Sedative burden in hospitalised patients taking at least one antipsychotic medication

by

Ruby Tszwai Au

Bachelor of Pharmaceutical Science

A thesis submitted for the degree of

Masters by Research (Pharmacy)

UniSA Clinical and Health Sciences

University of South Australia

March 2022

Table of Contents

Table of Contents ..... **ii**

List of Figures ..... **vi**

List of Tables ..... **vii**

List of Abbreviations ..... **x**

Glossary ..... **xi**

Summary ..... **xii**

Declaration ..... **xiv**

Acknowledgments ..... **xv**

1. Background **1**

1.1 Antipsychotics and psychoses 1

1.2 Recommended use of antipsychotics 2

1.3 Off label use of psychotropic medications in hospitals 3

1.4 Psychotropic medications and sedation 5

1.5 Concomitant use of psychotropic medications and risks associated with sedating medications 6

1.6 Drug Burden Index 8

1.7 Sedative Load Model 9

1.8 Prior studies that employed the DBI and SLM 10

1.9 Justification for this study 22

1.10 Objectives 23

2. Method **24**

2.1 Study design and source of data 24

2.1.1 Study population 24
2.1.2 Drug classification 25
2.1.3 Assumptions for discharge medications 25
2.2 Calculating the sedative burden 27
2.2.1 Drug burden calculation 27
2.2.2 Sedative load calculation 31
2.3 Other variables 31
2.4 Medication data 33
2.5 Statistical analysis 33
2.6 Ethics approval 34
3. Results 35
3.1 Description of the study population 35
3.2 Prevalence of prescriptions for sedating medications 39
3.3 Differences between sedative burden from pre-admission to discharge 42
3.4 Factors associated with the differences in the sedative burden 45
3.4.1 Univariate analyses to determine the associations of the variables with the changes in the sedative burden 45
3.4.2 Stratified analyses for variables with statistically significant associations with the changes in the Sed-DBI score and the sedative load 47
3.4.3 Baseline-adjusted linear regression analyses 49
3.4.4 Stepwise multiple regression analyses 51
3.5 Subgroup analyses: Patients admitted to acute mental health units 54
3.5.1 Description of patients admitted to acute mental health units 54

3.5.2 Prevalence of prescriptions for sedating medications among patients admitted to acute mental health units 56

3.5.3 Differences between sedative burden from pre-admission to discharge between patients admitted to acute mental health units and patients admitted to other units 57

3.5.4 Parameters associated with the differences in the sedative burden among patients admitted to acute mental health units 63

4. Discussion 70

4.1 Changes in sedative burden between admission and discharge 70

4.1.1 Comparison with prior studies that calculated the changes in Sed-DBI score in hospitals 70

4.1.2 Comparison with prior studies that calculated the sedative load 71

4.2 Associations between sedative burden and patients' characteristics 71

4.2.1 Parameters associated with the increased Sed-DBI scores and sedative load: Results from univariate and baseline-adjusted linear regressions 71

4.2.2 Independent predictors of the increased Sed-DBI score: Results from backward selection multiple regression 72

4.2.3 Independent predictors of the increased sedative load: Results from backward selection multiple regression 73

4.3 Subgroup analyses: Patients admitted to acute mental health units 74

4.4 Comparison of DBI and SLM 76

4.5 Prevalence of sedating medications 76

4.6 Applications of findings from previous studies to the present study population 76

4.6.1 Age and sedative burden 77

4.6.2 Physical and cognitive impairments significantly associated with the DBI score and the sedative load 77

4.7 Implications for future research 78

4.8 Strengths and limitations 80

5. Conclusion 83

6. References 85

7. Appendices 92

7.1 Appendix A 92

7.2 Appendix B 96

7.3 Appendix C 100

List of Figures

Figure 1. The process of patient selection and exclusion 35

Figure 2. Distribution of ten most frequently prescribed sedating medications at pre-admission and on discharge 41

Figure 3. Changes to doses of the five most frequently prescribed sedating medications 41

Figure 4. Frequency of the changes in DBI score (a) and sedative load (b) 44

Figure 5. Distribution of ten most frequently prescribed sedating medications among patients admitted to acute mental health units prior to admission and upon discharge 57

Figure 6. Frequency of the changes in DBI score (a) and sedative load (b) among patients admitted to acute mental health units 59

List of Tables

Table 1. Studies that used the DBI and the parameters associated with a greater DBI score 13

Table 2. Studies that used the SLM and the parameters associated with a greater sedative load 20

Table 3. Inclusion and exclusion criteria 25

Table 4. Assumptions for discharge medications 26

Table 5. Examples of determination of the minimum recommended daily dose based on the AMH and the TGA 30

Table 6. Variables derived from patients' parameters for descriptive and exploratory analyses 32

Table 7. Examples of selection of admission data that satisfy the inclusion criteria for patients with multiple visits 36

Table 8. Demographics of the study population 38

Table 9. Ten most frequently prescribed sedating medications prior to admission and on discharge by level 5 ATC code 40

Table 10. Sed-DBI scores and sedative load by patients' characteristics 43

Table 11. Paired samples t-test between pre-admission and discharge sedative burden 44

Table 12. Association of patients' characteristics with the changes in Sed-DBI score and sedative load during hospitalisation in the unadjusted linear regression models 46

Table 13. Changes in Sed-DBI score and sedative load from admission to discharge by categories in stratified paired samples t-tests 48

Table 14. Association of patients' characteristics with the changes in Sed-DBI score and sedative load during hospitalisation in baseline adjusted linear regression models 50

Table 15. Backward selection of predictor variables that predict the changes in Sed-DBI score during hospitalisation 52

Table 16. Backward selection of predictor variables that predict the changes in sedative load during hospitalisation 53

Table 17. Demographics of patients admitted to acute mental health units and other units 55

Table 18. Ten most frequently prescribed sedating medications at pre-admission and discharge by level 5 ATC code among patients admitted to acute mental health units 56
Table 19. Sed-DBI score by patients' characteristics between patients admitted to acute mental health units and patients admitted to other units..... 60
Table 20. Sedative load by patients' characteristics between patients admitted to acute mental health units and patients admitted to other units..... 61
Table 21. Independent samples t-tests between the changes in Sed-DBI score and sedative load among patients admitted to acute mental health units and patients admitted to other units 62
Table 22. Paired samples t-tests between pre-admission and discharge sedative burden among patients admitted to acute mental health units..... 62
Table 23. Associations of patients' characteristics with the changes in Sed-DBI score and sedative load during hospitalisation in unadjusted linear regression model among patients admitted to acute mental health units 64
Table 24. Changes in Sed-DBI score and sedative load from admission to discharge by the number of medication and gender in stratified paired samples t-tests..... 64
Table 25. Association of patients' characteristics with the changes in Sed-DBI score and sedative load during hospitalisation in baseline adjusted linear regression models among patients admitted to acute mental health units 66
Table 26. Backward selection of predictor variables that predict the changes in Sed-DBI score during hospitalisation for patients admitted to acute mental health units 68
Table 27. Backward selection of predictor variables that predict the changes in sedative load during hospitalisation for patients admitted to acute mental health units 69

