorder.
Abbreviations treatments: AP, antipsychotic; antiC, anticonvulsant; AD, antidepressant; AMP, amphetamine; ATOM, atomoxetine; BT, behaviour therapy; BUP, bupropion; BZ, benzodiazepine; CAR, carbamazepine; CLON, clonidine; DUL, duloxetine; ED, emergency department; GUAN, guanfacine; LI, LITH; MIRT, mirtazapine; MPH, methylphenidate; MS, mood stabiliser; MSA, mixed salts amphetamine; PROP, propranolol; RIS, risperidone; SGA, second-generation antipsychotic; STIM, stimulant; VAL, VAL; VEN, venlafaxine.
Notes:
a. Mixed salts amphetamines are not available in Australia.
b Multisystemic therapy involves the young person and their parents/carers. It has an explicit, supportive family focus, and provides intervention at individual, family, school, criminal justice and community levels. It typically consists of 3 to 4 meetings per week over a 3-to-5-month period.
c. The ordering of these adjunctive medications based on expert opinion, is from antidepressant (most beneficial) to benzodiazepines (least beneficial).

11.7 Appendix 7. Anxiety disorders guideline summaries

Guideline	GAD	Social Phobia	Phobia (specific)	Separation Anxiety Disorder	Panic disorder	OCD	PTSD	Other
eTG Complete (2019) – child and adolescent	**1st line**: behavioural intervention **2nd line**: (FLUV or SERT) +behavioural intervention **3rd line**: other SSRIs + behavioural intervention			**1st line (mild)**: family & behavioural intervention **2nd line (severe & longstanding)**: FLUV + family and behavioural intervention **3rd line (severe)**: IMIP+CBT		**1st line**: CBT[c] + psychoeducation **2nd line (severe)**: (FLUV[a], SERT[b], FLX) + CBT **3rd line (severe)**: CLOM+CBT (if >9 years)		
Hazell (2005)- child and adolescent	**1st line**: CBT **2nd line**: FLX, FLUV, SERT					**1st line**: CBT **2nd line**: SERT[b], FLUV[a], CLOM		**ACUTE DISTRESS** **1st line**: SGA (short-term) **2nd line**: THIOR (short-term)

Guideline	GAD	Social Phobia	Phobia (specific)	Separation Anxiety Disorder	Panic disorder	OCD	PTSD	Other
AACAP (2007) – (GAD, SAD, Social and specific phobia, Panic)- child and adolescent AACAP (2010, PTSD)- child and adolescent AACAP (2012)- OCD – child and adolescent	Note: • consider multimodal treatment, including education, therapy, school, and drugs **1st line (mild)**: psychotherapy **2nd line (moderate/ severe):** SSRIs (FLX, FLUV, SERT)[c]+therapy **3rd line**: non-SSRI (VEN, BUS) +therapy **COMORBID** **Depression**: Initiate SSRI early in treatment **ADHD** **1st line**: ADHD drug+behavioural **SUD** **1st line**: SUD treatment+CBT (for anxiety) **Bipolar** Concern with use of AD	Note: • consider multimodal treatment, including education, therapy, school, and drugs **1st line (mild)**: psychotherapy **2nd line (moderate/ severe):** SSRIs (FLX, FLUV, PAR) [c] +therapy **3rd line**: non-SSRI (VEN)+therapy **COMORBID** **Depression**: Initiate SSRI early in treatment **ADHD** **1st line**: ADHD drug+behavioural **SUD** **1st line**: SUD treatment+CBT (for anxiety) **Bipolar** Concern with use of AD	Note: • consider multimodal treatment, including education, therapy, school, and drugs **1st line**: CBT (graded exposure) **2nd line (moderate/ severe):** SSRI+therapy **COMORBID** **Depression**: Initiate SSRI early in treatment **ADHD** **1st line**: ADHD drug+behavioural **SUD** **1st line**: SUD treatment+CBT (for anxiety) **Bipolar** Concern with use of AD	**Separation anxiety** • consider multimodal treatment, including education, therapy, school, and drugs **1st line (mild)**: psychotherapy **2nd line (moderate/ severe):** SSRIs (FLX, SERT)[c] +therapy; **3rd line**: non-SSRI (VEN)+therapy	Note: • consider multimodal treatment, including education, therapy, school, and drugs **1st line (mild)**: psychotherapy **2nd line (moderate/ severe):** SSRI+therapy **3rd line**: non-SSRI (VEN)+therapy **4th line**: CLOM+therapy **COMORBID** **Depression**: Initiate SSRI early in treatment **ADHD** **1st line**: ADHD drug+behavioural **SUD** **1st line**: SUD treatment+CBT (for anxiety) **Bipolar** Concern with use of AD	**1st line mild/ moderate:**CBT **1st line (moderate/severe or unwilling/ unable to engage with CBT**): CBT+ (SERT[b], FLUV[a], FLX, PAR, CIT) **2nd line**: CLOM[d] **3rd line**: FLUV[a] +CLOM **4th line**: other SSRI+ (CLOM, VEN, DUL) **5th line**: SSRI+AP (espec RIS, HAL) **COMORBID** **Note**: medication for comorbid conditions is frequently needed. **ADHD** • Address OCD first – STIM may increase anxiety • If SRI mimic symptoms ADHD, consider ATOM or CLON **ODD** Address OCD first – STIM may increase anxiety **TICS/tourettes** **1st line**: CBT or CBT+medication (SERT[b], anxiolytic **2nd line**: SERT[b] or anxiolytic +(CLON, GUAN) **3rd line**: SGA **Mood** Aligns with OCD treatment **Bipolar** • Stabilise mood first **1st line**: CBT **2nd line**: CBT+MS	**1st line**: TF-therapy (CBT, psychodynamic, psychanalytic) **2nd line**: TF therapy+SSRI (CIT, FLX, SERT)[e] **3rd line**: may consider SGA, non-SSRI AD, MS, antiC, α&β adrenergic blockers (CLON, PROP) **COMORBID** If comorbid depression, GAD, OCD (i.e., conditions known to respond to SSRI), may benefit from SSRI earlier in treatment.	**1st line**: BZ (as adjunct short-term treatment only – to assist with engagement with CBT) **COMORBID** **Depression**: Initiate SSRI early in treatment **ADHD** **1st line**: ADHD drug+behavioural **SUD** **1st line**: SUD treatment+CBT (for anxiety) **Bipolar** Concern with use of AD

Guideline	GAD	Social Phobia	Phobia (specific)	Separation Anxiety Disorder	Panic disorder	OCD	PTSD	Other
APA (2009) – Panic disorder (adult) APA (2007) – (OCD) (adult)					**Note:** Unless otherwise stated, the general conditions for adults apply to children. Readers referred to AACAP 2007 guidelines for children for a detailed discussion. **1st line**: CBT **2nd line**: CBT+SSRI (CIT, ESCIT, FLX, FLUV, PAR, PAR-CR, SERT) **3rd line**: IMIP, BZ (CLONAZ, ALP)	**Note:** Unless otherwise stated, the general conditions for adults apply to children. Readers referred to AACAP 2012 guidelines for children for a detailed discussion. **1st line**: CBT or CBT+SRI **2nd line**: SRI		
BAP (2005) – child & adolescent	Relatively few controlled trials **1st line**: Psychological treatment **2nd line**: choose from SSRI recommended for adults • In 2004 the UK committee on Safety of Medications judged ESCIT, CIT, PAR, SERT, MIRT and VEN unfavourable for young people under 18 years.	Relatively few controlled trials **1st line**: Psychological treatment **2nd line**: choose from SSRI recommended for adults • In 2004 the UK committee on Safety of Medications judged ESCIT, CIT, PAR, SERT, MIRT and VEN unfavourable for young people under 18 years.	Relatively few controlled trials **1st line**: Psychological treatment **2nd line**: choose from SSRI recommended for adults • In 2004 the UK committee on Safety of Medications judged ESCIT, CIT, PAR, SERT, MIRT and VEN unfavourable for young people under 18 years.		Relatively few controlled trials **1st line**: Psychological treatment **2nd line**: choose from SSRI recommended for adults • In 2004 the UK committee on Safety of Medications judged ESCIT, CIT, PAR, SERT, MIRT and VEN unfavourable for young people under 18 years.	Relatively few controlled trials **1st line:** Psychological treatment **2nd line:** SSRI recommended for adults, CLOM In 2004 the UK committee on Safety of Medications judged ESCIT, CIT, PAR, SERT[b], MIRT and VEN unfavourable for young people under 18 years	Relatively few controlled trials **1st line**: Psychological treatment **2nd line**: choose from SSRI recommended for adults • In 2004 the UK committee on Safety of Medications judged ESCIT, CIT, PAR, SERT, MIRT and VEN unfavourable for young people under 18 years.	

Guideline	GAD	Social Phobia	Phobia (specific)	Separation Anxiety Disorder	Panic disorder	OCD	PTSD	Other
BAP (2005) - adult	**Notes:** • Psychological and drug approaches have similar efficacy in acute treatment. • Routinely combining drug and psychological approaches is not recommended for initial treatment. **1st line**: SSRI (ESCIT, PAR SERT) **2nd line**: • VEN, IMIP, BUS, ALP, DIAZ, HYDROX, CBT • consider switch to VEN, IMIP if non-response to SSRI **3rd line**: consider BZ if non-response to SSRI or SNRI **4th line**: consider drug + CBT **CONTINUATION** Further 6 months in responders– best evidence (ESC, PAR) **RELAPSE PREVENTION** **1st line**: ESC, PAR CBT may be better than drug	**Notes:** • Psychological and drug approaches have similar efficacy in acute treatment. • Routinely combining drug and psychological approaches is not recommended for initial treatment **1st line**: SSRI (ESCIT, PAR SERT, FLX, FLUV) **2nd line**: PHENEL, MOC, GABA, PREG, OLAN HYDROX, CBT **2nd line**: • consider VEN, if non-response to SSRI • consider +BUS if part response SSRI **3rd line**: consider BZ (CLONAZ, BROMAZ) if non-response to Ven/SSRI+BUS **4th line**: Consider drug +CBT **CONTINUATION** Further 6 months in responders– best evidence **1st line**: SSRI **2nd line**: CLONAZ, CBT **RELAPSE PREVENTION** **1st line**: SSRI **2nd line**: CLONAZ, consider CBT after response to drug	**1st line**: exposure techniques **2nd line**: PAR, BZ		**Notes:** • Psychological and drug approaches have similar efficacy in acute treatment. • Routinely combining drug and psychological approaches is not recommended for initial treatment. **1st line**: all SSRIs, **2nd line**: alternate SSRI, ALP, CLONAZ, DIAZ, LOR, VEN, REBOX, CBT if no response after 12 weeks **3rd line**: • consider CBT + (PAR, BUS) if part response • consider CBT+PAR if nonresponse **CONTINUATION** Further 6 months in responders **1st line**: SSRI or CBT+exposure therapy **2nd line**: IMIP **RELAPSE PREVENTION** **1st line**: SSRI or CBT+exposure therapy **2nd line**: IMIP			

Guideline	GAD	Social Phobia	Phobia (specific)	Separation Anxiety Disorder	Panic disorder	OCD	PTSD	Other
BAP (2014) - child & adolescent	**Notes** • The relative efficacy of drug and psychological approaches has not been established • In 2004 the UK committee on Safety of Medications judged ESCIT, CIT, PAR, SERT, MIRT and VEN unfavourable for young people under 18 years. **1st line**: psychological treatment **2nd line**: Choose from same range of AD as for adults SSRI first choice – FLX best risk/benefit balance	**Notes** • The relative efficacy of drug and psychological approaches has not been established • In 2004 the UK committee on Safety of Medications judged ESCIT, CIT, PAR, SERT, MIRT and VEN unfavourable for young people under 18 years. **1st line**: psychological treatment **2nd line**: Choose from same range of AD as for adults SSRI first choice – FLX best risk/benefit balance	**Notes** • The relative efficacy of drug and psychological approaches has not been established • In 2004 the UK committee on Safety of Medications judged ESCIT, CIT, PAR, SERT, MIRT and VEN unfavourable for young people under 18 years. **1st line**: psychological treatment **2nd line**: Choose from same range of AD as for adults SSRI first choice – FLX best risk/benefit balance	**Notes:** • The relative efficacy of drug and psychological approaches has not been established • In 2004 the UK committee on Safety of Medications judged ESCIT, CIT, PAR, SERT, MIRT and VEN unfavourable for young people under 18 years. **1st line**: psychological treatment **2nd line**: SSRI first choice – FLX best risk/benefit balance	**Notes** • SSRI treatment can be effective in children and adolescents • In 2004 the UK committee on Safety of Medications judged ESCIT, CIT, PAR, SERT, MIRT and VEN unfavourable for young people under 18 years. • Balance of risks and harms of SSRIs in the treatment of anxiety is more favourable than for depression. The relative efficacy of drug and psychological approaches has not been established	**Notes** • The relative efficacy of drug and psychological approaches has not been established • In 2004 the UK committee on Safety of Medications judged ESCIT, CIT, PAR, SERT[b], MIRT and VEN unfavourable for young people under 18 years. **1st line**: psychological treatment **2nd line**: Choose from same range of AD as for adults SSRI first choice – FLX best risk/benefit balance	**Notes** • The relative efficacy of drug and psychological approaches has not been established • In 2004 the UK committee on Safety of Medications judged ESCIT, CIT, PAR, SERT, MIRT and VEN unfavourable for young people under 18 years. **1st line**: psychological treatment **2nd line**: Choose from same range of AD as for adults SSRI first choice – FLX best risk/benefit balance	

Guideline	GAD	Social Phobia	Phobia (specific)	Separation Anxiety Disorder	Panic disorder	OCD	PTSD	Other
BAP (2014)-adult	**Notes:** • Psychological and drug approaches have similar efficacy in acute treatment. • Routinely combining drug and psychological approaches is not recommended for initial treatment. **1st line**: SSRI (CIT, ESCIT, PAR SERT), CBT, relaxation therapy **2nd line**: SNRI (DUL, VEN), PREG if SSRI unsuitable **3rd line**: switch to other EBT (alternate SSRI, BUS, DUL, VEN, AGOM, QUE, IMIP, HYDROX, TRAZ) **3rd line**: consider BZ if non-response to SSRI, SNRI, PREG, BUS **CONTINUATION** Up to 18 months or more in patients who have responded **RELAPSE PREVENTION** Stay on active medication 6-18 months	**Notes:** • Psychological and drug approaches have similar efficacy in acute treatment. • Routinely combining drug and psychological approaches is not recommended for initial treatment **1st line**: SSRI (ESCIT, FLX, FLUV, PAR, SERT), CBT **2nd line**: combine drug and psychological treatment **3rd line**: SSRI+BUS **4th line**: other EBT (alternate SSRI, VEN, PHEN, MOC, GABA, PREG, OLAN) **5th line**: BZ (BROM, CLONAZ) **CONTINUATION** At least 6 months for those who have responded to treatment **RELAPSE PREVENTION** Consider adding cognitive therapy with exposure after response to treatment	**1st line**: exposure techniques **2nd line**: SSRI	Treatment of adults with separation anxiety disorder has not been studied extensively.	**Notes:** • Psychological and drug approaches have similar efficacy in acute treatment. • Routinely combining drug and psychological approaches is not recommended for initial treatment. **1st line**: all SSRIs, CBT **2nd line**: combine drug and psychological treatment **3rd line**: other EBT (alternate SSRI, VEN, REBOX, CLOM, DESIP, IMIP, LOFEP, MOC, GABA, VAL, PREG, ALP, CLONAZ, DIAZ, LOR, OLAN) **CONTINUATION** At least 6 months for those who have responded to treatment **RELAPSE PREVENTION** Consider adding cognitive therapy to AD after response to treatment	**Notes:** • Psychological and drug approaches have similar efficacy in acute treatment. • Routinely combining drug and psychological approaches is not recommended for initial treatment. **1st line**: SSRIs, CLOM, CBT, CT, exposure therapy **2nd line**: consider switch between treatments in non-response **2nd line**: consider augment SSRI with AP, TOP, LAM, morphine, psychological treatment if non-response to SSRI 2nd line: consider augment CLOM with 5HT3 antagonist, AP, psychological treatment if non-response to CLOM **3rd line**: consider augment SSRI with RIL **CONTINUATION** At least 12 months in responders **1st line**: drug known to be efficacious **RELAPSE PREVENTION** **1st line**: drug known to be efficacious	**Notes:** • Psychological and drug approaches have similar efficacy in acute treatment. • Routinely combining drug and psychological approaches is not recommended for initial treatment. **1st line**: PAR, SERT, VEN, trauma-focused CBT, EMDR **2nd line**: combine drug and psychological treatment **2nd line**: consider augment AD with OLAN, RIS, PRAZ **4th line**: switch to other EBT (PAR, SERT, VEN) **CONTINUATION** At least 12 months in patients who have responded	