Supplementary Table 1. List of medications included in the present study..... 92
Supplementary Table 2. Estimates of Fixed Effects coefficients for interaction terms with period..... 98
Supplementary Table 3. Estimate of fixed effects coefficients for interaction terms with period for patients admitted to acute mental health units 99

Supplementary Table 4. Stepwise backward selection multiple regression models for the changes in DBI score 100
Supplementary Table 5. Stepwise backward selection multiple regression models for the changes in sedative load 103
Supplementary Table 6. Stepwise backward selection multiple regression models for the changes in DBI score for patients admitted to acute mental health units 105
Supplementary Table 7. Stepwise backward selection multiple regression models for the changes in sedative load for patients admitted to acute mental health units 106

List of Abbreviations

ABS	Australian Bureau of Statistics
AMH	Australian Medicines Handbook
ATC	Anatomical Therapeutic Chemical
CNS	Central nervous system
DBI	Drug burden index
DBI-WHO	Drug burden index calculated with the defined daily dose as defined by the World Health Organization
ED	Emergency department
EMR	Electronic medical records
FDA	Food and Drug Administration
FGA	First generation antipsychotic
GABA	Gamma-aminobutyric acid
LOS	Length of stay
PBS	Pharmaceutical Benefits Scheme
PRN	“Pro re nata", as needed medications
Sed-DBI	Sedative component of the Drug burden Index
SGA	Second generation antipsychotics
SLM	Sedative Load Model
TGA	Therapeutic Goods Administration

Glossary

Antipsychotics	A class of medications indicated for the management of psychosis
Antipsychotic polypharmacy	Concurrent use of more than one antipsychotic medications
Sedation	Suppress the CNS, induce drowsiness and relaxation
Sedative burden	Medication burden of using medications with sedating properties
Sedative load	Sedative burden quantified by the SLM
Drug burden	Medication burden quantified by the drug burden index, referring to studies that used both the anticholinergic and sedative component of the DBI
Polypharmacy	Concurrent use of five or more medications
Pre-admission	Prior to hospitalisation
Psychosis	A mental disorder characterised by symptoms such as hallucination, delusion, disordered thoughts and changes in behaviour and emotions
Psychotropic medication	Medications used for the management of mental illnesses
Psychotropic polypharmacy	Concurrent use of two or more classes of psychotropic medications
QT prolongation	Prolonged duration of ventricular depolarization and repolarization[1]

Summary

Antipsychotics are indicated for the treatment of psychosis. Although there is only limited evidence supporting the effectiveness of using multiple antipsychotics and in combination with other psychotropic medications (known as psychotropic polypharmacy), it remains common in clinical practice. The use of multiple medications with sedating properties can exacerbate central nervous system (CNS) depression and the medication burden associated with sedating medication is known as the sedative burden. The risks associated with a higher sedative burden have been widely investigated in many prior studies. However, no previous study has investigated the changes in sedative burden among hospitalised patients taking antipsychotics before admission.

The objective of this study was to investigate the changes in the sedative burden as quantified by the sedative component of the drug burden index (Sed-DBI) and the sedative load model (SLM), between admission and discharge among patients taking at least one antipsychotic medication before hospitalisation.

This retrospective observational study utilised existing inpatient data from Sunrise electronic medical records (EMR) from three South Australian public hospitals between 1 January to 31 December 2019. Patients taking at least one antipsychotic medication before admission, aged 18 years and above, with a length of hospitalisation of over 48 hours, and patients whose medication history had been documented or verified by a hospital pharmacist were included in the present study. The Sed-DBI and the SLM were developed and validated in the older population. By employing these models in this study, the present study was able to explore the opportunity to expand the scope and utility of the DBI and SLM in a broader population. Patients' demographics and hospital characteristics were analysed to identify parameters associated with the changes in the sedative burden. Subgroup analyses were also performed to investigate the differences between patients admitted to acute mental health units and patients admitted to non-acute mental health units.

711 patients who were taking antipsychotics before admission were included, but no significant differences were found in the Sed-DBI score and the sedative load between admission and discharge in the total study population. For patients admitted to acute mental health units (n=407), significant differences in the sedative burden were observed between admission and discharge (Sed-DBI: $p<0.0001$; SLM: $p=0.018$). For this subgroup of patients, a lower pre-admission Sed-DBI score ($p<0.0001$), younger age ($p=0.040$), male gender ($p=0.002$), a longer length of hospitalisation ($p=0.046$) and a greater mean number of medications ($p<0.0001$) were found to be predictors of increased Sed-DBI score at discharge. Patients' demographics and hospital characteristics found to be associated with the increased sedative load were a lower pre-admission sedative load (, $p<0.0001$), male gender ($p=0.001$), and a greater mean number of medications ($p<0.0001$).

The findings of the present study identified patients at a higher risk of being discharged with a significantly higher sedative burden. Due to the current lack of research in this patient group, more research is required to independently validate the findings of this study and explore the potential risks associated with increased sedation in this group of patients after discharge.

Declaration

I declare that:

this thesis presents work carried out by myself and does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; to the best of my knowledge it does not contain any materials previously published or written by another person except where due reference is made in the text; and all substantive contributions by others to the work presented, including jointly authored publications, is clearly acknowledged.

Ruby Tszwai Au 03 March 2022



Acknowledgments

I would like to acknowledge and thank my supervisors, Dr Vijayaprakash Suppiah and Dr Elizabeth Hotham for their ongoing support, advice, and patience. As well as my associate supervisor, Professor Sepehr Shakib for his invaluable feedback, extracting the data from the electronic medical records and giving me access to the de-identified data. This thesis would not have been possible without the guidance and support of my supervisors.

I would also like to acknowledge the support I received from Professor Adrian Esterman for his clear explanations and suggestions on the statistical analyses, and Dr Alex Choo for extracting part of the medication data and providing invaluable comments and suggestions in our meetings.

I also wish to acknowledge that this research is supported by the Australian Government Research Training Program (RTP) fee offset scholarship.

Lastly, I am grateful to my family and friends for always encouraging and supporting me.