Guideline	GAD	Social Phobia	Phobia (specific)	Separation Anxiety Disorder	Panic disorder	OCD	PTSD	Other
BMJ Best Practice GAD (2018)- adult (child or adolescent in red ink) BMJ Best Practice OCD (2017)-adult (child or adolescent in red ink)	**Child/adolescent** • CBT is recommended before medications for moderate or persistent GAD **Notes:** • A meta-analysis found that for paediatric patients with GAD, both SSRIs and SNRIs resulted in a clinically significant improvement compared with placebo • SSRIs were associated with a greater and more rapid improvement **Adult** **Notes:** relaxation, meditation, sleep hygiene, exercise and self-help approaches can be added to all options **1st line moderate/ persistent**: CBT **2nd line**: CBT+(SSRI) **If use drug –** **1st line**: • (ESCIT, SERT, PAR, DUL, VEN, PREG, BUS) +/- (BZ[CLONAZ, DIAZ]) • CBT, CT, psychodynamic **2nd line**: SGA (espec QUE-ER) **3rd line**: IMIP	**Child/adolescent** **1st line:** CBT, family-based therapy **2nd line:** CBT + SSRI (espec SERT) **3rd line:** FLX+BZ **Adults** **1st line**: SERT, PAR, ESCIT, SNRI VEN, CBT) +/- (CLONAZ, ALP) **2nd line**: (FLX, CIT, DUL) +/- (CLONAZ, ALP) **3rd line**: • MAOI (PHEN, MOC) • GABA, PREG **4th line**: alternative AD (MIRT, CLOM) **CONTINUATION** Up to 12 months for those who have responded to treatment **COMORBID** **Depression** **1st line**: (SSRI, SNRI) +CBT **2nd line**: MAOI +CBT **Anxiety** **1st line**: (SSRI, SNRI) + CBT **2nd line**: BZ +CBT **2nd line**: MAOI +CBT **Bipolar** **1st line**: MS (LI, VAL) + CBT				**Note: If condition is severe, drug option should be used first-line with CBT** **Child/adolescent** **1st line:** CBT **2nd line:** CBT + (FLX >7years, FLUV[a] >8 years, SERT[b] >6 years) **3rd line**: increase dose **4th line**: switch to alternate SSRI from 2nd line options **Adult** **1st line mild/ moderate**: • CBT-ERP • if CBT unavailable or patient prefers drug: FLX, FLUV[a], PAR, SERT[b] • (FLX, FLUV[a], SERT[b], PAR) +CBT **2nd line mild/ moderate if CBT unavailable or patient prefers drug**: CLOM+/- CBT-ERP **3rd line part responder** – 6th-8th week: increase dose **4th line part responder** – at 12 weeks- part response: switch to alternative drug or augment SSRI+ (CLOM, RIS, HAL, QUE, OLAN) **CONTINUATION/ MAINTENANCE** No time specified - The natural course is lifelong, and patients generally require lifelong treatment. (p.39) **COMORBID** **Depression**		

Guideline	GAD	Social Phobia	Phobia (specific)	Separation Anxiety Disorder	Panic disorder	OCD	PTSD	Other
	4th line: • switch to alternate drug (+/- BZ short-term 4-6 weeks) • augment with drug from different class **CONTINUATION & RELAPSE PREVENTION** At least 1 year for those who have responded to treatment **COMORBID SUD** **1st line**: BUS (not BZ) **Depression** Not BUS, PREG	**2nd line**: (SSRI, SNRI, PHEN) +CBT +/-BZ **SUD** **1st line**: detoxify +CBT +/- (SSRI, SNRI)				**1st line**: CBT + drug option		

Guideline	GAD	Social Phobia	Phobia (specific)	Separation Anxiety Disorder	Panic disorder	OCD	PTSD	Other
NICE – SAD (2013) - cg159 - child and adolescent section NICE – GAD (2013) – cg113 -only adult – no mention child, adolescent NICE-PTSD (2005) -cg26 -child and adolescent section NICE-OCD/BDD (2005) – cg31 -child and adolescent section	**1st line**: psychological interventions **2nd line**: SERT **3rd line**: alternate SSRI or SNRI **4th line**: PREG Do not offer BZ except as short-term crisis measure	Offer individual or group CBT focused on social anxiety to children and young people with social anxiety disorder Do not routinely offer pharmacological interventions to treat social anxiety disorder in children and young people. No drug recommendations given		**1st line**: individual or group CBT, appropriate to cognitive and emotional maturity of child		**1st line mild**: guided self-help + psychoeducation and family support **1st line moderate/ severe**: CBT-ERP (include family/ carers) **1st line moderate/ severe or decline/ cannot engage CBT-ERP**: offer SSRI (FLUV[a] > 8 years, SERT[b] > 6 years) **2nd line moderate/ severe**: CBT-ERP +increase dose **3rd line moderate/ severe**: CBT-ERP+ alternate SSRI or CLOM **4th line moderate/ severe**: CBT-ERP + drug (FLUV[a] > 8 years, SERT[b] > 6 years, CLOM) + AP **CONTINUATION** Continue at least 6 months after remission **MAINTENANCE** Review regularly for 12 months after remission **COMORBID MDD** Use FLX instead of (FLUV[a], SERT[b])	Note: drug treatments should not be routinely prescribed for children and young people with PTSD **1st line**: trauma-focused CBT	**BDD** **1st line mild**: guided self-help + psychoeducation and family support **1st line moderate/ severe**: CBT-ERP (include family/ carers **1st line moderate/ severe & decline/ cannot engage CBT-ERP**: offer FLX **2nd line moderate/ severe**: CBT-ERP+FLX **3rd line moderate/ severe**: CBT-ERP +increase dose **4th line moderate/ severe**: CBT-ERP+ alternate SSRI (FLUV> 8 years, SERT> 6 years), CLOM **5th line moderate/ severe**: CBT-ERP + drug (SSRI [FLUV> 8 years, SERT> 6 years), CLOM) + AP **CONTINUATION** Continue at least 6 months after remission **MAINTENANCE** Review regularly for 12 months after remission **COMORBID MDD** Use FLX instead of FLUV, SERT

Guideline	GAD	Social Phobia	Phobia (specific)	Separation Anxiety Disorder	Panic disorder	OCD	PTSD	Other
British Columbia GPAC (2010) – child and adolescent section (pp. 64-68)	**1st line – all levels of severity**: lifestyle and parenting interventions **1st line moderate**: CBT for anxiety disorders **2nd line moderate**: CBT+ (FLX, FLUV, SERT) **2nd line severe persistent**: (FLX, FLUV, SERT) + CBT+ referral to specialist **CONTINUATION** Continue 6-12 months before considering tapering and discontinuing drugs	**1st line – all levels of severity**: lifestyle and parenting interventions **1st line moderate**: CBT for anxiety disorders **2nd line moderate**: CBT+ (FLX, FLUV, SERT) **3rd line severe persistent**: (FLX, FLUV, SERT) + referral to specialist **CONTINUATION** Continue 6-12 months before considering tapering and discontinuing drugs	**1st line – all levels of severity**: lifestyle and parenting interventions **1st line moderate**: CBT for anxiety disorders **2nd line moderate**: CBT+ (FLX, FLUV, SERT) Did not specify drugs for severe. Recommend referral to specialist	**1st line – all levels of severity**: lifestyle and parenting interventions **1st line moderate**: CBT for anxiety disorders **2nd line moderate**: CBT+ (FLX, FLUV, SERT) Did not specify drugs for severe. Recommend referral to specialist	**1st line – all levels of severity**: lifestyle and parenting interventions **1st line moderate**: CBT for anxiety disorders **2nd line moderate**: CBT+ (FLX, FLUV, SERT) Did not specify drugs for severe. Recommend referral to specialist	**1st line – all levels of severity**: lifestyle and parenting interventions **1st line moderate**: CBT for anxiety disorders **2nd line moderate**: CBT+ (FLX, FLUV[a], SERT[b]) **3rd line severe persistent**: FLX, FLUV[a], SERT[b] **CONTINUATION** Continue 6-12 months before considering tapering and discontinuing drugs	**1st line – all levels of severity**: lifestyle and parenting interventions **1st line moderate**: CBT for anxiety disorders **2nd line moderate**: CBT+ (FLX, FLUV, SERT) Did not specify drugs for severe. Recommend referral to specialist	
CPA (2006) – child and adolescent	**1st line**: CBT (e.g., CopingCAT) **2nd line severe**: • CBT alone • CBT+FLX, FLUV, SERT NOT ALP	**1st line**: CBT (e.g., CopingCAT) **2nd line severe**: • CBT alone • CBT+FLX, FLUV, PAR, VEN) **3rd line severe**: • CBT alone • CBT + SERT NOT ALP	**1st line**: CBT (e.g., CopingCAT) **2nd line severe**: No details of specific drugs listed in table 9.4. However, it is noted that SSRIs and TCAs have been trialled in youth with SSRIs better tolerated.	**Separation anxiety** **1st line**: CBT (e.g., CopingCAT) **2nd line severe**: CBT alone or CBT + (FLX, FLUV)	**1st line**: CBT (e.g., CopingCAT) **2nd line severe**: • CBT alone • CBT +BZ (CLONAZ, ALP) (Note that only level 3 evidence for BZ – uncontrolled trial)	**1st line**: CBT (specific to OCD) **2nd line severe**: • CBT alone • CBT+ (FLX, FLUV[a], SERT[b], PAR, CLOM) **3rd line**: • CBT alone • CBT+CIT **4th line**: • CBT alone • CBT+CLONAZ	**1st line**: CBT (e.g., CopingCAT) **2nd line severe**: • CBT alone • CBT + (FLX, CLOMIP) **3rd line severe**: • CBT alone • CBT + (FLUV, SERT, PAR) **3rd line severe**: • CBT alone • CBT + CIT **4th line severe**: • CBT alone • CBT + CLONAZ	**School refusal**: **1st line**: CBT (e.g., CopingCAT) **2nd line severe**: • CBT alone • CBT+IMIP **3rd line severe**: • CBT alone • CBT+CIT NOT ALP

Guideline	GAD	Social Phobia	Phobia (specific)	Separation Anxiety Disorder	Panic disorder	OCD	PTSD	Other
Katzman (2014) – child and adolescent section (pp. 39-42)	**Notes:** • For children and adolescents, psychological treatments are generally preferred over drugs. • RCTs comparing combined drug and psychological treatments in younger patients with anxiety have demonstrated efficacy equal or superior to either treatment alone. • Refer to AACAP 2007 guidelines for complete treatment recommendation **1st line**: CBT **2nd line**: CBT + (FLX, FLUV) **3rd line**: CBT + SERT NOT ALP	**Notes:** • For children and adolescents, psychological treatments are generally preferred over drugs. • RCTs comparing combined drug and psychological treatments in younger patients with anxiety have demonstrated efficacy equal or superior to either treatment alone. • Refer to AACAP 2007 guidelines for complete treatment recommendation • **1st line**: CBT **2nd line**: CBT + (FLX, FLUV, PAR, VEN) **3rd line**: CBT + (SERT, ESCIT, MIRT) NOT ALP	**Notes:** • For children and adolescents, psychological treatments are generally preferred over drugs. • RCTs comparing combined drug and psychological treatments in younger patients with anxiety have demonstrated efficacy equal or superior to either treatment alone. • Refer to AACAP 2007 guidelines for complete treatment recommendation **1st line**: CBT (exposure) No mention of any drug treatments specific to this disorder	**Notes:** • For children and adolescents, psychological treatments are generally preferred over drugs. • RCTs comparing combined drug and psychological treatments in younger patients with anxiety have demonstrated efficacy equal or superior to either treatment alone. • Refer to AACAP 2007 guidelines for complete treatment recommendations **1st line**: CBT **2nd line**: CBT + (FLX, FLUV) NOT CLONAZ	**Notes:** • For children and adolescents, psychological treatments are generally preferred over drugs. • RCTs comparing combined drug and psychological treatments in younger patients with anxiety have demonstrated efficacy equal or superior to either treatment alone. • Refer to AACAP 2007 guidelines for complete treatment recommendations **1st line**: CBT **2nd line**: CBT + (CLONAZ, ALP) (Note that only level 4 evidence for BZ)	**Notes:** • For children and adolescents, psychological treatments are generally preferred over drugs. • RCTs comparing combined drug and psychological treatments in younger patients with anxiety have demonstrated efficacy equal or superior to either treatment alone. • Refer to AACAP 2007 guidelines for complete treatment recommendations **1st line**: CBT **2nd line**: CBT + (FLX, CLOM) **3rd line**: CBT + (CIT, FLUV[a], PAR, SERT[b]) **4th line (treatment resistant)**: (FLX, CLOM, CIT, FLUV[a], PAR, SERT[b]) +ARIP **5th line (treatment resistant)**: RIL	**Notes:** • For children and adolescents, psychological treatments are generally preferred over drugs. • RCTs comparing combined drug and psychological treatments in younger patients with anxiety have demonstrated efficacy equal or superior to either treatment alone. • Refer to AACAP 2007 guidelines for complete treatment recommendations **1st line**: CBT NOT SERT as monotherapy or adjunct	**School refusal** **Notes:** • For children and adolescents, psychological treatments are generally preferred over drugs. • RCTs comparing combined drug and psychological treatments in younger patients with anxiety have demonstrated efficacy equal or superior to either treatment alone. • Refer to AACAP 2007 guidelines for complete treatment recommendations • **1st line**: CBT **2nd line**: CBT + (FLX adjunct IMIP) NOT ALP

Abbreviations organisations/institutions: AACAP, American Academy of Child and Adolescent Psychiatry; APA, American Psychological Association; BAP, British Association of Psychopharmacology; GPAC, Guidelines and protocols Advisory Committee; CPA, Canadian Psychiatric Association; NICE, National Institute for Health and Care Excellence.

Abbreviations disorders: BDD, body dysmorphic disorder; GAD, generalised anxiety disorder; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; PD, personality disorder; PTSD, post-traumatic stress disorder; SAD, separation anxiety disorder; SUD, substance use disorder.

Abbreviations treatments: AD, antidepressant; ALP, alprazolam; antiC, anticonvulsants; AP, antipsychotic; ARIP, aripiprazole; ATEN, atenolol; BUP, bupropion; BUS, buspirone; BZ, benzodiazepine; CBT, cognitive behaviour therapy; CBT-ERP, CBT with exposure and response prevention; CIT, citalopram; CLOM, clomipramine; CLONAZ, clonazepam; CLON, clonidine; CT, cognitive therapy; DESIP, desipramine; DIAZ, diazepam; EBT, evidence based treatment; ESCIT, escitalopram; ET, exposure therapy; FLX, fluoxetine; FLUV, fluvoxamine; GABA, gabapentin; GUAN, guanfacine; HAL, haloperidol; IMIP, imipramine; ISOCARB, isocarboxazid; LAM, lamotrigine; LOFEP, lofepramine; LOR, lorazepam; MAOI, monoamine oxidase inhibitor; MIRT, mirtazapine; MOC, moclobemide; MS, mood stabilisers; NEFAZ, nefazodone; NOR, nortriptyline; OLAN, olanzapine; PAR, paroxetine; PAR-CR, paroxetine controlled-release; PHEN, phenelzine; PRAZ, prazosin; PREG, pregabalin; PROP, propranolol; REBOX, reboxetine; RIL, riluzole; RIS, risperidone; SERT, sertraline; SGA, second-generation antipsychotic; SNRI, serotonin noradrenaline reuptake inhibitor; SRI, serotonin reuptake inhibitor; SSRI, selective serotonin re-uptake inhibitor; STIM, stimulant; TCA, tricyclic antidepressant; TF-therapy, trauma-focused therapy; THIOR, thioridazine; TOP, topiramate; TRAN, tranylcypromine; TRAZ, trazodone; VAL, VAL; VEN, venlafaxine.

Notes:

a. Fluvoxamine is approved in Australia by the TGA for OCD in children aged 8 and over.

b. Sertraline is approved in Australia by the TGA for OCD for children 6 years and over.

c. The authors state that at the time of writing (2007): "There [was] no empirical evidence that a particular SSRI is more effective than another for treatment of childhood anxiety disorders." (p.277). However, information on specific SSRIs for specific disorders has been extracted from Table 1 of the paper and included in the present summary.
d. Clomipramine was first approved by the FDA for children with OCD in 1989. Trials show it is superior to SSRIs but is rarely used now due to concerns with cardiac adverse events.
e. There was no good evidence from trials in children at the time of writing. The use of fluoxetine, sertraline or citalopram is suggested from a few poorly designed trials and evidence in adult studies. Some non-SSRI options as third line also have a poor evidence base for children and adolescents and are based mainly on adult studies.

11.8 Appendix 8. Psychotic disorders guideline summaries

Guideline	Prodromal/ UHR psychosis	First episode psychosis (FEP)	Maintenance/relapse prevention/early recovery	Negative symptoms un-improved with first line therapy	Treatment resistant/ late /problematic recovery
eTG Complete (2019) -child and adolescent	Antipsychotic drugs have a similar range of efficacy in adolescents to that in adults; however, adolescents appear to be more prone to a wide range of adverse effects.				
eTG Complete (2019) - adult	**1st line**: close monitoring, CBT, SSRI, Omega3, ultra-low dose AP	**1st line**: SGA (AMIS, ARIP, OLAN, PAL, QUE, RIS, ZIP): NOT CLOZ, SERTIN **2nd line**: ASEN **3rd line**: SERTIN **If** no response by 4 weeks or part-response 6-12 weeks **4th line**: Switch to alternate SGA **5th line**: CHLOR, HAL, PER, TRIFLU **COMORBID** **Symptoms of anxiety, agitation, insomnia, activation syndrome**: add DIAZ	**1st line**: use best tolerated lowest dose oral AP used in treatment FEP: minimum 2 years **If full remission**: taper cautiously over 3 months **If relapse**: continue AP for minimum 5 years **2nd line**: depot (FLUZ, FLUP, PAL, RIS-IM, ZUC) **3rd line**: OLAN-IM **COMORBID:** **Affective symptoms**: AP+ (LI, VAL, CAR)	**1st line:** AMIS, CLOZ, SGA (non-CLOZ) +AD (pref FLX) **2nd line**: CLOZ + AD (pref FLX), CLOZ + LAM	**1st line**: CLOZ **2nd line**: CLOZ+(AMIS, HAL, LAM, omega3) **2nd line**: schizoaffective: CLOZ+ (LI, VAL, LAM) **3rd line**: ECT
Orygen (2016) – child and adolescent (minimal advice, p.62)		**Note: no dosing recommendations for:** • <18-year-olds for AMIS, ARIP, OLAN, ZIP • <16-year-olds CLOZ • <15-year-olds RIS • OLAN not recommended 1st line due to weight gain **1st line:** not CLOZ; not AMIS pre-pubertal **2nd line:** OLAN **3rd line:** CLOZ			

Guideline	Prodromal/ UHR psychosis	First episode psychosis (FEP)	Maintenance/relapse prevention/early recovery	Negative symptoms un-improved with first line therapy	Treatment resistant/ late /problematic recovery
Orygen (2016)- adult Orygen (2016)- summary for practitioners	**Note**: do not prescribe AP unless at least 1 week of frank psychotic symptoms **1st line**: CBT + supportive counselling **COMORBID** Psychological and, where appropriate drug management of comorbid conditions, following relevant guidelines, should be implemented before considering drug treatment for attenuated psychotic symptoms	**Notes**: • Do not give AP within 48 hours to facilitate assessment • Take side effects profile into consideration when choosing AP • SGAs with propensity to cause weight gain (e.g., OLAN) should be avoided as 1st line treatment in children and adolescents • Trauma-focused therapies may help to reduce PTSD and psychotic symptoms • In general, avoid polypharmacy, especially multiple APs **COMORBID CONDITIONS**: • Generally, treat psychosis as primary in conjunction with treatment for comorbidity with relevant guidelines • May need to treat comorbid condition as primary (if impacts the treatment of psychosis), or simultaneously **NON-AFFECTIVE PSYCHOSIS** **1st line**: SGA (AMIS, ARIP, QUE, RIS, ZIP) **If insufficient response at 3 weeks** **2nd line**: increase dose + psychosocial interventions **If non-response at 6-8 weeks** **3rd line**: switch to alternate SGA **4th line**: OLAN **5th line**: CLOZ **COMORBID SYMPTOMS (NON-AFFECTIVE PSYCHOSIS)** **Symptoms of agitation/ depression**: +BZ (e.g., DIAZ)	**Notes:** • Use medication found effective in FEP • Continue treatment for at least 2-5 years • If incomplete remission, consider long-term treatment • Treatment response and adherence should be regularly reviewed • All young people should be seen at least weekly by case manager and fortnightly by a GP in the early recovery phase • CBT interventions may be indicated • Trauma-focused therapies may help to reduce PTSD and psychotic symptoms • SGAs as a class may be more effective than FGA in preventing relapse • Medication should be recommenced or increased at early signs of relapse • In general, avoid polypharmacy, especially multiple APs • **COMORBID CONDITIONS**: • Generally, treat psychosis as primary in conjunction with treatment for comorbidity with relevant guidelines • May need to treat comorbid condition as primary (if impacts the treatment of psychosis), or simultaneously **AFFECTIVE PSYCHOSIS** **MANIC EPISODE WITH MIXED FACTORS**	**1st line**: AMIS	**Note:** psychological interventions may improve psychopathology for treatment resistant individuals **1st line**: CLOZ **2nd line**: CLOZ+SGA **3rd line**: CLOZ+ECT

Guideline	Prodromal/ UHR psychosis	First episode psychosis (FEP)	Maintenance/relapse prevention/early recovery	Negative symptoms un-improved with first line therapy	Treatment resistant/ late /problematic recovery
		Symptoms of anxiety: +BZ (e.g., LOR) **Sleep disturbance**: +BZ (e.g., TEM) **AFFECTIVE PSYCHOSIS** **MANIC EPISODE WITH MIXED FACTORS** **1st line**: LI + SGA (RIS, QUE, ZIP, ARIP) **If non-response to MS** **2nd line**: VAL + SGA (RIS, QUE, ZIP, ARIP) **3rd line**: other MS (CAR, OXCAR, combination MS) + SGA (RIS, QUE, ZIP, ARIP) **4th line**: ECT **If non-response to SGA** Follow 1st to 5th line for affective psychosis **AFFECTIVE PSYCHOSIS** **PSYCHOTIC DEPRESSION (MDD)** **Note**: There is mounting evidence that SGAs may have a direct antidepressant effect via improvement in psychotic symptoms. **1st line**: low dose SGA (RIS, QUE, AMIS, ZIP, ARIP) +AD **If non-response to SGA** **2nd line**: switch SGA **If non-response to AD** **2nd line**: switch to other AD **3rd line**: consider MS (e.g., LI, LAM) **4th line**: ECT	**Continuation**: 2-6 months using the same medications as used in acute phase **Maintenance**: • No time period stated – can range from 1 year to indefinite • Monotherapy is gold standard, with MS considered first **AFFECTIVE PSYCHOSIS** **PSYCHOTIC DEPRESSION (MDD)** **Continuation**: medication until symptom recovery to premorbid state **Maintenance** • No time period stated – can range from 1 year to indefinite • Role of AP medications unclear • Availability and response to psychological interventions can influence decision to use medications		

Guideline	Prodromal/ UHR psychosis	First episode psychosis (FEP)	Maintenance/relapse prevention/early recovery	Negative symptoms un-improved with first line therapy	Treatment resistant/ late /problematic recovery
		AFFECTIVE PSYCHOSIS **PSYCHOTIC DEPRESSION (BD)** **1st line**: [low dose SGA (RIS, QUE, AMIS, ZIP, ARIP) +MS (pref LI, LAM)] or QUE as monotherapy **2nd line**: • **If non-response to SGA -** switch SGA • **If non-response to MS - +** other MS or (SGA+FLX) **3rd line**: ECT **COMORBID SYMPTOMS (AFFECTIVE PSYCHOSIS)** **Symptoms of agitation/ depression**: +BZ (e.g., DIAZ) **Symptoms of anxiety**: +BZ (e.g., LOR)			

Guideline	Prodromal/ UHR psychosis	First episode psychosis (FEP)	Maintenance/relapse prevention/early recovery	Negative symptoms un-improved with first line therapy	Treatment resistant/ late /problematic recovery
Orygen (2002) – booklet for GP management of early psychosis – adult and adolescent		**Notes:** Psychoeducation and psychological therapies are an essential adjunct to drug therapy **During first 24 hours of observation** **Agitation/ aggression:** DIAZ **Anxiety**: LOR **NON-AFECTIVE PSYCHOSIS** **1st line**: OLAN, RIS, QUE If no response after 6-7 weeks **2nd line**: switch to alternative SGA **AFFECTIVE PSYCHOSIS** **1st line:** (LI, VAL) + (OLAN, RIS, QUE) **2nd line**: • **If no response to MS** - switch to alternative MS (LI, VAL, CAR) + SGA • **If no response to SGA** - MS + switch to alternative AP (OLAN, RIS, QUE, CHLOR) **If sedation needed**: **Add** long-acting BZ (DIAZ, LOR), low-dose CHLOR	**Maintenance** Continue at least 12 months after FEP Continue at least 2 years if high risk category	SGA appear to have better effect on negative symptoms and cognitive dysfunction	

Guideline	Prodromal/ UHR psychosis	First episode psychosis (FEP)	Maintenance/relapse prevention/early recovery	Negative symptoms un-improved with first line therapy	Treatment resistant/ late /problematic recovery
NICEcg155 (2013) -children and adolescents <18 years	**1st line**: CBT+/- family intervention **COMORBID** Offer treatments recommended by NICE for anxiety disorders, depression, emerging PDs, substance misuse	**1st line:** oral AP + (family intervention+ individual CBT) **1st line: 15-17 years and intolerant to RIS**: ARIP **1st line: non-drug** (family intervention + CBT for young person)- • Advise that psychological interventions are more effective with drugs • Allow 1 month or less before treatment review	**Notes**: • Review AP annually • Do not routinely offer intermittent dosage maintenance unless unwilling to take continuous drug, or contra-indicated **Relapse** **1st line**: oral AP or review existing drug + (family intervention and individual CBT for young person) **Continuation**: 1-2 years		**Note:** First review: • Diagnosis • Adherence to medication • Adequacy of engagement with psychological interventions • Other possible causes of non-response (e.g., substance misuse, concurrent medications, physical illness) If not respond to an adequate trial (6-8 weeks) of at least 2 different APs, consider CLOZ **1st line**: trial 2 different APs **2nd line**: CLOZ if not response to 2 APs **2nd line**: CLOZ+AP (with effects that do not compound effects of CLOZ)- 8-10 weeks

Guideline	Prodromal/ UHR psychosis	First episode psychosis (FEP)	Maintenance/relapse prevention/early recovery	Negative symptoms un-improved with first line therapy	Treatment resistant/ late /problematic recovery
AACAP (2013) – child and adolescent	There are no interventions with conclusive evidence for treatment	**Note:** Psychological interventions and psychoeducation should be provided in combination with drug therapy[a] **1st line**: AP[b] (except CLOZ) **2nd line**: OLAN **COMORBID SYMPTOMS** **Symptoms of depression, negative symptoms**: +AD **Symptoms of aggression, mood instability**: +MS **Symptoms of anxiety, insomnia**: +BZ	**Notes**: • Most youth with early onset schizophrenia remain chronically impaired, even with treatment. • Psychological interventions[a] and psychoeducation should be provided in combination with drug therapy **Maintenance**: • Use lowest effective dose to minimise adverse effects • Small number of youths may be able to discontinue APs – need to monitor long term • Provide psychological interventions[a] to reduce risk of relapse • Address comorbid conditions (e.g., Substance abuse) to reduce risk of relapse • Provide psychoeducation for all conditions		**Note**: Psychological interventions[a] and psychoeducation should be provided in combination with drug therapy **1st line**: CLOZ + PT + psychoeducation **2nd line: severe or catatonic**: ECT

Guideline	Prodromal/ UHR psychosis	First episode psychosis (FEP)	Maintenance/relapse prevention/early recovery	Negative symptoms un-improved with first line therapy	Treatment resistant/ late /problematic recovery
BMJ Best Practice (2018) – adult (child or adolescent in red ink)	**1st line**: CBT **COMORBID** Screen for anxiety, depression, substance abuse and PDs and treat according to guidelines	There is currently a lack of trial data to guide the choice of treatment in children and adolescents with first onset of psychosis. Such data is crucial, as extrapolation from adult studies cannot necessarily be assumed. Since all psychotropic drugs are associated with important adverse effects, a careful risk/benefit analysis is essential before initiating treatment in children and adolescents. (p.25) **Notes:** These recommendations are for acute episodes, which may be FEP, psychotic decompensation or antipsychotic resistance FEP should be started on lower doses **1st line: FEP**: AP (RIS, PAL, QUE, ZIP, ARIP, ILOP[c], ASEN, LUR, BREX, ZOT, AMIS, SERTIN) **2nd line: FEP**: OLAN, CARIP, CLOZ **3rd line: FEP**: HAL, FLUZ, PERPHEN, LOX (inhaled) **If decompensation or AP-resistant** **1st line**: increase dose or switch to alternate AP **COMORBID** **Symptoms of aggression or suicidality**: **1st line**: CLOZ **1st line: extreme agitation or violence**: (OLAN-IM, ZIP-IM) +/- (LOR-IM, ECT)	**Notes**: • These recommendations are for ongoing treatment • SGA appear to be better than FGA for preventing relapse • Medications should be used in conjunction with psychosocial interventions[d] • LAIs may be useful if history of poor adherence **Maintenance** • For multiple episodes, maintain for a minimum of 2-5 years • In severe cases maintenance should be lifelong • Sometimes combination AP is given to improve symptoms, but there is no evidence for relapse prevention. **1st line**: AP (RIS, PAL, QUE, ZIP, ARIP, ILOP[c], ASEN, LUR, BREX, ZOT, AMIS, SERTIN, OLAN, PENFLUR) **2nd line**: CARIP, CLOZ **3rd line**: HAL **4th line**: FLUZ, PERPHEN **5th line**: ARIP-IM, ARIP-ER-IM, RIS-IM, PAL-IM, OLAN-IM **6th line**: HAL-IM, FLUZ-IM **COMORBID** **Symptoms of aggression or suicidality**: **1st line**: CLOZ **1st line: extreme agitation or violence**: (OLAN-IM, ZIP-IM) +/- (LOR-IM, ECT)	If prominent negative symptoms **1st line**: • + (FLX, TRAZ, MIRT, MINO, ONDAN, GINK) • SGA + (DON, RIV, GAL, MEM) • RIS + MINO	**Note**: • If no response to 2 different SGAs trial CLOZ for at least 8 weeks • If no response by 6 months, change to alternate medication **1st line:** try 2 different APs **2nd line**: CLOZ if no response to 1st line APs **3rd line**: CLOZ + AMIS **4th line**: CLOZ + ECT