1. Background

1.1 Antipsychotics and psychoses

Psychosis is a common mental illness among Australians, with reports as high as 1 in 200 Australian adults experiencing one psychotic episode in any given year [2]. Psychosis is associated with manifestations such as hallucinations, delusions, disordered thoughts and changes in behaviour and emotions [2].

The most recent Australian national psychosis survey reported a high prevalence of psychotropic medication use amongst patients experiencing psychosis [3]. Patients with psychosis are treated with a variety of medications, including second generation (atypical) antipsychotics (SGAs) (78.4%), antidepressants (37.2%), mood stabilisers (26.5%), first generation (typical) antipsychotics (FGAs) (18.2%), anxiolytics and hypnotics (17.2%). Most participants reported some degree of deterioration in mental and physical health after illness onset, with the adverse effects of antipsychotics being one of the main contributors to this impairment [3]. More than half (61%) of the participants reported deterioration in daily activities due to adverse effects associated with the medications [3].

Antipsychotics are indicated for the treatment of psychotic disorders such as schizophrenia, and bipolar disorder [4, 5]. Antipsychotic medications are classified into two groups, first and second generation antipsychotics, also known as typical and atypical antipsychotics respectively [4, 6]. FGAs are mostly dopamine D2 receptor antagonists, while SGAs are dopamine D2 receptor and serotonin 5HT2 receptor antagonists [7]. Compared to SGAs, FGAs have a greater affinity to dopamine D2 receptors, which are associated with a higher risk of extrapyramidal side effects [7]. Other common adverse effects related to both groups of antipsychotics include anticholinergic effects such as blurred vision, constipation, and dry mouth, cardiometabolic effects such as weight gain, hyperglycaemia, and hypertension, as well as hyperprolactinaemia, orthostatic hypotension, QT prolongation, and sedation [8]. These adverse effects are induced by their non-selective broad affinities to various receptors and are dependent on the substance

and dosage [8]. Apart from the dopamine D2 and serotonin 5HT2 receptors, antipsychotics can also antagonise muscarinic receptors, adrenergic receptors and histamine receptors [9].

One global study investigated the prevalence of antipsychotic use in 16 countries between 2005 and 2014 [10]. In this study, an increasing trend was observed in 10 countries, particularly, an increasing prevalence of SGA in all populations studied [10]. In a more recent study, the global prevalence of psychotropic medication use was found to be higher in 2020 compared to 2015, an average of 4% increase per annum was reported between 2015 and 2020 [11]. Additionally, the use of antipsychotic medications increased by an average of 2.5% annually during the study period [11].

Similarly, recent Australian data also demonstrated an increasing trend in prescriptions of psychotropic medications between 2013 and 2020. In 2013, a total of 3,771,618 patients were dispensed mental health-related medications (antipsychotics, anxiolytics, hypnotics and sedatives, antidepressants, and psychostimulants, agents used for ADHD and nootropics), of which 430,171 (11.4%) were antipsychotics [12]. In 2020, 4,398,426 patients were prescribed mental health-related medications, inclusive of 483,300 individuals prescribed antipsychotics, 39,205 of the latter were South Australians prescribed antipsychotics [12]. Over this 7 year study period, there was a 16.6% increase in the number of patients prescribed mental health-related medications, and a 12.4% increase in the number of patients prescribed antipsychotics [12].

Another Australian study also reported a similar increase in the prescriptions of antipsychotics from 2006 to 2018 [13]. In this study, olanzapine had the highest cumulative prescription count, followed by quetiapine and risperidone [13]. This study highlighted the popularity of SGAs as preferred agents for the treatment of mental illnesses [13]. A literature review has also highlighted the concurrent use of antipsychotics among individuals with severe mental illnesses [14]. However, the practice of prescribing multiple antipsychotics is generally not recommended in guidelines [6].

1.2 Recommended use of antipsychotics

According to the Australian Medicines Handbook (AMH) [4], the primary indications for antipsychotics are acute and chronic psychoses, and bipolar disorder. The Royal Australian and New Zealand College of Psychiatrists' clinical practice guidelines for the management of schizophrenia and related disorders [15] recommend that antipsychotics such as amisulpride, aripiprazole, asenapine, chlorpromazine, clozapine, haloperidol, lurasidone, olanzapine, paliperidone, periciazine, quetiapine, risperidone, trifluoperazine, ziprasidone, and zuclopenthixol hydrochloride can be used in the management of symptoms of schizophrenia. Additionally, for patients experiencing distress and agitation, or patients with mood or anxiety symptoms, benzodiazepines, mood stabilisers, and antidepressants have also been recommended [15].

Apart from schizophrenia and related disorders, antipsychotics such as olanzapine are also recommended as oral sedatives for acute behavioural disturbances [16]. Although not approved by the Therapeutic Goods Administration (TGA) for the treatment of delirium, haloperidol, olanzapine, risperidone and quetiapine have been suggested for the management of hyperactive delirium [17]. Olanzapine, risperidone and quetiapine are also used to treat patients with dementia with behavioural and psychological symptoms [18]. The Royal Australian and New Zealand College of Psychiatrists' clinical practice guidelines recommended the use of oral risperidone for behavioural and psychological symptoms of dementia for individuals experiencing severe agitation, aggression and psychosis symptoms who are otherwise unresponsive to non-pharmacological interventions and have a significant risk of harm [19]. However, the use of other antipsychotics for this indication is considered as off-label use [19].

1.3 Off label use of psychotropic medications in hospitals

The TGA and AMH do not recommend the use of antipsychotics among non-psychotic individuals due to their serious adverse effects [4, 5]. Prescribing of medications for indications that are not recommended in the approved product information are known as off-label prescribing.

In 2013, the Drug Utilisation Sub-Committee of the Pharmaceutical Benefits Advisory Committee reported an increase in SGA prescriptions among middle-aged adults [20, 21]. In particular, quetiapine was identified as the major contributor to this increase [20, 21]. Prescribing of 25 mg quetiapine was found to be associated with off-label indications such as sleep related problems and anxiety [20]. Consequently, the number of repeats for quetiapine was amended to discourage the use of 25 mg quetiapine for non-subsidised conditions [20]. A 24 months follow up review reported a decrease in prescriptions of 25 mg quetiapine. Despite this, the Drug Utilisation Sub-Committee expressed their concern about the number of patients who continued to receive multiple supplies of 25 mg quetiapine [22].