Guideline	Prodromal/ UHR psychosis	First episode psychosis (FEP)	Maintenance/relapse prevention/early recovery	Negative symptoms un-improved with first line therapy	Treatment resistant/ late /problematic recovery
		2nd line: extreme agitation or violence: LOX-inhaled+/- (LOR-IM, ECT) **Bipolar** **1st line**: AP+ (LI, CAR, VAL) **MDD** **1st line**: +AD (FLX, PAR, SERT, MIRT) **Anxiety** **1st line**: + (ALP, CLONAZ, DIAZ, BUS)	**2nd line: extreme agitation or violence**: LOX-inhaled+/- (LOR-IM, ECT) **Bipolar** **1st line**: AP+ (LI, CAR, VAL) **MDD** **1st line**: +AD (FLX, PAR, SERT, MIRT) **Anxiety** **1st line**: + (ALP, CLONAZ, DIAZ, BUS)		
WFSBP (2017) - adult		**Note:** A combination of AP and psychosocial interventions must be offered to every patient with schizophrenia **1st line**: OLAN, RIS, QUE, HAL (not CLOZ) If no response after 2-8 weeks **2nd line**: Switch AP (do not switch from FGA to FGA) **COMORBID** **Depression symptoms** **1st line**: AMIS, ARIP, CLOZ, OLAN, QUE **MDD (including suicidality)** **1st line**: +AD, LI **SUD** **Non-nicotine**: treat in specialised centres **Nicotine: after stabilise psychosis** **1st line**: nicotine replacement therapy **2nd line**: + BUP	**Note:** A combination of AP and psychosocial interventions must be offered to every patient with schizophrenia **Maintenance**: • SGAs are preferred over FGAs • LAIs have good evidence for maintenance (ARIP-IM, RIS-IM, PAL-IM, OLAN-IM, FLUP-IM, FLUZ-IM, HAL-IM, PERPH-IM, ZUC-IM) • Maintain at least 1 year after FEP • Maintain at least 2-5 years after multiple, recurrent episodes • Treatment should be continuous	**Note:** A combination of AP and psychosocial interventions must be offered to every patient with schizophrenia SGAs preferred for prominent negative symptoms **1st line**: • AMIS, OLAN • AP + MIRT **2nd line**: QUE, ZIP	**Note:** A combination of AP and psychosocial interventions must be offered to every patient with schizophrenia **1st line**: CLOZ

Guideline	Prodromal/ UHR psychosis	First episode psychosis (FEP)	Maintenance/relapse prevention/early recovery	Negative symptoms un-improved with first line therapy	Treatment resistant/ late /problematic recovery
SIGN (2013) - adult		**Note:** • CBT for psychosis should be given to all individuals diagnosed with schizophrenia whose symptoms have not adequately responded to APs • LAI should be offered to individuals that request it, or for patients with poor adherence **1st line**: AP (consider benefits and harms in choosing) If no response after 4 weeks, or after 8 weeks for part response **2nd line**: switch to alternative AP **COMORBID** **Symptoms of aggression/ hostility** **1st line**: CLOZ Symptoms of cognitive dysfunction **1st line**: ACH inhibitors **Anxiety** **1st line**: sedative AP **2nd line**: treat with appropriate guidelines	**Note:** • CBT for psychosis should be given to all individuals diagnosed with schizophrenia whose symptoms have not adequately responded to APs • LAI should be offered to individuals that request it, or for patients with poor adherence **Maintenance**: After FEP: continue at least 18 months Chronic or multiple episode psychosis: continue at least 2 years **1st line**: medication used for last acute episode **2nd line**: AMIS, OLAN, RIS, low potency CHLOR **COMORBID** **Symptoms of depression** **1st line**: SGA	**Note:** • CBT for psychosis should be given to all individuals diagnosed with schizophrenia whose symptoms have not adequately responded to APs • LAI should be offered to individuals that request it, or for patients with poor adherence **1st line**: +AD, LAM, AMIS	**Note:** • CBT for psychosis should be given to all individuals diagnosed with schizophrenia whose symptoms have not adequately responded to APs • LAI should be offered to individuals that request it, or for patients with poor adherence **1st line**: CLOZ **2nd line**: CLOZ + (SGA, LAM)

Guideline	Prodromal/ UHR psychosis	First episode psychosis (FEP)	Maintenance/relapse prevention/early recovery	Negative symptoms un-improved with first line therapy	Treatment resistant/ late /problematic recovery
Tsuang and Fong (2005)		**Dual diagnosis schizophrenia and SUD** • FGA not effective • Some positive evidence for RIS, OLAN, HAL-IM, FLUZ-IM **Limited evidence for individual addictions** • **Alcoho**l: CHLOR, CLONAZ, DISUL. NAL • **BZ:** Some evidence for long-acting BZ (CHLOR, CLONAZ) • **Opioid:** CLON, METH, BUP • **Stimulant:** HAL, BROMO, TCA • **Cocaine:** AP+TCA, SEL, MAZ, AMAN • **Nicotine:** nicotine replacement, CLON, CLOZ			

Guideline	Prodromal/ UHR psychosis	First episode psychosis (FEP)	Maintenance/relapse prevention/early recovery	Negative symptoms un-improved with first line therapy	Treatment resistant/ late /problematic recovery
BAP (2011) - adult	**Notes**: If APs used should be short-term, very low dose and carefully monitored **1st line**: watchful waiting **2nd line**: CBT	**Notes:** • All APs are equally efficacious. The choice depends on an individual risk/ harm analysis and previous medication tolerance (if acute recurrence) • Depot formulations should be considered if adherence is a problem • Consider CLOZ if persistent symptoms of aggression or hostility **1st line**: AP **2nd line**: switch to alternate AP **COMORBID SUD** • **While psychosocial approaches will be the mainstay, drug should be offered where possible.** • **Consider CLOZ as alternative option as has been reported to be associated with reducing a range of substance misuse problems** **Nicotine:** + nicotine dependence treatments (e.g., patches, VAR, BUP) **Alcohol:** AP+(ACAM, NAL) **Cocaine**: AP + psychosocial approaches **Opioid:** AP + METH **Other illicit drugs**: none recommended except BZ to assist with insomnia during withdrawal **Associated suicidality/ aggression/ hostility:** **1st line**: CLOZ **2nd line**: CLOZ + (BZ) **3rd line**: CLOZ + (LI, VAL, CAR)	**Notes**: AP should be taken continuously **Continuation**: after FEP: 1-2 years **Maintenance**: **1st line**: AP with prior effective response -at least 6 months to 2 years	**1st line**: AP **2nd line**: • AP+ SSRI • **If CLOZ**: +LAM	**1st line**: CLOZ If inadequate response after trial of CLOZ 3-6 months **2nd line**: CLOZ + AP **3rd line**: combined high-dose AP **4th line**: ECT

Abbreviations organisations/institutions: AACAP, American Academy of Child and Adolescent Psychiatry; APA, American Psychological Association; BAP, British Association of Psychopharmacology; eTG Complete, Electronic Therapeutic Guidelines Complete; NICE, National Institute for Health and Care Excellence; SIGN, Scottish Intercollegiate Guidelines Network; WFSBP, World Federation of Societies of Biological Psychiatry.
Abbreviations disorders: FEP, first episode psychosis; MDD, major depressive disorder; PD, personality disorder; PTSD, post-traumatic stress disorder.
Abbreviations treatments: ACAM, acamprosate; ACH, acetylcholine; AD, antidepressant; ALP, alprazolam; AMAN, amantadine; AMIS, amisulpride; AP, antipsychotic; ARIP, aripiprazole; ASEN, asenapine; BROMO, bromocriptine; BUP, bupropion; BUS, buspirone; BZ, benzodiazepine; CAR, carbamazepine; CARIP, cariprazine; CBT, cognitive behaviour therapy; CHLOR, chlorpromazine; CLONAZ, clonazepam; CLON, clonidine; CLOZ, clozapine; DIAZ, diazepam; DISUL, disulfiram; DON, donazepine; ECT, electro-convulsive therapy; FGA, first generation antipsychotic; FLX, fluoxetine; FLUV, fluvoxamine; FLUP, flupenthixol decanoate; FLUZ, fluphenazine; GAL, galantamine; GINK, ginkgo; HAL, haloperidol; ILOP, iloperidone; IM, intra-muscular (depot); LAI, long acting injectable; LAM, lamotrigine; LOR, lorazepam; LOX, loxapine; LUR, lurasidone; MAZ, mazindol; MEM, memantine; METH, methadone; MINO, minocycline; MIRT, mirtazapine; MS, mood stabilisers; NAL, naltrexone; ONDAN, ondansetron; OLAN, OLAN; OXCAR, oxcarbazepine; PAL, paliperidone; PAR, paroxetine; PENFLUR, penfluridol; PER, periciazine; PERPHEN, perphenazine; PHEN, phenelzine; PT, psychological therapy; QUE, quetiapine; RIS, risperidone; RIV, rivastigmine; SGA, second-generation antipsychotic; SEL, selegeline; SERT, sertraline; SERTIN, sertindole; SSRI, selective serotonin re-uptake inhibitor; SUL, sulpiride; TCA, tricyclic antidepressant; TEM, temazepam; THIOR, thioridazine; TRAZ, trazodone; TRIFLU, trifluoperazine; VAL, VAL; VAR, varenicline; ZIP, ziprasidone; ZOT, zotepine; ZUC, zuclopenthixol.
Notes:
a. Psychological interventions include CBT, social skills training, cognitive remediation and family interventions, problem-solving skills and as well as basic life skills training.
b. As at the time of publication of this guideline, RIS, ARIP, QUE, PAL, OLAN and HAL are approved by the FDA for treating schizophrenia in youth 13 years and over. OLAN is not preferred as first line due to problems with weight gain.
c. In 2017 the EMA refused to approve iloperidone due to significant risk of QT prolongation. However, it is available in the US and some European countries. It has been rejected by the TGA in 2011 and is not available in Australia.
d Psychosocial interventions include, CBT, cognitive rehabilitation, motivational interviews, cognitive remediation, family interventions, psychoeducation, assertiveness training.

11.9 Appendix 9. Adverse event monitoring recommendations in guidelines for psychotic disorders

Medication	eTG Complete (2019)	Orygen (2016)	BMJ Best practice
AP	Monitor for: **Movement disorders** (akathisia, EPS) • Highest risk: FGA • Treat acute dystonias with benztropine • Treat Parkinsonism with benztropine (1st line) or benzhexol (2nd line) • Treat akathisia with ➢ **1st line**: propranolol ➢ **2nd line**: diazepam ➢ **3rd line**: cyproheptadine, mirtazapine, clonidine **Weight** Highest risk SGA: OLAN, CLOZ Highest risk FGA: CHLOR Lowest risk SGA: AMIS, ARIP, ZIP Lowest risk FGA: HAL, TRIFLU • Measure baseline and every visit while APs are being taken • Measure height, weight, BMI • For adolescents use BMI-for-age percentiles • Treat significant weight gain: ○ >5% increase in BMI during first 3 months ○ Child falling into overweight category (85th to 95th BMI percentile) with the presence of one other obesity-related complication (e.g., hypertension, dyslipidaemia, hyperglycaemia) ○ Child entering into obesity (95th BMI percentile) **Glucose** • Baseline fasting glucose • 3 months – if abnormal and BMI stable every 6-12 months • If high risk for metabolic adverse effects – monitor more regularly **Lipids** • Baseline serum lipids • 3 months – if abnormal and BMI stable every 6-12 months • If high risk for metabolic adverse effects – monitor more regularly **Sedation**	Monitor for: **Metabolic parameters**: see heti.nsw.gov.au **Weight**: monitor 1-2 weekly for first 6-8 weeks after start or change of drug Intensify nutritional counselling, review/ switch medication if: • Increased BMI>84th centile ○ BMI>94th centile: consider metformin • weight >5kg over 3 months • waist/height ratio>=0.5 • waist increase >5cm over 3 months (monitor quarterly) • >89 centile for SBP or DBP (monitor baseline, then 3, 6, 12 months) • FPG>=5.6mmol/L (monitor baseline then 3, 6, 12 months) ○ If FPG 5.6-6.9mmol/L: OGTT, consider metformin • RPG>=11.1 mmol/L (monitor baseline then 3, 6, 12 months) • HbA1c>=42mmol/mol (>=6%) (monitor baseline then 3, 6, 12 months) ○ If HbA1c 42-47mmol/L: OGTT • Total cholesterol>=5.2mmol/L (monitor baseline then 3, 6, 12 months) • LDL>=3.4mmol/L (monitor baseline then 3, 6, 12 months) • HDL<=1.03mmol/L (monitor baseline then 3, 6, 12 months) • TRIG>=1.7mmol/L (monitor baseline then 3, 6, 12 months) • Polycystic ovary syndrome (delayed menarche, no periods for 3 months, acne, hirsutism) ○ Check prolactin, consider metformin	Monitor for: **Movement disorders** EPS (akathisia, parkinsonism, dystonia) **Weight** • Measure weight and waist circumference every visit • Increase of 1 point on BMI – consider alternative AP **Glucose** • Baseline fasting glucose • Every 4 months and then yearly • If weight gain present – every 4 months • If abnormality present – manage with antidiabetic therapy **Lipid profile** • Baseline • If LDL normal – every 2 years • If LDL>3.37mmol/L – every 6 months • If abnormality present – manage with lipid lowering therapy **Hyperprolactinaemia** (galactorrhoea, gynaecomastia, amenorrhoea) **Postural hypotension** **Anticholinergic effects** **ECG changes (monitor if family history)** QT prolongation T-wave flattening Torsades de Pointes **Neutropenia**

Medication	eTG Complete (2019)	Orygen (2016)	BMJ Best practice
	○ FGA (CHLOR, PER) ○ SGA (OLAN, QUE) • Hyperprolactinaemia ○ AMIS, RIS, CHLOR, HAL, PERIC, TRIFLU • Cardiometabolic ○ OLAN, QUE, SERTIN, ZIP, CHLOR, HAL • Orthostatic hypotension • QTc prolongation **Hyperprolactinaemia**: monitor **Neuroleptic Malignant Syndrome (NMS)**: discontinue drug and consider BZ for mild cases		
AMIS	**Adverse events** Hyperprolactinaemia	**Adverse events/ medication effects** Hyperprolactinaemia EPS Akathisia Insomnia Anxiety	
ASEN	**Adverse events** Oral hypoesthesia	**Adverse events/ medication effects** Weight gain (moderate) Akathisia Sedation Somnolence Hypoesthesia	
ARIP	**Adverse events** Agitation	**Adverse events/ medication effects** EPS Akathisia Tremor Anxiety Sleep disturbance	
CHLOR	**Adverse events** Sedation Anticholinergic effects Movement disorders Orthostatic hypotension Weight gain Cardiometabolic effects Hyperprolactinaemia		

Medication	eTG Complete (2019)	Orygen (2016)	BMJ Best practice
CLOZ	**Monitor** **Neutrophil counts**: first 18 weeks **Cardiac parameters**: body temperature, pulse, blood pressure, respiratory rate C-reactive protein: weekly for 1st 4 weeks ECG: baseline, then repeated based on results **Metabolic parameters**: see description for AP above	**Adverse events/ medication effects** Weight gain (high) Metabolic syndrome Diabetic complications Cardiovascular Respiratory arrest Akathisia Bradykinesia Hypersalivation Sedation Cognitive deficits	**Monitor for neutrophil count** • Weekly first 6 months • Every 2 weeks for next 6 months • Monthly after 6 months Monitor plasma levels
HAL	**Adverse events** QTc prolongation Movement disorders Hyperprolactinaemia		
LUR		**Adverse events/ medication effects** EPS Akathisia Somnolence Insomnia Nausea	
OLAN	**Adverse events** Sedation Weight gain Cardiometabolic effects	**Adverse events/ medication effects** Weight gain (high) Metabolic syndrome Diabetic complications Akathisia Tremor Insomnia Anxiety Cognitive deficits	
PAL	**Adverse events** Hyperprolactinaemia Orthostatic hypotension		
PER	**Adverse events** QTc prolongation Anticholinergic effects Hyperprolactinaemia		
QUE	**Adverse events** Sedation Weight gain Cardiometabolic effects	**Adverse events/ medication effects** Weight gain (moderate) Hypotension Somnolence Akathisia Tremor	

Medication	eTG Complete (2019)	Orygen (2016)	BMJ Best practice
RIS	**Adverse events** Hyperprolactinaemia Orthostatic hypotension	**Adverse events/ medication effects** Hyperprolactinaemia EPS Weight gain (moderate) Dystonia TD Insomnia Anxiety Sexual dysfunction	
SERTIN	**Adverse Events** **QTc prolongation** If family history of heart problems • ECG before and after starting treatment		
TRIFLU	**Adverse events** Movement disorders Hyperprolactinaemia		
ZIP	**Adverse Events** **QTc prolongation** If family history of heart problems • ECG before and after starting treatment	**Adverse events/ medication effects** QTc prolongation Akathisia Tremor Somnolence	
ZOT		**Adverse events/ medication effects** ECG changes Weight gain (moderate) Dystonia Parkinsonism Somnolence	

Abbreviations for metabolic parameters: BMI, body mass index; DBP, diastolic blood pressure; ECG, electrocardiogram; EPS, extrapyramidal symptoms; FPG, fasting plasma glucose; HbA1c, haemoglobin 1c; HDL, high density lipoprotein; LDL, low density lipoprotein; OGTT, oral glucose tolerance test; RPG, random plasma glucose; SBP, systolic blood pressure; TD, tardive dyskinesia; TRIG, triglycerides.