Prescribing of quetiapine for non-psychiatric indications was also reported in a recent Australian study [23]. Among 1,259 patients admitted to a metropolitan hospital over five years, 793 patients were admitted for non-psychiatric reasons and were prescribed quetiapine [23]. The authors randomly selected and reviewed 87 medical records and reported 55% of potential off-label prescriptions, mainly for the management of agitation or delirium [23]. Among these 87 patients, 33 patients had newly prescribed quetiapine during hospitalisation, with a third of them continuing quetiapine on discharge and over 70% of these prescriptions that were continued upon discharge were found to be potentially off-label [23].

Other antipsychotic medications such as risperidone, haloperidol and olanzapine have also been prescribed in hospitals for various reasons unrelated to schizophrenia and related disorders, such as agitation, anxiety, and the management of behavioural symptoms related to delirium and dementia [24, 25]. One study identified hospitalised patients admitted for reasons unrelated to mental disorders and reported that 9% of the 1,537 patients were prescribed antipsychotics during hospitalisation [25]. Among these patients, over half (55%) were newly prescribed antipsychotics, of which 26% were continued on discharge [25]. In a subgroup analysis of 100 randomly selected patients who were newly prescribed antipsychotics, the most common indication was for the management of delirium (53%) [25].

Besides antipsychotics, other psychotropic medications can also be prescribed in hospitals for non-psychiatric indications. Authors of an Australian study reported that 45% (n=89) of the patients were prescribed one or more psychotropic medications such as antipsychotics, antidepressants, mood stabilisers, and benzodiazepines for both psychiatric and non-psychiatric indications [24]. In this study, indications that were not approved by the TGA included aggression and agitation, delirium, dementia, pain, and nausea [24]. 60% of the prescribed psychotropic medications were identified as being potentially inappropriate due to the lack of documented indications [24]. The initiation and continuation of psychotropic medications on discharge, as well as the reasons for prescribing dosages higher than the recommended dose, became unclear. Hence, the appropriateness of the prescriptions cannot be determined [24].

These studies have highlighted that the use of psychotropic medications is common in hospitals for non-psychiatric indications and poorly documented indications, as well as the likelihood of continuing newly prescribed psychotropic medications on discharge. While the use of psychotropic medications for selected non-mental health diagnoses may be justifiable and can result in the desired therapeutic outcomes, this practice is potentially problematic as the use of more than one medication with sedating properties can compound this risk.

1.4 Psychotropic medications and sedation

Sedation is a common adverse effect induced by antipsychotics and the extent of sedation is agent and dose dependent [6, 8]. Sedation is caused by the inhibition of the histamine H1 receptor [26] which results in the reduction of neurotransmission in the central nervous system (CNS), suppressing the action of histamine which promotes wakefulness [27, 28]. Olanzapine, followed by clozapine and zotepine (currently not available in Australia) are three SGAs with the highest affinities for histamine H1 receptors, and hence, more likely to induce sedation [26]. However, quetiapine which has a lower affinity for the histamine H1 receptors could exhibit a greater sedating effect at increased doses [29].

Besides antipsychotics, many other medications also have sedating properties. These include antihistamines, benzodiazepines, antidepressants and mood stabilisers [30]. Similar to antipsychotics, these psychotropic medications can also inhibit various receptors within the CNS leading to sedation [30]. However, the pharmacology of these medications varies. Antihistamines and antidepressants, like antipsychotics, also inhibit the histamine H1 receptors, while benzodiazepines bind to the gamma-aminobutyric acid (GABA) receptors to cause sedation [30].

1.5 Concomitant use of psychotropic medications and risks associated with sedating medications

Concomitant use of psychotropic medications can increase the sedative burden, which is defined as the medication burden of using medications with sedating properties [31, 32]. Even though concomitant use of antipsychotics is often not recommended by the Australian Therapeutic Guideline [6], patients can be prescribed multiple antipsychotic medications [33]. The 2010 Australian survey of psychosis reported that 63.4% of the participants were taking more than one psychotropic medication and 27.4% taking two or more antipsychotics [3]. In addition, one Australian study that focused on antipsychotic polypharmacy among patients with schizophrenia or schizoaffective disorder reported that 43.2% of the study cohort was prescribed two or more antipsychotics [34]. Another Australian study reported an increased prevalence of SGA polypharmacy between 2006 and 2015 [35]. Among the classes of medications observed in this study (which were antipsychotic, antidepressant, benzodiazepine, lithium, and attention deficit hyperactive disorder medications), antipsychotics had the highest prevalence of polypharmacy [35], suggesting that concomitant antipsychotic prescriptions are relatively common.

In comparison to antipsychotics, individuals taking other psychotropic medications such as benzodiazepines and antidepressants are less likely to take other medications in the same drug class concomitantly [35]. However, concomitant use of different classes of psychotropic medications is fairly common [35]. A previous study exploring the side effect burden among individuals taking antipsychotics found that patients with schizophrenia were more likely to take antipsychotics alone (66.6%) in

comparison to patients with unspecified psychosis symptoms (17.9%), bipolar disorder (13.1%), and major depression with psychotic symptoms (2.4%) [36]. Additionally, 49.1% of the patients taking antipsychotics in combination with other psychotropic medications were patients with schizophrenia, followed by patients with bipolar disorder (33.5%), unspecified psychosis symptoms (11.1%), and major depression with psychotic symptoms (6.3 %) [36]. In a study cohort of 1,087 individuals with severe mental disorders, 42.3% of them were taking antipsychotics in combinations with other psychotropic medications, followed by patients taking antipsychotic medications alone (34.4%), other psychotropic medications alone (17.6%), and not taking any medications (5.7%) [36]. The burden of side effects was evaluated by both the participants and the investigators [36]. In both instances, a higher percentage of patients who were taking antipsychotics in combination with other psychotropic medications reported a more severe side effect burden in comparison to those taking antipsychotics only [36]. Those taking antipsychotics only also reported an increased burden of side effects when compared to individuals taking other psychotropic medications [36]. Among the reported psychological side effects, sedation and increased duration of sleep were significantly more prevalent among individuals taking antipsychotics in combinations with other psychotropic medications [36]. Additionally, increased duration of sleep was also significantly more prevalent in individuals taking antipsychotics alone compared to participants not taking any medications [36]. Therefore, this study suggested that individuals taking antipsychotics alone and in combination with other psychotropic medications have a higher side effect burden and a greater likelihood of experiencing excessive sedation [36].

A study examining the potential drug-related problems associated with long-term use of sedating medications prior to admission and the prescriptions of new sedating medications during hospitalisation reported that 90% of the patients may experience additional CNS depressant effects [37]. Moreover, it was postulated that the remaining 6% and 4% of the patients may experience QT prolongation and an increase in other adverse effects, respectively [37]. These drug-drug interactions are likely to exacerbate in patients with mental illness, as they are often taking multiple medications with sedating properties [37].

1.6 Drug Burden Index

The Drug Burden Index (DBI) and Sedative Load Model (SLM) are two validated measures that have been used previously to determine medication burden in various settings.

DBI is a tool developed by Hilmer et al. [31], designed to quantify the cumulative effects of anticholinergic and sedating medications. The model involves categorising medications into those with anticholinergic properties and those with sedating properties [31]. The DBI score for each medication can be calculated by the daily dose taken by the individual and the minimum recommended daily dose defined by the U.S. Food and Drug Administration (FDA) [38]. The cumulative drug burden for each patient can then be calculated, as shown in the following equations [31]:

$$DBI = \sum \frac{D}{\delta + D}$$

$$DB = B_{AC} + B_S$$

where the drug burden index score (DBI) is the sum of the daily dose taken by the patient (D) divided by the sum of the minimum recommended daily dose (δ) and D [31]. The total drug burden (DB) for an individual is the sum of the anticholinergic component of the drug burden (B_{AC}) and the sedative component of the drug burden (B_S) [31]. While the total drug burden is defined as the addition of the two components of the DBI, previous studies have examined the anticholinergic and sedative components separately [39-44]. In this study, only the sedative component of the DBI (Sed-DBI) will be investigated.

As mentioned above, the DBI calculation used the minimum recommended daily dose as defined by the FDA. However, the minimum recommended daily dose and the definition of anticholinergic and sedating medications can vary between different countries. This creates some level of confusion that can be observed in previous Australian studies where some authors have used the minimum recommended daily dose and the sedative and anticholinergic properties of the medications as defined by the Monthly Index

of Medical Specialities handbook [45-48] or the TGA [39, 49-56] while others have used the FDA recommendations [42, 57, 58].

A variation to the DBI was published in 2013 to take into account the differences in the minimum recommended daily dose observed in different countries. It was suggested that a modified international version of DBI (DBI-WHO) could be utilised as a measure to compare drug burden across different countries by substituting the minimum recommended daily dose with the defined daily dose (DDD) approved by the World Health Organisation [59].

$$\text{DBI-WHO} = \sum \frac{D}{DDD+D}$$

However, as noted by the authors of the original DBI model, the modified international version of the DBI substituted the minimum recommended daily dose with the DDD, which is the assumed average maintenance adult daily dose for the main indication of the medication [60, 61]. The average maintenance dose is substantially higher for some medications in comparison to their minimum recommended daily dose, which could result in a lower DBI score [60]. Consequently, this modified model has not been employed as commonly as the original DBI model. As such, only the original DBI model was used in this study.

1.7 Sedative Load Model

The SLM is a measure used to quantify the cumulative sedative burden [32]. Unlike the DBI, the SLM is a rating system dependent on the indication and side effect profile of the medication [32]. The SLM was developed in 2003 to categorise prescription medications in Finland between 1998 to 2001 [32].

In this model, medications were classified into four groups [32, 62]:

i. Group 1 included primary sedatives, which are psychotropic medications with sedating properties as their therapeutic effects.

   All medications in Group 1 have a sedative rating of 2.

ii. Group 2 consisted of medications with sedation as a prominent side effect.

Medications in Group 2 have a sedative rating of 1.

iii. Group 3 included medications with sedation as a potential adverse effect.

iv. Group 4 consisted of medications with no known sedating properties or with uncertain sedating effects.

Medications in Groups 3 and 4 were both given ratings of 0.

The total sedative load can be determined by calculating the sum of the individual sedative scores as indicated in the formula below, where n is the number of medications and SR_k is the sedative rating of drug k [63, 64]. The summation notation indicates that the total sedative load for an individual is the sum of the sedative ratings of all of their prescribed medications.

$$Sedative\ load = \sum_{k=1}^{n} SR_k$$

Minor modifications of the classification system of the SLM were necessary to apply the model to the Australian context. In an Australian study, clinical pharmacists identified medications that were not included in the original SLM and classified them into four groups in accordance with the original model [65].

1.8 Prior studies that employed the DBI and SLM

Previous studies have found significant associations between a greater DBI score and a higher sedative load with impaired physical [31, 39, 40, 44, 51, 63, 66-69] and cognitive functions [31, 50, 70], poorer functional status [39, 66, 68, 71], and quality of life [54, 72, 73]. Among hospitalised patients, a greater DBI score was found to be associated with a longer length of hospitalisation [40, 74], and an increased risk of readmission after discharge [75, 76]. Additionally, one study identified hospitalised patients above the age of 80 years, diagnosed with insomnia and taking a greater number of medications as predictors of having a greater DBI score [77]. Other studies that measured the medication burden with the DBI or the

SLM have reported significant associations with increased risk of falls [78, 79], hospitalisations [74, 80], fall related hospitalisations [81], as well as increased frequency of general practitioner visits [81], and poorer oral health [82, 83]. Further, some studies also explored the relationship between medication burden and variables such as frailty [47, 84, 85], risk of hip fracture [86] and mortality [74, 81], while others have found no associations between these factors and the cumulative medication burden [40, 71, 78, 80, 87-89].

Additionally, some studies have investigated specific study populations. A greater DBI score was found to be associated with individuals with epilepsy who were above the age of 60 years [90]. Other studies reported a greater DBI score among patients who were taking analgesics [91] or opioids [92] in hospitals. One study that focused specifically on patients with type 2 diabetes mellitus, reported a significant association between a higher DBI score and poorer immediate memory among patients aged 55 and above [93]. A significant association was also reported between a higher DBI score and a greater comorbidity burden among patients with autism spectrum disorder and comorbid intellectual disability [94].

Among studies that explored the medications burden using the DBI and SLM, many have focused on examining the associations between the medication burden and functional impairments, with a limited number of studies having investigated the changes in the medication burden in hospitals [41, 45, 78, 95].

One Australian study investigated the changes in DBI and polypharmacy from admission to discharge in older patients aged 65 and above [45]. Even though the overall difference was not significant, an increase in the DBI score was found to be associated with delirium related hospital admission (OR = 2.82, 95% CI = 1.48–5.40) [45]. However, the risk of falls was not associated with DBI and polypharmacy [45]. In a similar study conducted in French geriatric hospitals [78], the authors measured the changes in DBI and DBI-WHO scores between admission and upon discharge or when the patient experienced a fall. Their results suggested that an increase in the DBI and DBI-WHO scores were associated with an increased risk of in-hospital falls ($p = 0.03$) but not with in-hospital mortality [78]. Additionally, two studies have

identified that the change in DBI scores in hospitals can be predicted by patient characteristics. Both studies included patients aged 65 years and above. One recruited patients admitted to geriatric hospitals who were receiving at least one medication on admission (n=337) and reported that increased DBI score during hospitalisation was associated with male gender, hospitalisation due to stroke, patients being unable to stay home, patients with diabetes mellitus, and a greater number of medications at admission [95]. The other study found that greater drug burden at admission and more severe illness were associated with the escalated DBI score during hospitalisation [41]. Increased cognitive decline was also reported among patients with an increased or stable DBI score during hospitalisation compared to patients whose DBI score decreased [41].