Abbreviations treatments: AMIS, amisulpride; AP, antipsychotic; ARIP, aripiprazole; ASEN, asenapine; CARIP, cariprazine; CHLOR, chlorpromazine; CLOZ, clozapine; FGA, first generation antipsychotic; FLUP, flupenthixol decanoate; FLUZ, fluphenazine; HAL, haloperidol; LUR, lurasidone; OLAN, OLAN; PAL, paliperidone; PER, periciazine; QUE, quetiapine; RIS, risperidone; SGA, second-generation antipsychotic; SERTIN, sertindole; TRIFLU, trifluoperazine; ZIP, ziprasidone; ZOT, zotepine.

11.10 Appendix 10. Autism spectrum disorders guideline summaries

Guideline	Core ASD symptoms	Maladaptive behaviours/ comorbidities associated with ASD
eTG Complete (2019)	**Note:** An experienced paediatrician or child psychiatrist should confirm diagnosis and supervise any drug treatments **1st line**: Focus on special education, behaviour modification programs, family support, respite	**Note:** when APs are used, monitor every 3-6 months to assess efficacy and determine need for continuation **Maladaptive behaviours associated with ASD** (e.g., aggression, temper tantrums, stereotypies hyperactivity, distractibility) **1st line**: Focus on special education, behaviour modification programs, family support, respite **2nd line:** RIS[a] + non-drug management programs **3rd line: (**PER, TRIFLU) + non-drug management programs
AACAP (2014)	**Note:** Drug interventions may increase the ability of persons with ASD to benefit from other interventions and remain if less restrictive environments. **1st line**: structured educational, communication and behavioural interventions	**Note:** Drug interventions may increase the ability of persons with ASD to benefit from other interventions and remain if less restrictive environments. **Challenging behaviours** - irritability, aggression, severe tantrums **1st line**: structured educational, communication and behavioural interventions **2nd line**: (RIS, ARIP) + parent training **3rd line**: RIS[b], ARIP[b] **COMORBID ANXIETY** **1st line**: structured educational, communication and behavioural interventions **2nd line**: CBT (in high functioning ASD) **3rd line**: pharmacological (not specified)
NICE cg170 (2013)	**Note:** Do not use AP, AD or antiC for core symptoms of ASD **1st line**: **no coexisting mental health or behavioural problem**: Psychosocial intervention (e.g., social-communication and pay-based interventions)	**Note:** • AP medication should be prescribed and monitored by a paediatrician or psychiatrist • Review medication after 3 to 4 weeks • Stop medication if no improvement after 6 weeks **1st line**: challenging behaviours: Psychosocial intervention **2nd line**: challenging behaviours: AP **COMORBID CONDITIONS:** **ANXIETY**: **1st line**: CBT Offer psychosocial and drug interventions in line with NICE guidelines for the condition

Guideline	Core ASD symptoms	Maladaptive behaviours/ comorbidities associated with ASD
BMJ Best practice (2018)	**Note**: No medication is available to treat ASD core difficulties **Children** **1st line:** behavioural (e.g. ABA) and educational interventions **Adolescents** **1st line**: social skills training and ABA	**Notes**: • Drugs should only be used when other non-drug interventions are insufficient, or the risk to the person or others is very severe(e.g., violence, aggression, irritability, self-injury) • Should be initiated by specialist **CHILDREN** **Challenging behaviours** **1st line:** behavioural (e.g. ABA) and educational interventions **With repetitive behaviours**: **2nd line**: BUS **With hyperactivity:** **2nd line:** MPHEN, ATOM **With sleep disturbances**: **2nd line**: MEL **With depression or anxiety**: FLX **ADOLESCENTS** **With aggression, sexualised behaviours** **2nd line**: RIS, ARIP (older children) **3rd line**: OLAN **4th line**: QUE, HAL **With obsessive/ repetitive behaviour** **2nd line**: FLX, FLUV **COMORBID DISORDERS**: epilepsy, Tourette's, anorexia nervosa, schizophrenia, MDD, anxiety disorders: Treat as indicated with comorbid condition

Guideline	Core ASD symptoms	Maladaptive behaviours/ comorbidities associated with ASD
BAP (2017)	**Note**: There is no evidence for any medication for core symptoms	**Note**: • APs have only modest effect on repetitive behaviours • Non-drug treatments are beyond scope of this guideline **With irritability** **1st line**: RIS[ab], ARIP[c] (preferred if risk of hyperprolactinaemia) **COMORBID** **MOOD DISORDERS**: SSRIs (Follow BAP guidelines for depression) **ANXIETY, OCD**: cautiously follow BAP guidelines for anxiety **1st line**: cautious SSRI trial **2nd line**: RIS **SLEEP**: **1st line**: MEL + behavioural intervention **2nd line**: BZ (but not prolonged use) **ADHD**: **1st line**: MPHEN **2nd line**: ATOM, CLON, GUAN **TICS**: case by case basis (Possibly CLON, CUAN)
SIGN (2016)	**Note**: There is no evidence for any medication for core symptoms **1st line**: behavioural and educational interventions	**Note**: • Medications may be considered to manage co-existing psychiatric and neurodevelopmental conditions. • Medications should be prescribed by doctors with appropriate training • Review AP medication after 3 to 4 weeks, and discontinue after 6 weeks if no response **1st line**: behavioural and educational interventions **With irritability/ hyperactivity**: **2nd line:** ARIP (for up to 8 weeks – not long-term) **With challenging/ repetitive behaviours** **2nd line**: RIS **With attention difficulties/ hyperactivity** **2nd line**: MPHEN **With depression**: **2nd line**: SSRI **3rd line**: TCA **With sleep problems**: **2nd line**: MEL + behavioural intervention

Guideline	Core ASD symptoms	Maladaptive behaviours/ comorbidities associated with ASD
NZ (2016)[d]	**Note**: • Comprehensive treatment plans include behavioural, educational, psychosocial and communication interventions, and the suitability (or not) of medication • No medications have been identified that cure ASD • Some medications can be used for core symptoms by appropriately experienced clinicians who keep up to date with current information in relation to safety and efficacy of drugs they prescribe **1st line**: educational, psychological and behavioural approaches **2nd line**: social relatedness/ emotional reactivity: SSRI **2nd line**: stereotypies: SSRI, AP **2nd line**: repetitive/ compulsive behaviours: SSRI **2nd line**: insufficient evidence – may possibly be used by experienced clinicians: CLON, BZ, A-HIST	**Note**: In severe or life-threatening situations medication may be the best therapy **1st line**: educational, psychological and behavioural approaches **With aggression, irritability, self-injurious behaviour** **2nd line**: RIS **3rd line**: ARIP **4th line:** HAL **5th line**: THIOR **With anxiety/ obsessive symptoms** **2nd line**: SSRI (not CIT for repetitive behaviours) **COMORBID ADHD**: **2nd line**: MPHEN, DEX, CLON **With sleep problems**: **2nd line**: MEL+ behavioural strategies **COMORBID bipolar:** manage in consultation with experienced psychiatrist **2nd line:** MS

Guideline	Core ASD symptoms	Maladaptive behaviours/ comorbidities associated with ASD
AAP (2007)	**1st line**: Behavioural techniques and environmental modification	**Note**: Consider medications to target specific symptoms which interfere with learning and socialisation, comorbid psychiatric diagnoses or suboptimal response to non-drug treatments[e] **1st line**: Behavioural techniques and environmental modification **Repetitive behaviour/ OCD symptoms:** **2nd line**: FLX, FLUV, RIS, VAL **3rd line**: CIT, ESC, PAR, SERT, ARIP, OLAN, QUE, ZIP **Hyperactivity, impulsivity, inattention:** **2nd line**: MPHEN, CLON, ATOM, RIS, OLAN **3rd line**: DEX, MSA, GUAN, ARIP, QUE, ZIP **Aggression, explosive outbursts, self-injury:** **2nd line**: RIS, CLON, FLX, FLUV **3rd line**: ARIP, OLAN, QUE, ZIP, GUAN, LEV, TOP, VAL, CIT, ESC, PAR, SERT, PROP, NAD[f], MET, PIN **Sleep dysfunction:** **2nd line**: MEL, DIP, CLON, GUAN, HYD[g], MIRT **Anxiety:** **2nd line**: FLX, FLUV **3rd line**: CIT, ESC, PAR, SERT, BUS, MIRT **Depression:** **2nd line**: FLX, FLUV **3rd line**: CIT, ESC, PAR, SERT, MIRT **COMORBID DIAGNOSES**: refer to guideline to treat condition
Malow (2012) – Insomnia in ASD		**Note**: medication can be considered if sleep education and non-drug treatments are insufficient **Sleep problems:** **1st line:** sleep education **2nd line**: MEL **3rd line**: RIS, MIRT, CLON
Mahajan (2012) – ASD with ADHD symptoms		**Note**: Most drugs for ADHD have not been studies in sufficient depth **1st line**: Optimise medical, educational and behavioural interventions before trialling drugs for ADHD **2nd line**: MPHEN, short-acting **3rd line: MPHEN** – long-acting **4th line**: MSA, ATOM, GUAN, CLON, RIS, ARIP

Guideline	Core ASD symptoms	Maladaptive behaviours/ comorbidities associated with ASD
Vasa (2016) – ASD with anxiety		**Note:** • Many children with ASD have atypical anxiety symptoms that do not meet disorder categories in the DSM • First address psychosocial stressors and suboptimal behavioural and educational supports **1st line**: psychoeducation and coordination of care **2nd line**: modified CBT **3rd line**: SERT, FLX, CIT, ESC **3rd line**: Anxiety with sleep disturbance: MEL, CLON, TRAZ **3rd line**: Anxiety with physiological symptoms: CLON, GUAN, PROP **3rd line**: Anxiety with behavioural dysregulation: CLON, GUAN **3rd line**: Situational anxiety: LOR, PROP
McGuire (2016) – ASD with irritability and problem behaviour		**Note:** If using drugs • Implement and monitor a treatment plan • Expect some response within 4 to 8 weeks • Re-evaluate plan every 3 months • After 12 months symptom free consider discontinuing psychiatric drugs **1st line**: assess and address any psychosocial stressors, comorbid psychiatric and physical disorders before using medications for behaviour problems. Only use drugs if severe and dangerous. **2nd line**: RIS, ARIP **3rd line**: N-acetylcysteine, CLON **With sleep problems:** **1st line**: sleep hygiene strategies **2nd line**: MEL

Abbreviations: DSM, Diagnostic and statistical manual of mental disorders.
Abbreviations organisations/institutions: AACAP, American Academy of Child and Adolescent Psychiatry; AAP, American Academy of Pediatrics; BAP, British Association of Psychopharmacology; eTG Complete, Electronic Therapeutic Guidelines Complete; NICE, National Institute for Health and Care Excellence; NZ, New Zealand
Abbreviations disorders: ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorder.
Abbreviations treatments: ABA, applied behavioural analysis; AP, antipsychotic; ARIP, aripiprazole; ATOM, atomoxetine; BUS, buspirone; BZ, benzodiazepine; CBT, cognitive behaviour therapy; CIT, citalopram; CLON, clonidine; DEX, dexamphetamine/dexamfetamine; DIP, diphenhydramine; ESC, escitalopram; FLX, fluoxetine; FLUV, fluvoxamine; GUAN, guanfacine; HAL, haloperidol; HYD, hydroxyzine; LEV, levetiracetam; LOR, lorazepam; MEL, melatonin; METOP, metoprolol; MIRT, mirtazapine; MPHEN, methylphenidate; MS, mood stabilisers; MSA, mixed salts amphetamines; NAD, nadolol; OLAN, OLAN; PAR, paroxetine; PER, periciazine/periciazine; PIN, pindolol; PROP, propranolol; QUE, quetiapine; RIS, risperidone; SERT, sertraline; SSRI, selective serotonin re-uptake inhibitor; TCA, tricyclic antidepressant; THIOR, thioridazine; TOP, topiramate; TRAZ, trazodone; TRIFLU, trifluoperazine; VAL, VAL; ZIP, ziprasidone.
Notes:
a. Risperidone is approved in Australia for the treatment of behavioural disorders associated with autism in children.
b. Risperidone and aripiprazole have been approved by the FDA for the treatment of irritability, consisting primarily of aggression, and severe tantrums.
c. Aripiprazole has been approved by the FDA for treatment of irritability in children with ASD.

d. The New Zealand guideline is considered a “Living Guideline”. This ensures that the guideline is regularly updated to reflect new research findings and changing user needs. Every year since 2009 the NZ ASD guideline has prioritised one topic for updating.
e. Drugs with at least one published placebo-controlled trial supporting use in patients with ASD were listed as first line medication (second line after non-drug alternatives) in this table. If studies were open-label, case reports or reviews, the drug was listed as second-line medications.
f. Nadolol was discontinued for commercial reasons in 2016 and is currently unavailable in Australia.
g.: Hydroxyzine is an antihistamine sold mostly over the counter in Australia in Zyrtec and Benadryl.