Table 1. Studies that used the DBI and the parameters associated with a greater DBI score

Study	Year	Study population	Age	Associations with a higher DBI score:
[31] [a]	2007	Community-dwelling individuals, United States (n=3,075)	70-79	Poorer physical and cognitive performance determined by the Health Aging and Body Composition physical performance score and the Digit Symbol Substitution Test
[39] [a]	2009	Community-dwelling older men, Australia (n=1,705)	≥70	Poorer outcome for three tasks of the physical performance battery: walking speed, narrow walk speed, and balance Poorer muscle strength determined by a dynamometer Poorer functional status measured by the Instrumental Activities of Daily Living scale
[80]	2012	Community-dwelling individuals, Finland (n=339)	≥75	Increase the risk of hospitalisation Not associated with longer length of hospitalisation
[50]	2012	Community-dwelling older men, Australia (n=987)	≥70	Poorer cognitive function and performance determined by the Addenbrooke's Cognitive Examination and the Trail Making Task cognitive tests in the unadjusted model
[40] [a]	2012	Hospitalised patients admitted to acute geriatric medicine units, United Kingdom (n=362)	> 60	Poorer physical function measured by the Barthel Index, Increased length of hospitalisation Not associated with in-hospital mortality

[66]	2012	Community-dwelling individuals, Finland (n=700)	≥75	Poorer outcome for two tasks of the physical performance battery: 10-m walking speed, chair stands test Poorer functional mobility and functional status measured by timed up and go test, Instrumental Activities of Daily Living Scale and Barthel Index
[51]	2012	Older people living in self-care retirement villages, Australia (n=115)	≥ 70	Poorer physical functioning measured by Short Performance Physical Battery Not associated with muscle strength measured by a dynamometer
[72]	2012	People with dementia in residential aged care facilities, Australia (n=351)	≥65	DBI > 0 was found to be associated with poorer quality of life measured by the Quality of Life – Alzheimer's disease questionnaire
[45]	2013	Hospitalised older patients, Australia (n=329)	≥65	Associated with delirium related hospital admission Not associated with fall-related admission
[78]	2014	Hospitalised patients admitted to geriatric hospitals, France (n=337)	≥65	Increased DBI during hospitalisation was associated with an increased risk of falls Not associated with mortality during hospital stay

[81]	2014	Individuals who received prescription medication, New Zealand (n = 537,387)	≥65	Increased risks of fall-related hospitalisations, general practitioner visits, and mortality
[75]	2014	Hospitalised patients, United States (n=229)	≥65	Increased risk of readmission within 30 days of discharge
[74]	2014	People with and without Alzheimer's disease, Finland (n=16,603)	≥65	Longer length of hospitalisation, greater rate of admissions, and mortality for patients with and without Alzheimer's disease
[47]	2016	Community-dwelling older men, Australia (n=1,705)	≥70	Increased risk of transitioning from the robust states to prefrail states, and from the robust state to death measured by the Fried frailty phenotype criteria
[88]	2017	Hospitalised patients admitted to geriatric ward, France (n=315)	≥65	Not associated with the risk of fall
[87][a]	2017	Patients with dementia in nursing home, Netherlands (n=140)	≥70	Not associated with physical and cognitive functions
[95]	2017	Hospitalised patients admitted to geriatric hospitals, France (n=337)	≥ 65	Increased DBI during hospitalisation was associated with being male, stroke-related hospitalisation, hospitalisation due to patient's inability to stay in their

				own home, patients with diabetes mellitus, and a greater number of medications at admission
[67]	2018	Individuals with intellectual disability, Ireland (n=677)	≥ 40	Poorer physical function measured by Barthel index was found to be associated with DBI ≥1
[54]	2018	Older adults with a high prevalence of cognitive impairment and dementia, Australia (n=537)	Mean= 85.5	Poorer quality of life determined by EuroQol Five Dimensions Questionnaire, but not associated with the quality of life when determined by the Dementia Quality of Life Questionnaire
[79]	2018	Community-dwelling individuals, New Zealand (n=71,859)	≥65	Increased risk of fall
[77]	2019	Hospitalised patients in the geriatric department with polypharmacy, China (n=611)	≥65	Individuals aged ≥80, with a greater number of medications, and insomnia were found to be associated with DBI>0
[93]	2019	Patients with type 2 diabetes mellitus and taking oral	≥18	Poorer immediate memory measured by the Repeatable Battery for the Assessment of Neuropsychological Status among individuals aged ≥55

		antihyperglycemic medication or insulin, United States (n=105)		
[44]	2019	Individuals with intellectual disability, Ireland (n=677)	≥ 40	Poorer physical function determined by the Barthel Index, but not when physical function was measured by grip strength and the timed up and go assessment
[86]	2019	Frail community-dwelling individuals, New Zealand (n= 70,533)	≥ 65	Increased risk of hip fracture
[94]	2019	Patients with Autism spectrum disorder and comorbid intellectual disability, France (n=63)	> 20	Associated with greater comorbidity burden measured by Cumulative Illness Rating Scale
[92]	2020	Hospitalised patients prescribed five or more medications on discharge, South Australia (n=1,192)	≥ 75	Opioid users were found to be more likely to have a greater median DBI

[70]	2020	Healthy community-dwelling individuals at risk of Alzheimer's Disease, United States (n=206)	≥45	Associated with subjective cognitive decline with increasing age
[41] [a]	2020	Cognitively intact hospitalised patients, Israel (n=550)	≥65	Associated with increased cognitive decline in patients with an increased DBI and DBI remained unchanged compared to patients whose DBI decreased
[91]	2020	Older hospitalised patients with polypharmacy, Australia (n=1,192)	≥ 75	Significantly greater DBI score for analgesic user
[68]	2020	Community-dwelling individuals, Netherland (baseline, n=2,627)	55–85	Poorer outcomes of cognitive function measured by the Alphabet Coding Task, Auditory Verbal Learning Test, and Raven Colored Progressive Matrices Poorer physical function measured by Cardigan Test, Chair Stands Test and self-reported Functional Independence, but not when physical function was measured by the Walking Test and Balance Test
[90]	2020	Individuals with or without epilepsy, Netherlands (cases, n=24,185, control, n=46,861)	≥ 18	Significantly greater DBI for individuals with epilepsy, and individuals aged >60

[76]	2020	Patients identified as having "high risk for fall" and fell during hospitalisation, United States (n=113)	≥50	Increased DBI score between admission and first in-hospital fall was found to be associated with a greater readmission rate within 30 days of discharge
[85]	2021	Random sample of Medicare beneficiaries, United States (n=4,137,384)	≥66	DBI>2 was found to be associated with being female, younger individuals, white race, number of prescriptions, frailty, and individuals with psychosis
[73]	2021	Community-dwelling individuals living with chronic conditions and taking multiple medications, Australia (n=367)	Median: 64	Poor quality of life measured by two domains of the Medication-Related Burden Quality of Life tool, psychological burden domain and functional and role limitation domain, but not with routine and regimen complexity domain, therapeutic relationship domain, or social burden domain

[a] Studies that reported findings of the sedative component of the DBI

Table 2. Studies that used the SLM and the parameters associated with a greater sedative load

Study	Year	Study population	Age	Associations with a higher sedative load:
[64]	2011	Community-dwelling individuals, Finland (n=700)	≥75	Being female, poorer self-rated health, loneliness, and poorer daily functioning measured by instrumental activities of daily living
[88]	2017	Hospitalised patients admitted to a geriatric ward, France (n=315)	≥65	Not statistically significantly associated with the risk of fall
[82]	2016	Community-dwelling, non-smoking, dentate individuals, Finland (n=152)	≥75	Lower salivary flow rate, and increased risk of xerostomia among individuals with sedative load ≥3
[83]	2017	Community-dwelling, dentate, non-smoking individuals who had an oral clinical examination during 2004–2005, Finland (n=158)	≥75	Increased risk of having a greater number of carious teeth
[84]	2015	Community-dwelling adults, Ireland (n=3,446)	≥65	Associated with frailty determined by the International Physical Activity Questionnaire, and the frailty deficit index, as well as measuring walking speed and grip strength

[69]	2012	Community-dwelling individuals, Finland (n=700)	≥75	Sedative load >0 was found to be associated with poorer balance and mobility measured by the Maximal walking speed test, Timed Up and Go test and lower Berg Balance Scale
[63]	2011	Community-dwelling individuals, Finland (n=700)	≥75	Sedative load >0 was found to be associated with muscle strength with the chair stands test and by measuring grip strength
[71]	2012	Community-dwelling older men, Australia (n=1,696)	≥70	Poorer functional status measured by the activities of daily living and instrumental activities of daily living scale Not associated with physical performance measured by physical performance battery, and cognitive impairment measured by cognitive assessments after adjusting for covariates
[89]	2012	Community-dwelling individual, Finland (baseline, n=700)	≥75	Not associated with increased risk of mortality

1.9 Justification for this study

Previous studies have reported increasing trends in prescribing of antipsychotic medications in Australia [12, 13]. Individuals prescribed antipsychotic medications are often exposed to their significant adverse effects [3]. In addition to the impairments associated with psychosis, it had been previously reported that the adverse effects of antipsychotics can exacerbate the deterioration in mental and physical health [3]. Besides schizophrenia and related disorders, antipsychotics are also commonly prescribed for off-label indications, which are not recommended by Australian guidelines. Even though antipsychotic polypharmacy is also not recommended, studies have shown that patients prescribed antipsychotics are likely to experience antipsychotic and psychotropic polypharmacy [3, 14, 33-36].

Concomitant use of medications with sedating properties is associated with multiple consequences. Prior studies have developed and utilised the DBI and SLM to calculate the medication burden. Impaired physical functions were one of the most investigated parameters that were found to be associated with the cumulative medication burden (Table 1 and Table 2). However, prior studies that explored the cumulative medication burden have focused specifically on the elderly, generally, individuals aged 65 years and above. This is because older individuals are more likely to have multiple comorbidities and hence, at a higher risk of polypharmacy [96]. Additionally, they are also more vulnerable to the adverse effects associated with their medications [96].

Although majority of these studies had only included the elderly, other studies have reported that younger individuals are more likely to experience adverse effects. One study that explored the side effect burden among patients taking antipsychotics and other psychotropic medications had reported a significant association between younger patients and the increased likelihood of experiencing sedation [36]. Another study suggested a negative correlation between the dosage of psychotropic medications and age [97]. The latter found that increase in age was associated with the reduction in the doses of antipsychotic and antiepileptic medications [97]. Further, an increased incidence of adverse drug reactions induced by antipsychotics was reported among patients aged 60 years or younger in comparison to patients aged above 60 [97]. As such, although the risks of having multiple

comorbidities and polypharmacy might be lower for some younger individuals, the risks associated with sedating medications can be a significant problem among patients taking antipsychotics, regardless of age.

Additionally, hospitals are an ideal setting for medication reviews and initiating changes in medication regimens. However, very few studies have investigated the changes in medication burden in hospitals. Among the studies that did, they were again limited to older individuals. The changes in medication burden during hospitalisation among a more inclusive cohort of individuals taking antipsychotics, some of whom have psychotic disorders, remain to be addressed.

1.10 Objectives

The primary objective of this study is to quantify the changes in sedative burden between admission and discharge in patients using at least one antipsychotic medication at admission.

Secondary objectives are

i) to determine factors associated with changes in sedative burden among patients using antipsychotics prior to admission;
ii) to identify differences in sedative burden and characteristics of patients admitted to acute mental health and non-acute mental health units.

2. Method

2.1 Study design and source of data

This retrospective observational study utilised existing inpatient data from Sunrise electronic medical records (EMR), a system adopted by many public hospitals and healthcare facilities in South Australia [98]. The data were collected from hospitalised patients admitted to three public South Australian hospitals between 1 January 2019 to 31 December 2019.

These de-identified data included medication information such as medication name, dosage, route of administration, prescription status (pre-admission, during hospital stay, or on discharge), frequency, and the type of medication (regular or pro re nata (PRN)), and patient data such as patients' visit type, admission and discharge date and time, admission unit, and discharge status. The only patients' demographic characteristics available for analyses were age and gender.

2.1.1 Study population

The present study included patients admitted to a metropolitan acute care teaching hospital (Facility A), a metropolitan hospital with a range of services including 24/7 community emergency department (ED) and inpatient mental health facilities (Facility B), and a regional acute care hospital with 70 beds (Facility C) [99-102].