11.11 Appendix 11. Eating disorder guideline summaries

Guideline	Anorexia Nervosa (AN)	Bulimia Nervosa (BN)	ARFID/EDNOS	Binge eating disorder (BED)
eTG Complete (2018) - adult	**Note:** • Drugs are not beneficial for the treatment of primary AN • Depressive symptoms may be secondary to starvation and may need to prioritise weight gain for treatment **Symptoms of extreme agitation:** **1st line**: OLAN, QUE, AMIS **Symptoms of extreme insomnia**: **1st line**: AD (not TCA, niMAOI) **COMORBID** **MDD**: not caused by starvation **1st line**: CBT, DBT, CBT-E **2nd line**: AD (not TCA, niMAOI)	**1st line**: CBT, DBT, CBT-E **2nd line**: FLX +/- (CBT, DBT, CBT-E) **3rd line**: (CIT, FLUV, SERT) +/- (CBT, DBT, CBT-E) **4th line**: TOP **Symptoms of depression** **1st line**: CBT, DBT, CBT-E		**Note:** • Less is known about BED than AN or BN • Drugs to enhance behavioural interventions are experimental **1st line**: CBT, DBT, IPT, CBT-E **2nd line**: TOP, ORL
RANZCP (2014) child and adolescent section	**Notes:** • There is insufficient evidence to recommend psychotropic medication • Use of anxiolytics or antidepressants or other medications to relieve symptoms with caution in adolescents with AN • SSRIs are not indicated for acute or maintenance stages of AN **1st line**: FBT **2nd line**: CBT	**No recommendations**	**Notes:** ARFID: no studies to guide treatment)	**No recommendations**

Guideline	Anorexia Nervosa (AN)	Bulimia Nervosa (BN)	ARFID/EDNOS	Binge eating disorder (BED)
RANZCP (2014) - adult	Notes: • Only weak evidence for the drug treatment of AN • Low-dose antipsychotics (e.g., OLAN) may be useful in reducing anxiety and obsessive thinking • Exercise caution when prescribing for comorbid conditions/ symptoms until it is clear that such symptoms are not secondary to starvation **1st line**: psychological therapies **2nd line**: OLAN, AMIS	**Notes:** • Drugs may be used where psychological therapy is not available, ineffective, or where there is a comorbid disorder **1st line**: non-pharmacological (not FBT) **2nd line**: FLX +/- CBT **3rd line**: SSRI (other than FLX) +/- CBT **4th line**: (TCA, MAOI, TOP) +/- CBT **5th line**: other ADs +/- CBT **COMORBID** **Mood disorder** **1st line**: non-pharmacological (not FBT) **2nd line**: AD or TOP	**Notes:** ARFID: no studies to guide treatment)	**Notes:** • Drugs may be used where psychological therapy is not available, ineffective, or where there is a comorbid disorder **1st line**: non-pharmacological (not FBT) **2nd line**: (SSRI [esp FLX], TOP) +/- CBT **3rd line**: (ATOM, ZON) +/- CBT **With obesity:** **1st line**: non-pharmacological (not FBT) **2nd line**: TOP +/- ORL **COMORBID** **Mood disorder** **1st line**: non-pharmacological (not FBT) **2nd line**: AD or TOP
NICE (2004) – ages >7 years	**Notes:** • Medication should not be sole or primary treatment for AN • Caution should be exercised with medications for comorbid conditions (e.g., DEP, OCD), as they may resolve when weight increased • Use caution with drugs with cardiac side effects (AP, TCA, Macrolide Antibiotics, some AHIST) • Therapies should be age and developmentally appropriate for children & adolescents **1st line:** (CAT, CBT, IPT, FPT, FT) with focus on ED	**Notes:** • Consider no other drugs than SSRIs • Preferred SSRI, FLX • Therapies should be age and developmentally appropriate for children & adolescents **1st line:** EB-SHP, SSRI, SSRI+EB-SHP **2nd line:** CBT-BN, SSRI, SSRI+CBT-BN **3rd line**: IPT-BN, SSRI, IPT-BN+SSRI	It is recommended that the clinician considers following the guidance on the treatment of the eating problem that most closely resembles the individual patient's eating disorder	**Notes:** • Suitably adapted psychological treatments should be offered to adolescents **1st line:** EB-SHP, SSRI, SSRI+EB-SHP **2nd line:** CBT-BED SSRI, SSRI+CBT-BED **3rd line**: IPT-BED, SSRI, IPT-BED+SSRI

Guideline	Anorexia Nervosa (AN)	Bulimia Nervosa (BN)	ARFID/EDNOS	Binge eating disorder (BED)
NICE (2017) – all ages	**Notes**: • Do not offer medication as sole treatment for AN • When prescribing consider impact of malnutrition and compensatory behaviour on medication effectiveness • When prescribing medication for people with an eating disorder and comorbid mental or physical health conditions, take into account the impact malnutrition and compensatory behaviours can have on medication effectiveness and the risk of side effects **1st line**: CBT-ED, MANTRA, SSCM **2nd line**: alternate therapy form 1st line options, FPT-ED Child/ adolescent **1st line**: FT-AN **2nd line**: CBT-ED, AFP-AN	**Notes**: • Do not offer medication as sole treatment for BN • When prescribing consider impact of malnutrition and compensatory behaviour on medication effectiveness • When prescribing medication for people with an eating disorder and comorbid mental or physical health conditions, take into account the impact malnutrition and compensatory behaviours can have on medication effectiveness and the risk of side effects. • Therapies should be age and developmentally appropriate for children & adolescents **1st line**: EB-SHP **2nd line**: CBT-ED **Child/adolescent:** **1st line**: FT-BN **2nd line**: CBT-ED	For people with OSFED, consider using the treatments for the eating disorder it most closely resembles.	**Notes**: • Do not offer medication as sole treatment for BED • When prescribing consider impact of malnutrition and compensatory behaviour on medication effectiveness • When prescribing medication for people with an eating disorder and comorbid mental or physical health conditions, take into account the impact malnutrition and compensatory behaviours can have on medication effectiveness and the risk of side effects. • For children and young people with binge eating disorder, offer the same psychological treatments recommended for adults with binge eating disorder. **1st line**: EB-SHP **2nd line**: CBT-ED
AACAP (2015) – child and adolescent	**Notes:** • Evidence base in younger people is limited. Need to draw on adult studies • Use of drugs should be reserved for comorbid conditions and refractory cases • Obsessionality and depressed mood often improve with weight gain alone **1st line**: FBT **2nd line**: individual therapies **3rd line**: SSRI, **COMORBID Conditions** Follow guidelines for specific condition	**Notes:** • Evidence base in younger people is limited. Need to draw on adult studies • Use of drugs should be reserved for comorbid conditions and refractory cases **1st line**: CBT **2nd line**: FLX + CBT **3rd line**: other SSRI +CBT **COMORBID conditions** Follow guidelines for specific condition **Depression** **1st line:** SSRI + CBT		

Guideline	Anorexia Nervosa (AN)	Bulimia Nervosa (BN)	ARFID/EDNOS	Binge eating disorder (BED)
BMJ Best Practice (2018) – AN – all ages BMJ Best Practice (2018) – BN – all ages	**Notes:** • Drugs are ineffective at benefitting people with AN • Despite a lack of data, SSRIs are often prescribed due to a lack of awareness of evidence base and frustration with limited treatment options • ADs may not be as effective in low weight people **1st line**: FT-AN (child or adolescent) **With depression symptoms** **1st line**: FT-AN (child or adolescent) **2nd line**: (FLX, SERT) + FT-AN **3rd line**: other SSRIs + FT-AN **With OCD symptoms** **1st line**: FT-AN (child or adolescent) **2nd line**: (FLX, SERT, CLOM) + BT **3rd line**: OLAN + BT **COMORBID** Mood, anxiety and OCD disorders are most common, but due to overlap of symptoms with AN, it is preferable to normalise weight before diagnosing	**Notes:** • SSRIs or SNRIs should only be used if CBT unavailable or not desired or ineffective • ADs should only be used for 1 to 2 weeks to reduce bingeing • Drugs only recommended for non-pregnant patients **1st line**: CBT (+Family support therapy for adolescents) **2nd line**: FLX + CBT **3rd line**: SERT + CBT **4th line**: VEN + CBT **5th line**: Other AD (NOT BUP) +CBT **COMORBID** **Depression** **1st line**: CBT +SSRI (NOT BUP)	**No recommendations** ARFID replaced by OSFED and UFED in DSM 5 • OSFED • UFED	

Guideline	Anorexia Nervosa (AN)	Bulimia Nervosa (BN)	ARFID/EDNOS	Binge eating disorder (BED)
APA (2006) – adult APA (2012) – guideline update	**Notes**: • Among the youngest patients with early onset (i.e., ages 7– 12 years), obsessional behaviour and depression are common (406). Children often present with physical symptoms such as having nausea, experiencing abdominal pain, feeling full, or being unable to swallow • SSRIs in conjunction with CBT are widely used in treatment of AN even though they do not help with weight gain • SSRIs may be considered for patients with persistent depressive, anxiety and OCD symptoms • SGAs (i.e., OLAN, RIS, QUE) have no studies supporting their benefits, but clinical reports suggest they may be useful for severe, unremitting AN, severe OCD thinking or delusional denial • APA upgraded evidence in 2012 – OLAN (Grade B evidence); Other SGA – (Grade C evidence) **1st line**: CBT (FT for adolescents) **2nd line**: SSRI (NOT BUP, MIRT) **3rd line**: OLAN **4th line**: RIS, QUE **5th line**: SGA (other than OLAN, RIS, QUE)	**Notes:** • Among the youngest patients with early onset (i.e., ages 7–12 years), obsessional behaviour and depression are common (406). Children often present with physical symptoms such as having nausea, experiencing abdominal pain, feeling full, or being unable to swallow • BN is rarely seen in children under 12 • ADs are effective component of initial treatment for most BN patients (SSRIs most evidence) • Doses of SSRIs are higher in BN than for depression, but doses of TCA and MAOI are the same • Attend to black box warnings for ADs • Continue AD treatment for 9 months to 1 year **1st line**: CBT (FT for adolescents) **1st line**: if no qualified CBT therapists available: FLX **2nd line**: FLX + CBT (after 10 ineffective sessions CBT) **3rd line**: SERT **4th line**: TCA, MAOI **5th line**: TOP (no data for child & adolescents) **COMORBID:** **Bipolar** **1st line**: VAL (NOT LITH) (no data for child & adolescents) **ADHD** **1st line**: MPHEN	**Notes:** • Patients with subsyndromal anorexia nervosa or bulimia nervosa who meet most but not all of the DSM-IV-TR criteria (e.g., weight >85% of expected weight, binge and purge frequency less than twice per week) merit treatment similar to that of patients who fulfill all criteria for these diagnoses	**Notes:** • For most BED patients AD plus CBT is not better than AD alone for binge suppression **1st line**: CBT (FT for adolescents) **2nd line**: FLX+CBT [FT for adolescents] **3rd line**: SIB (removed from 2012 guideline update), TOP **4th line**: ZON **With depressive symptoms** **1st line**: CBT **2nd line**: FLX + CBT

Guideline	Anorexia Nervosa (AN)	Bulimia Nervosa (BN)	ARFID/EDNOS	Binge eating disorder (BED)
WFSBP (2011)	**Notes:** • Drugs are not first choice for AN. Only use as adjunct to psychotherapies or treating comorbid conditions • Many compounds have been tested – TCA, SSRI, SNRI, SGA, AHIST, LITH, NAL, CLON • Grade B evidence available for OLAN for weight gain, Grade C evidence for other SGA	**Notes**: • Drugs are not first choice for BN. • Many compounds have been tested – TCA, SSRI, RIMA, NRI, antiC, d-fenfluramine, LITH, NAL, MPHEN • Grade A evidence for TCA, FLX: Grade B for TOP • Some evidence for FLX to reduce binge/ purge in adolescents		**Notes**: • Drugs are not first choice for BED. • Many compounds have been tested – TCA, SSRI, SNRI, NRI, antiC, d-fenfluramine, ORL, NAL, BAC • SERT, TOP – Grade A evidence
Brewerton & D'Agostino (2017)			ARFID – **1st line**: non-pharmacological **2nd line**: adjunctive OLAN	
Gray et al. (2018)			ARFID – **1st line**: non-pharmacological **2nd line**: adjunctive MIRT	

Abbreviations organisations/institutions: AACAP, American Academy of Child and Adolescent Psychiatry; APA, American Psychological Association; eTG Complete, Electronic Therapeutic Guidelines Complete; NICE, National Institute for Health and Care Excellence; RANZCP, Royal Australian and New Zealand College of Psychiatrists; WFSBP, World Federation of Societies of Biological Psychiatry.
Abbreviations disorders: AN, anorexia nervosa; ARFID, avoidant/restrictive food intake disorder; BED, binge eating disorder; BN, bulimia nervosa; DSM, diagnostic and statistical manual; EDNOS, eating disorder, not otherwise specified; MDD, major depressive disorder; OSFED, other specified feeding or eating disorder; UFED, unspecified feeding or eating disorder.
Abbreviations treatments: AD, antidepressant; AHIST, antihistamine; AMIS, amisulpride; antiC, anticonvulsant; ATOM, atomoxetine; BAC, baclofen; BUP, bupropion; CBT, cognitive behaviour therapy; CBT-E, CBT enhanced; CIT, citalopram; CLON, clonidine; DBT, dialectal behaviour therapy; EB-SHP, evidence-based self-help program; FBT, family based therapy; FLUV, fluvoxamine; FBT-ED, focal psychodynamic therapy -eating disorder; FLX, fluoxetine; FT-AN, family therapy – anorexia-focussed; IPT, interpersonal psychotherapy; LITH, lithium; MANTRA, Maudsley anorexia nervosa treatment for adults; MAOI, monoamine oxidase inhibitors; MIRT, mirtazapine; niMAOI, non-selective irreversible monoamine oxidase inhibitors; NRI, noradrenaline re-uptake inhibitor; MIRT, mirtazapine; MPHEN, methylphenidate; NAL, naltrexone; OLAN, olanzapine; ORL, orlistat; QUE, quetiapine; RIMA, reversible monoamine oxidase inhibitor; SGA, second-generation antipsychotic; SERT, sertraline; SIB, sibutramine; SNRI, serotonin noradrenaline re-uptake inhibitor; SSRI, selective serotonin re-uptake inhibitor; TCA, tricyclic antidepressant; TOP, topiramate; VAL, valproate; VEN, venlafaxine; ZON, zonisamide.

11.12 Appendix 12. Sleep disorder guideline summaries

Guideline	Sleep disorders - general	Insomnia	Parasomnias[a]	Other sleep disorders
eTG Complete (2018) -child	**Note**: Some clinicians prescribe melatonin for severe insomnia[b] Generally, medications are not to be used in children **1st line**: good sleep practices		**Note**: • Nightmares in children are usually related to recent experience and usually resolve without resort to medication • Sleep terrors and sleepwalking generally occur in episodes of short duration and pharmacotherapy is seldom indicated	
eTG Complete (2020) - adult		**Notes:** • Good sleep practices and non-drug approaches should always be first line therapy • There is no evidence of efficacy of sedating ADs such as TCAs, MIRT, AGOM in treating insomnias in absence of depression • There is no evidence of efficacy of AHIST for insomnia, and can cause significant adverse events, especially in children. • APs have no role in the treatment of insomnia **CHRONIC** **1st line: chronic**: CT, Relaxation therapy, stimulus control, sleep restriction **2nd line: chronic**: TEM, ZOL, ZOP **3rd line: chronic**: MEL **ACUTE** **1st line:** non-pharmacological **2nd line: acute**: TEM, ZOL, ZOP **3rd line: acute**: MEL **COMORBID:** **MDD** **1st line**: CT, Relaxation therapy, stimulus control, sleep restriction **2nd line**: MEL, TEM, ZOL, ZOP, TCA, MIRT, AGOM	**Notes**: • Parasomnias are most common in children and decrease in frequency with age • Where there is a risk of physical injury, pharmacotherapy may be required • Parasomnias are rare adverse events associated with ZOL • Many drugs can cause nightmares (e.g., β-blockers, SSRIs, BZ) **SLEEP TERRORS & SLEEPWALKING** **1st line**: non-pharmacological **2nd line**: HYP **NIGHTMARES & RBD** **1st line**: non-pharmacological **2nd line**: CLONAZ (low dose)	

Guideline	Sleep disorders - general	Insomnia	Parasomnias[a]	Other sleep disorders
AASM (2015) – child/ adolescent sections	Notes: • MEL appears safe for healthy adults, but caution should be used with children and adolescents • Studies of MEL in children and adolescents are rare			**Notes**: • MEL appears safe for healthy adults, but caution should be used with children and adolescents • Studies of MEL in children and adolescents are rare **DSWPD** **1st line**: non-pharmacological **2nd line**: strategically timed MEL[c] **ISWRD with neurologic disorders** **1st line**: non-pharmacological **2nd line**: strategically timed MEL[c]
BAP (2010) – child/ adolescent section	**Notes**: • Most sleep disorders in childhood respond well to behavioural treatments • CLON, chloral hydrate (ORION) and triclofos are commonly used in treatment, but evidence for use in children and adolescents is lacking **1st line**: behavioural treatments	**Notes**: • Most sleep disorders in childhood respond well to behavioural treatments • CLON, chloral hydrate (ORION) and triclofos are commonly used in treatment, but evidence for use in children and adolescents is lacking **COMORBID** **ADHD with sleep onset insomnia** **1st line**: behavioural treatments **2nd line: not on STIM**: MEL **3rd line**: AHIST (short-term) **Learning disorders** **1st line**: parent education, behavioural treatments **2nd line**: MEL	**Notes**: • There is no mention of treatment for children and adolescents, and poor-quality evidence for adults	

Guideline	Sleep disorders - general	Insomnia	Parasomnias[a]	Other sleep disorders
BMJ Best (2018) -child and adolescent	**Notes:** • Sleep specialists should be consulted before prescribing drugs		**Notes:** Sleep specialists should be consulted before prescribing drugs **SLEEPWALKING** **1st line**: environmental adjustments and scheduled awakening **2nd line**: (DIAZ, CLONAZ, LOR) + environmental adjustments and scheduled awakening **SLEEP TERRORS** **1st line**: environmental adjustments **2nd line**: (DIAZ, CLONAZ) + environmental adjustments **3rd line**: (PAR, TRAZ) + environmental adjustments **4th line**: (TCA, FLX, TRYP) + environmental adjustments **NIGHTMARES** **1st line**: environmental adjustments + PT **2nd line**: (TCA, SSRI) + environmental adjustments + PT **RBD** **1st line**: environmental adjustments **2nd line**: (CLONAZ, MEL) + environmental adjustments **ISOLATED RECURRENT SLEEP PARALYSIS without narcolepsy** **1st line**: environmental adjustments **2nd line**: anxiolytic (e.g., DIAZ) **ISOLATED RECURRENT SLEEP PARALYSIS with narcolepsy** **1st line**: environmental adjustments **2nd line**: STIM	

Guideline	Sleep disorders - general	Insomnia	Parasomnias[a]	Other sleep disorders
BMJ Best (2018) – dyssomnias: child and adolescent	**Notes**: • Sleep specialists should be consulted before prescribing drugs	**Notes:** • Sleep specialists should be consulted before prescribing drugs • MEL is not a treatment for insomnia except in very rare circumstances, but may give added small benefit in conjunction with behavioural modification **1st line**: behavioural modification **2nd line**: MEL + behavioural modification		**Notes:** • Sleep specialists should be consulted before prescribing drugs • MEL has been used to induce sleep in children with ASD or ADHD with good results **DSPD** **1st line**: sleep hygiene + behavioural schedule **2nd line**: MEL+ light exposure regulation + chronotherapy **NARCOLEPSY with daytime sleepiness** **1st line**: frequent scheduled naps **2nd line**: frequent scheduled naps + STIM (e.g., MPHEN, MOD, DEX) **NARCOLEPSY with cataplexy** **1st line**: frequent scheduled naps **2nd line**: frequent scheduled naps + (CLOM, IMIP, PROTRYP, VEN, FLX)
CPS (2012) – child & adolescent	**Notes**: • MEL is recommended for short-term use only in adults and is off-label for children and adolescents • There is no evidence to support the use of MEL in children < 2 years • Although no evidence for use, short-acting is used for sleep initiation and long-acting for sleep maintenance • Medications used to treat ADHD may increase sleep difficulties	**Notes**: • MEL is recommended for short-term use only in adults and is off-label for children and adolescents • There is no evidence to support the use of MEL in children < 2 years • Although no evidence for use, short-acting is used for sleep initiation and long-acting for sleep maintenance • Medications used to treat ADHD may increase sleep difficulties **SLEEP ONSET INSOMNIA** **1st line**: sleep hygiene **2nd line**: MEL **COMORBID** **ADHD** **1st line**: sleep hygiene **2nd line**: MEL **ASD** **1st line**: sleep hygiene **2nd line**: MEL		**Notes**: • MEL is recommended for short-term use only in adults and is off-label for children and adolescents • There is no evidence to support the use of MEL in children < 2 years • Although no evidence for use, short-acting is used for sleep initiation and long-acting for sleep maintenance **DSPD** **1st line**: sleep hygiene **2nd line**: MEL

Guideline	Sleep disorders - general	Insomnia	Parasomnias[a]	Other sleep disorders
Malow (2012) with ASD	**Note**: • Although medications and supplements are often used to treat insomnia experienced by children and adolescents who have ASD, the evidence base for pharmacologic treatment is limited	**Note**: • Although medications and supplements are often used to treat insomnia experienced by children and adolescents who have ASD, the evidence base for pharmacologic treatment is limited **COMORBID** **ASD** **1st line**: parent education and behavioural approaches **2nd line**: MEL **3rd line**: RIS, MIRT, CLON		

Abbreviations organisations/institutions: AASM, American Academy of Sleep Medicine; eTG Complete, Electronic Therapeutic Guidelines Complete; BAP, British Association for Psychopharmacology; CPA, Canadian Paediatric Society.
Abbreviations disorders: ASD, autism spectrum disorder; ADHD; attention deficit hyperactivity disorder; DSPD, delayed sleep phase disorder; DSWPD; delayed sleep-wake phase disorder; ISWRD, irregular sleep-wake rhythm disorder; MDD, major depressive disorder; RBD, REM sleep behaviour disorder.
Abbreviations treatments: AD, antidepressant; AGOM, agomelatine; AP, antipsychotic; ATOM, atomoxetine; BZ, benzodiazepine; CLOM, clomipramine; CLON, clonidine; CLONAZ, clonazepam; CT; cognitive therapy; DEX, dexamphetamine; DIAZ, diazepam; FLX, fluoxetine; HYP, hypnotics; IMIP, imipramine; LOR, lorazepam; MEL, melatonin; MIRT, mirtazapine; MOD, modafinil; MPHEN, methylphenidate; PAR, paroxetine; PROTRIP, protriptyline; PT, psychological therapy; RIS, risperidone; SSRI, selective serotonin re-uptake inhibitor; STIM, stimulant; TCA, tricyclic antidepressant; TEM, temazepam; TRAZ, trazodone; TRYP, tryptophan; VEN, venlafaxine; ZOL, zolpidem; ZOP, zopiclone.
a Parasomnias include sleepwalking, sleep terrors, nightmares, REM sleep behaviour disorders (RBDs), and sleep-related eating and enuresis.
b. Melatonin was approved for use in children from May 2020 for the treatment of insomnia in children and adolescents aged 2-18 years with autism spectrum disorder and/or Smith-Magenis syndrome.
c The evidence for MEL in children with DSWPD and ISWRD is weak, based on one trial, but clinical experience suggests better than no treatment.

11.13 Appendix 13. Childhood enuresis guideline summaries

Guideline	Enuresis
RCHM (2019)	**Notes:** • Treatment is not usually started before the age of 6 • If constipation is present, this should be addressed first • Evaluate maturational appropriateness of DESMO for child <7 years • If no response to DESMO after 4 weeks, consider cessation • Withdraw DESMO for at least 1 week every 3 months to assess for relapse and need for ongoing medication • TCAs are no longer recommended **>6 years** **1st line**: general advice on fluids and toileting **2nd line**: alarm **3rd line**: DESMO
Nankivell (2014)	**1st line**: education, fluid intake, manage constipation **2nd line**: alarm **3rd line**: DESMO (≥ 6 years)[a] **4th line**: anticholinergic (e.g., OXYBUT) +/- (alarm or DESMO)[b] **5th line**: IMIP (> 6 years)[c]
NICE (2010)	**Notes**: • DESMO can be considered for children from 5-7 years if they require rapid relief or who find an alarm inappropriate or undesirable • Do not use DESMO if only have daytime bedwetting • Assess response to DESMO at 4 weeks and continue for 3 months if signs of response (& possibly up to 6 months) **<5 years** **1st line**: non-pharmacological options **5-7 years:** • as for >7 years, but with reservations, and only if alarm inappropriate or ineffective **>7 years** **1st line**: advice on fluids, toileting **2nd line**: alarm **3rd line (if no response after 4 weeks)**: DESMO (>7 years) +/- alarm **4th line**: Anticholinergic (NOT with IMIP) **5th line**: IMIP

Guideline	Enuresis
BMJ Best (2020) Enuresis	**Notes:** • In patients who are refractory to conventional therapies for enuresis and have comorbid ADHD, imipramine may be prescribed **<7 years** **1st line**: non-pharmacological, reassurance **≥7 years** **1st line**: education, lifestyle, behavioural methods **2nd line**: alarm therapy + 1st line measures **3rd line**: DESMO + 1st line measures **4th line**: alarm + DESMO + 1st line measures +/- detrusor relaxing drugs (OXYBUT, TOLT) **5th line**: IMIP + 1st line measures
AACAP (2004)	**Notes**: • Psychotherapy is not indicated unless there is a psychological issue associated with the onset of secondary enuresis **1st line**: educate parents + behavioural methods (e.g., diary, reduce fluids, awaken during night) **2nd line**: alarm **3rd line**: DESMO **4th line**: IMIP
International consensus on ICCS guidelines (2012)	**1st line:** education, behavioural and lifestyle advice **2nd line:** alarm or DESMO **3rd line**: IMIP (not to be prescribed in primary care without specialist approval)
International consensus on ICCS guidelines for primary care (2017)	**1st line:** education, behavioural and lifestyle advice **2nd line:** alarm or DESMO **3rd line**: IMIP (not to be prescribed in primary care without specialist approval)

Abbreviations organisations/institutions: AACAP, American Academy of Child and Adolescent Psychiatry; NICE, National Institute for Health and Care Excellence; ICCS, International Children's Continence Society; RCHM, Royal Children's Hospital of Melbourne.
Abbreviations treatments: DESMO, desmopressin; IMIP, imipramine; OXYBUT, oxybutynin; TCA, tricyclic antidepressant; TOLT, tolterodine.
a. Desmopressin is approved in Australia for use in children over 5 years of age for nocturnal enuresis.
b. Oxybutynin is approved in Australia for children over 5 years of age for overactive bladder.
c. Imipramine is approved in Australia for children from 5 years of age for the treatment of nocturnal enuresis. Note that the article in Australian prescriber quotes over 6 years of age.
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11.14 Appendix 14. Summary of guideline recommendations for use of antipsychotics in children and adolescent with mental disorders

Antipsychotic	Psychotic disorders	Bipolar disorder	DBD	ASD	ED	Anxiety disorders	MDD	Sleep disorders	PD
AP	**1st**-psychotic – prodromal (ultra-low-dose) (eTG) **1st** -FEP (NICE, SIGN, BAP) 1st-FEP except CLOZ, OLAN (AACAP)	**2nd**-manic, severe (BAP) **3rd**-manic mixed (WFSBP) 2nd dep + AD (BAP) 2nd maint +VAL/LI (BAP)	1st-CD (AACAP) 1st-aggress (AACAP)	1st-stereotypies/ aggress/irritability with ASD (NICE, NZ)		2nd-OCD adjunct SSRI (BMJ) 4th-OCD adjunct FLUV or SERT (BMJ) 5th-OCD adjunct SSRI if moderate/severe (AACAP)	1st-psychotic depress, adjunct SSRI (AACAP, TMAP)		1st - PDs, for aggress, mood/anxiety, cognitive distortions (NHMRC, WFSBP)
FGA	**2nd**-FEP (WFSBP)								
Chlorpromazine	**4th**-FEP (eTG)	**3rd**-manic (CANMAT)							1st - PDs, for aggress, mood/anxiety, cognitive distortions (NHMRC)
Droperidol									
Flupenthixol	2nd maint (eTG) 3rd maint (WFSBP)								1st - PDs, for aggress, mood/anxiety, cognitive distortions (NHMRC, WFSBP)
Fluphenazine[a]	**3rd**-FEP (BMJ) **2nd** maint (eTG) **3rd** maint (WFSBP) **4th** maint (BMJ)	**2nd**-maint (BAP)							
Haloperidol	**2nd**-FEP (WFSBP) **3rd**-FEP (BMJ) **4th**-FEP (eTG) **2nd**-TR (eTG) 2nd maint (WFSBP) 4th maint (eTG) 6th maint (BMJ)	**1st**-manic (RANZCP, NICE, BAP) **2nd**-manic (eTG, CANMAT) 2nd-maint (BAP)	2nd-aggress (T-MAY)	3rd-aggress, sexualised behaviours with ASD (BMJ) 3rd-irritability, aggress, self-injury with ASD (NZ)		2nd-OCD adjunct SSRI (BMJ) 5th-OCD adjunct SSRI if moderate/severe (AACAP)			1st - PDs, for aggress, mood/anxiety, cognitive distortions (NHMRC, WFSBP)
Periciazine	**4th**-FEP (eTG)			1st-stereotypies/ aggress/irritability with ASD (eTG)					
Sertindole[b]	**1st**-FEP (BMJ)								

Antipsychotic	Psychotic disorders	Bipolar disorder	DBD	ASD	ED	Anxiety disorders	MDD	Sleep disorders	PD
	3rd-FEP (eTG)								
Trifluoperazine[c]	**4th**-FEP (eTG)			1st-stereotypies/ aggress/irritability with ASD (eTG)					1st - PDs, for aggress, mood/anxiety, cognitive distortions (NHMRC, WFSBP)
Zuclopenthixol	**2nd**- maint (eTG) **3rd**-maint (WFSBP)	1st-manic (RANZCP) if APs fail							
SGA	**1st**-FEP (not CLOZ) (eTG, orygen, BMJ, SIGN, WFSBP) 2nd TR + CLOZ (orygen)	**1st**-manic (BB, eTG) 3rd dep +TCA (CANMAT) 3rd maint (CANMAT)	1st-CD (AACAP) 1st- aggress (AACAP)			2nd-PTSD (AACAP) 1st-extreme distress (Hazell)	1st-psychotic depress, adjunct SSRI (AACAP, TMAP) 3rd- moderate /severe depression – augment with inadequate response to 2nd SSRI (BMJ)		1st - PDs, for aggress, mood/anxiety, cognitive distortions (NHMRC, WFSBP)
Amisulpride	**1st**-FEP (eTG, orygen, BMJ, WFSBP) 2nd TR + CLOZ (eTG, BMJ))				1st-AN (RANZCP) 1st- AN with extreme agitation (eTG)				
Aripiprazole	**1st**-FEP (eTG, orygen, BMJ, WFSBP) **1st**-FEP 15-17 years (NICE)	**1st**-manic **(**RANZCP**)** **1st-manic** (RANZCP, AACAP) 1st-manic >12years, ,<=12weeks (NICE, BAP) 1st-manic mixed (WFSBP) **1st** dep +AD (eTG) **2nd**-manic (eTG) **2nd** manic (CANMAT) 2nd-manic (CANMAT)	2nd- aggress (T-MAY)	1st-stereotypies/ aggress/irritability with ASD (AACAP,BMJ, BAP, SIGN) 2nd-stereotypies/ aggress/irritability with ASD (NZ, AAP)		3rd-OCD adjunct (FLX, CLOM, CIT, FLUV, SERT, PAR) (ADAC)	3rd- moderate /severe depression – augment with inadequate response to 2nd SSRI (BMJ)		1st - PDs, for aggress, mood/anxiety, cognitive distortions (NHMRC, WFSBP)

Antipsychotic	Psychotic disorders	Bipolar disorder	DBD	ASD	ED	Anxiety disorders	MDD	Sleep disorders	PD
		1st-maint (eTG, RANZCP, CANMAT) **2nd**-mania (BAP) 2nd maint (BAP) **3rd** maint (WFSBP)							
Asenapine	**1st**-FEP (BMJ) **2nd**-FEP (eTG)	**1st**-manic (RANZCP, CANMAT) 1st dep +AD (eTG) **2nd**-manic (eTG) **3rd**-mixed manic (WFSBP) 1st-maint (eTG) 3rd-maint (CANMAT)							
Brexpiprazole	**1st**-FEP (BMJ)								
Clozapine	Not 1st **3rd**-FEP (orygen, BMJ) **1st**-TR (eTG, orygen, NICE, BMJ, SIGN, BAP, WFSBP) 1st-TR (AACAP)	**3rd**-manic (RANZCP, CANMAT) **3rd**-manic (AACAP) 6th -manic (CABF) **4th**-manic TR (BAP) **5th**-manic mixed (WFSBP) 3rd-maint (CANMAT) 4th-maint TR (BAP)	2nd-aggress (T-MAY)						1st - PDs, for aggress, mood/anxiety, cognitive distortions (WFSBP)
Lurasidone[d]	**1st**-FEP (BMJ) 1st maint (BMJ)	**1st**-dep (BAP) 2nd dep (CANMAT) **2nd**-dep mixed (WFSBP) 1st-maint (BAP)							
Olanzapine	**1st**-FEP (eTG) **2nd**-FEP, psychotic depression (Orygen, BMJ) **2nd**-FEP (AACAP) 1st maint (eTG, BMJ	1st-manic (RANZCP, AACAP, CABF) 1st-manic (eTG, RANZCP, CANMAT, NICE) 1st-dep (BAP) 1st-depress +FLX (AACAP) 1st dep +AD (eTG)	2nd-aggress (T-MAY)	2nd-aggress, sexualised behaviours with ASD (BMJ) 2nd-repetitive/ OCD/ADHD/ aggress, self-injury with ASD (AAP)	1st – AN (RANZCP, WFSBP) 1st- AN with extreme agitation (eTG) 2nd-AN severe, or	2nd-OCD adjunct SSRI (BMJ)	3rd- moderate /severe depression – augment with inadequate response to 2nd SSRI (BMJ)		1st - PDs, for aggress, mood/anxiety, cognitive distortions (NHMRC, WFSBP)

Antipsychotic	Psychotic disorders	Bipolar disorder	DBD	ASD	ED	Anxiety disorders	MDD	Sleep disorders	PD
	2nd maint (AACAP)	1st dep +FLX (NICE) 2nd-manic (BAP) 1st-maint (eTG, RANZCP, CANMAT) 1st-maint (BB, AACAP, CABF) 2nd-maint (NICE, BAP) 2nd-depress mixed (WFSBP)			with OCD, delusions (BMJ, APA) 2nd-ARFID (article JCAP)				
Paliperidone	**1st**-FEP (eTG)	**1st**-manic (CANMAT) **1st** dep +AD (eTG) **2nd**-manic (eTG, RANZCP) **1st**-maint (eTG) **2nd**-maint (BAP, CANMAT) **2nd**-manic mixed (WFSBP)	2nd-aggress (T-MAY)		1st- AN with extreme agitation (eTG)				
Quetiapine	**1st**-FEP (eTG, orygen, BMJ, WFSBP) 1st maint (eTG, BMJ)	1st-manic (CANMAT, NICE) 1st-manic (AACAP,CABF, CANMAT) 2nd-manic (eTG) 2nd-manic (BAP) 1st-dep (eTG, RANZCP, BAP, CANMAT, NICE) 1st-depress (BB) 2nd-manic mixed (WFSBP) 1st-maint (eTG, RANZCP, CANMAT, WFSBP) 2nd maint (BAP)	2nd-aggress (T-MAY)	3rd-aggress, sexualised behaviours with ASD (BMJ) 2nd-repetitive/ OCD/ADHD/ aggress, self-injury with ASD (AAP)	1st AN + extreme agitation (eTG) 3rd-AN severe, or with OCD, delusions (APA)	2nd-OCD adjunct SSRI (BMJ)	3rd- moderate /severe depression – augment with inadequate response to 2nd SSRI (BMJ)		1st - PDs, for aggress, mood/anxiety, cognitive distortions (WFSBP)
Risperidone	**1st**-FEP (eTG, orygen, BMJ)	1st-manic (eTG, RANZCP, CANMAT, NICE)	1st-CD (AACAP,	1st-stereotypies/ aggress/irritability with ASD (eTG)	3rd-AN severe, or with OCD,	2nd-OCD adjunct SSRI (BMJ)	3rd- moderate /severe depression –	2nd-ASD and sleep	1st - PDs, for aggress, mood/anxiety, cognitive distortions (WFSBP)

Antipsychotic	Psychotic disorders	Bipolar disorder	DBD	ASD	ED	Anxiety disorders	MDD	Sleep disorders	PD
	1st maint (eTG, BMJ)	1st-manic (AACAP, CABF) 2nd-manic (CANMAT, BAP) 1st dep +AD (eTG) 2nd-manic mixed (WFSBP) 1st-maint (eTG, CANMAT) 2nd-maint (BAP) 3rd-maint (WFSBP)	eTG, NICE) 1st-aggress (AACAP, eTG, T-MAY)	1st-stereotypies/ aggress/irritability with ASD (eTG, AACAP,BMJ, BAP, SIGN, NZ)	delusions (APA)	5th-OCD adjunct SSRI if moderate/severe (AACAP)	augment with inadequate response to 2nd SSRI (BMJ)	disorder (ATN)	
Ziprasidone	**1st**-FEP (eTG, orygen, BMJ, WFSBP) 1st maint (eTG, BMJ)	1st-manic (CANMAT) 1st-manic (RANZCP, AACAP) 1st dep mixed (WFSBP) 1st dep +AD (eTG) 5th-manic (CABF) 2nd-manic (eTG) 3rd-manic mixed (WFSBP) 1st-maint (eTG, CANMAT) 3rd-maint (WFSBP)	2nd-aggress (T-MAY)	2nd-repetitive/ OCD/ADHD/ aggress, self-injury with ASD (AAP)			3rd- moderate /severe depression – augment with inadequate response to 2nd SSRI (BMJ)		1st - PDs, for aggress, mood/anxiety, cognitive distortions (NHMRC, WFSBP)
Zuclopenthixol		1st manic (RANZCP)							

Notes: To clarify which entries relate specifically to children and adolescents, paediatric recommendations are noted in red text with the guideline noted in brackets. All other guideline recommendations were extracted from adult guidelines and the guideline title(s) in brackets afterwards. If the adult guideline was Australian, it was highlighted in blue ink. For example, the Australian guidelines eTG Complete recommend antipsychotics as first-line for psychotic disorders without separately referring to children or adolescents and are therefore noted in brackets in blue ink after the table entry. Similarly, Orygen guidelines for psychosis focus on late adolescence and early adulthood, but do not distinguish between recommendations for those aged up to 18 years and young adults. Therefore, this guideline has also been highlighted in blue ink. On the other hand, NICE guidelines have a specific recommendation for 15-17-year-olds for aripiprazole, so this is highlighted in red and the guideline is noted in brackets afterwards. ADHD and enuresis were omitted from the table due to no recommendations for antipsychotics for the primary diagnosis being recorded in any guidelines.

Abbreviations organisation/institution: AACAP, American Academy of Child and Adolescent Psychiatry; AAP, American Academy of Pediatrics; ADAC, Anxiety Disorders Association of Canada; ATN, Autism Treatment Network; BAP, British Association for Psychopharmacology; BB, beyond Blue; BMJ, BMJ Best Practice; CABF, Child and Adolescent Bipolar Foundation; CANMAT, Canadian Network for Mood and Anxiety Treatments; eTG complete, Electronic Therapeutic Guidelines Complete; JCAP, Journal of Child and Adolescent Psychopharmacology; NICE, National Institute for Health and Care Excellence; NZ, New Zealand guidelines; RANZCP, Royal Australian and New Zealand College of Psychiatrists; SIGN, Scottish Intercollegiate Guidelines Network; T-MAY, Treatment of Maladaptive Aggression in Youth; WFSBP, World Federation of Societies of Biological Psychiatry.

Disorder abbreviations: ADHD, attention-deficit hyperactivity disorder; aggress; aggression; AN, anorexia nervosa; ASD, autism spectrum disorder; FEP, first episode psychosis; maint, maintenance; OCD, obsessive-compulsive disorder; TR, treatment resistant.
Treatment abbreviations: AD, antidepressant; AP, antipsychotic; CIT, citalopram; CLOM, clomipramine; CLOZ, clozapine; FGA, first generation antipsychotic; FLUV, fluvoxamine; FLX, fluoxetine; PAR, paroxetine; SERT, sertraline; SGA, second-generation antipsychotic; SSRI, selective serotonin re-uptake inhibitor.
a. Fluphenazine was discontinued in Australia in 2017.
b. Sertindole was discontinued in Australia in 2014.
c. Trifluoperazine was discontinued in Australia in 2018.
d. Lurasidone was approved to treat schizophrenia in Australia in April 2014. Although the Product Information document listed indications for adolescents 13-17 years, it was not officially approved for this age group until April 2018.

11.15 Appendix 15. Conference poster: Trends in psychotropic prescribing

MORE KIDS BEING PRESCRIBED PSYCHOTROPIC DRUGS

Julie Klau[1], Carla Bernardo[2], David Gonzalez-Chica[2], Melissa Raven[1], Jon Jureidini[1]

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[2] Discipline of General Practice, Adelaide Medical School, University of Adelaide

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BACKGROUND

- Prescriptions of psychotropic drugs to children and adolescents are increasing worldwide[1]
- Few psychotropics are approved for under 19-year-olds in Australia, and none for depression
- No recent studies looking at the number of children and adolescents taking psychotropic drugs in Australian general practice

METHODS

- Longitudinal study of prescribing in a national general practice database, MedicineInsight
- 537,371 regular (3 visits in 2 years) patients under 19 years
- 5 main drug classes and melatonin analysed

RESULTS

- From 2011 to 2018, prescriptions increased for antidepressants (43.2%), antipsychotics (60.7%) and ADHD drugs (96.2%)
  - ❖ Highest increase was seen in 10-14-year-olds
- 14,075 (4.2%) of patients under 19 years received a psychotropic drug (including melatonin) in 2018
- In 2018 melatonin was prescribed 3 times more than all other psychotropics combined in 0-4-year-olds

CONCLUSION

- Prescriptions of psychotropic drugs to children and adolescents in Australia are increasing
- Need to investigate the reasons for these prescribing patterns in Australian primary care, and their impact on child and adolescent health and wellbeing

Drug class by age in 2018

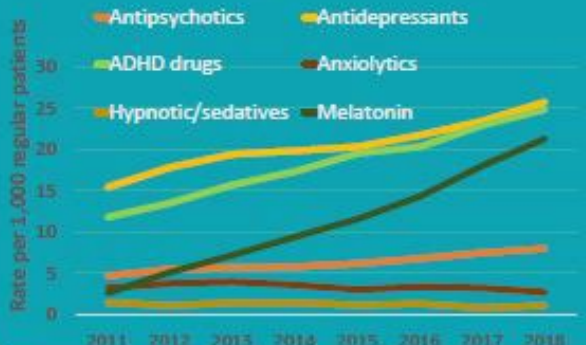


Hypnotics/sedatives decreased by 40%, but melatonin increased 7-fold



1 in 10 teenagers on antidepressants in 2018

Trends in 10-14-year-olds 2011 to 2018





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CEMH website: UA.edu.au/cemh

Reference
1. Barczyk, Z A et al. (2020). Psychotropic Medication Prescription Rates and Trends for New Zealand Children and Adolescents 2008–2016. *Journal of Child & Adolescent Psychopharmacology* 30(2): 87-96

11.16 Appendix 16. Conference poster: Antipsychotic prescribing patterns

Antipsychotic prescribing patterns in children and adolescents in Australian general practice

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BACKGROUND

- Antipsychotics are approved for children and adolescents for psychoses, severe destructive behaviours in autism, behaviour disorders (disruptive behaviour, aggression, conduct disorders) and childhood bipolar disorder[1]
- Any other prescribing is "off-label" – that is, it is not approved by regulatory authorities for this age group[2]
- Antipsychotics have serious adverse effects, especially in youth, and should be used with great caution in children and adolescents[3]

METHODS

- Sample of 168,009 0-18-year-old general practice patients in 2011, and 301,643 in 2017
- Extract mental health diagnoses and prescriptions from electronic health records in large general practice database, MedicineInsight
- Match prescription and diagnosis in same calendar year
- Compare proportion of diagnoses associated with antipsychotic prescribing in 2011 & 2017
- Compare off-label prescribing 2011 & 2017
- Examine co-prescribing of other types of psychotropic drugs on same day as antipsychotic prescription

KEY FINDINGS

1. More antipsychotics were prescribed in 2017 compared with 2011 for most mental health diagnoses
2. The main diagnosis associated with antipsychotics was depression/anxiety in both years
3. Most prescribing was off-label – 69.7% of prescriptions for mental health conditions in 2011 and 79.7% in 2017
4. Teenagers 15-18-years were 21.6% more likely to be prescribed off-label in 2017 than 2011
5. Compared with 2011, off-label prescribing was higher in 2017 for patients living in outer regional and remote areas (34.3%) and those living in the most disadvantaged areas (19.7%)
6. Patients with eating disorders were 6.5 times more likely to receive an antipsychotic in 2017 compared with 2011
7. The three most prescribed antipsychotics were risperidone, quetiapine and olanzapine

CONCLUSION

- Most antipsychotics prescribed to children and adolescents are off-label
- There is increasing use of antipsychotics for depression/anxiety
- Further research into factors influencing prescribing patterns in general practice is needed



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Proportions of children and adolescents with a psychiatric diagnosis prescribed an antipsychotic in 2011 and 2017

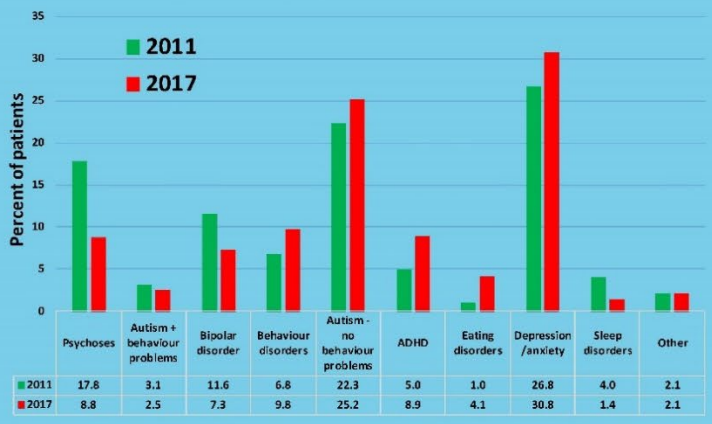
	2011		2017		Difference 2017 to 2011	
	N with diagnosis	Prescribed antipsychotic Adjusted (%)	N with diagnosis	Prescribed antipsychotic Adjusted (%)	%(95% CI)	p value
All mental health diagnoses	8418	2.0	27412	2.9	0.9 (0.5, 1.4)	<0.001
Psychoses	67	45.7	209	34.0	-11.7 (-25.8, 2.5)	0.105
Autism with behaviour problems	63	10.8	244	8.9	-1.9 (-9.5, 5.7)	0.616
Bipolar disorder	82	21.6	156	41.5	19.9 (8.7, 31.0)	<0.001
Disruptive behaviour/conduct disorder	852	1.3	2798	2.9	1.6 (0.4, 2.9)	0.011
Autism without behaviour problems	1100	3.7	3086	6.1	2.4 (0.2, 4.5)	0.030
ADHD	893	0.9	3517	1.8	0.9 (0.1, 1.7)	0.022
Eating disorders	182	1.1	523	7.2	6.1 (3.1, 9.1)	<0.001
Depression or anxiety	2872	1.5	10183	2.5	1.0 (0.4, 1.5)	0.001
Sleep disorders	729	0.9	2630	0.4	-0.4 (-1.1, 0.3)	0.210
Other mental health	1578	0.2	4066	0.4	0.3 (-0.1, 0.5)	0.099



70% of patients were co-prescribed another psychotropic drug with an antipsychotic in both years

Antidepressants were the most co-prescribed – 56% for all psychiatric diagnoses, and over 80% for depression/anxiety

Main diagnosis among children and adolescents receiving an antipsychotic in 2011 and 2017



	Psychoses	Autism + behaviour problems	Bipolar disorder	Behaviour disorders	Autism - no behaviour problems	ADHD	Eating disorders	Depression /anxiety	Sleep disorders	Other
2011	17.8	3.1	11.6	6.8	22.3	5.0	1.0	26.8	4.0	2.1
2017	8.8	2.5	7.3	9.8	25.2	8.9	4.1	30.8	1.4	2.1

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