The inclusion criteria for this study were patients aged 18 and above, admitted to an inpatient unit or emergency department and whose medication history had been documented or verified by a hospital pharmacist. Patients who were admitted for less than 48 hours were excluded, as a 48 hours period was considered to be insufficient for prescribers to make changes to the patients' medications. Patients were only included if they were taking regular antipsychotic/s prior to admission with documentation of the dosage. Therefore, patients were excluded if they were only taking PRN antipsychotic medications prior to admission, or only taking antipsychotics during their hospital stay or on discharge. Additionally, patients admitted to palliative care, surgical, or oncology units were excluded. Patients not discharged from the hospitals were also excluded, as outlined in the inclusion and exclusion criteria below (Table 3).

Table 3. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria

• Aged 18 years and above
• Patients admitted to the inpatient unit or emergency department
• Use of at least one regular antipsychotic medication on admission with dosage documented
• Length of hospitalisation > 48 hours
• Patients whose medication history has been documented or verified by a hospital pharmacist
	• Patients admitted to
	  ○ Palliative care units
	  ○ Surgical units
	  ○ Oncology units
	• Patients transferred to another hospital or who died during their hospital stay
	• Patients that became maintenance patients

2.1.2 Drug classification

All medications taken by patients included in this study were classified according to the Anatomical Therapeutic Chemical (ATC) classifications system. This system categorises medications into fourteen main groups in the first level classification [103]. Every medication is further categorised into four additional levels based on their therapeutical, pharmacological and chemical properties [103]. In this study, level 5 ATC codes were used to categorise all medications.

2.1.3 Assumptions for discharge medications

In the present study, data on medications prescribed on discharge were not extracted from patients' discharge summaries. Assumptions were made according to the medications codes to determine the discharge medications. All medications in the dataset were coded against one of three classifications: HISA, DISCD and AUA1. These correspond to medications the patients were taking prior to admission (HISA), medications that were prescribed during hospitalisation and were discontinued automatically upon discharge (DISCD), and medications that were prescribed on discharge (AUA1).

To ensure consistency in the interpretation of the data, the following assumptions were made in determining whether the medications were given upon discharge, and their dose and frequency (Table 4):

1) For medications with a status of AUA1 (prescribed and supplied on discharge medications), the documented dose and frequency will be the AUA1 dose and frequency
2) For medications with both statuses DISCD (discontinued on discharge medications) and AUA1 (prescribed and supplied on discharge medications), their documented doses and frequencies will be the AUA1 doses and frequencies
3) For medications with both statuses HISA (pre-admission medications) and DISCD (discontinued on discharge medications), it is assumed that these medications were continued upon discharge and their documented doses and frequencies would be the same as the DISCD doses and frequencies (that is, what the patients were taking during their hospital stay)
4) For medications with a status of HISA (pre-admission medications) only, it is assumed that these medications were discontinued
    i. Exception: the medication is a depot medication with no equivalent prescribed as DISCD or AUA1
5) For medications with a status of DISCD (discontinued on discharge medications) only, it is assumed that these medications were discontinued
    i. Exception: the medication is a depot medication with no equivalent prescribed as AUA1

Table 4. Assumptions for discharge medications

	HISA	DISCD	AUA1	Continued on discharge	Dose and frequency
Assumption 1			✓	YES	AUA1
Assumption 2		✓	✓	YES	AUA1
Assumption 3	✓	✓	X	YES	DISCD
Assumption 4	✓	X	X	NO	N/A
Assumption 5	X	✓	X	NO	N/A

Note. Medications with the specific order status (HISA/DISCD/AUA1) are indicated by "✓", medications without the specific order status are indicated by "X", boxes coloured in grey indicate that the status of the medication will not impact the outcome of the assumptions

These algorithms were developed based on the following assumptions. If a patient was given medication with a code of DISCD, it was assumed that the medication was initiated during the

patient's hospital stay and discontinued upon discharge. However, if the medication had both HISA and DISCD codes, it was assumed that the patient was taking this medication prior to admission and was also given this medication during the patient's hospital stay. Hence, it was unlikely that the medication was stopped abruptly on discharge. The reasons for the missing AUA1 code could be that the patient was taking the medication regularly and did not require an additional Pharmaceutical Benefits Scheme (PBS) script for an additional supply of medications. However, it is also possible that this medication could have been a long-acting medication, such as a depot injection.

Additional assumptions for calculating the sedative burden include:

- Oral medication forms such as a tablet, orally disintegrating tablet, wafer, and controlled release tablet are interchangeable
- Medications that were originally given as a combination but given as individual medications during the hospital stay, were documented as an unchanged regimen
- For medications with a status of AUA1 with missing dosage and/or frequency information, the documented dose and frequency will be recorded as the DISCD dose and frequency as per Assumption 3
- Medications with a slow-release profile, such as antipsychotics depot injections and opioid transdermal patches were assumed to be evenly released over time

2.2 Calculating the sedative burden

The sedative burden was calculated based on both the sedative component of the DBI and the SLM.

2.2.1 Drug burden calculation

DBI is a prescription tool developed by Hilmer et al. [104] in 2007 to quantify the cumulative effects of anticholinergic and sedative medications. Since the focus of the present study was the sedative burden, only the sedative component of the DBI was used (Sed-DBI). The original study utilised the minimum recommended daily dose as defined by the U.S. Food and Drug Administration [104].

However, the minimum recommended daily dose varies across different countries. To ensure relevance to the Australian context, the minimum recommended daily dose in the present study was determined as guided by the TGA [5] and the AMH [4]. Further validations were sought from four literature sources [66, 86, 105, 106] (as per assumptions described below). For the purpose of determining the minimum recommended daily dose for this study the following assumptions were made:

1) The lowest starting dose recommended by both the TGA and AMH was used as the minimum daily dose
2) For medications where the minimum daily dose recommended varied for different indications, as shown in Table 5
    a. A common dose that is within the range of the daily dose recommended by both sources for most of the indications was used (e.g., Alprazolam)
    b. For medications where a common dose cannot be determined, the lowest dose for the most common indication was used (e.g., Risperidone)
    c. For medications where the most common indication cannot be determined, the lowest dose among all the indications was used (e.g., Aripiprazole)

Additionally, four reference studies [66, 86, 105, 106] were examined to compare against the selected minimum recommended daily dose in the present study.

3) For medications that were given in combination, only the minimum daily dose of the sedative component was included in the Sed-DBI calculation
4) Medications with a slow-release profile such as depot injections and transdermal patches were assumed to be evenly released over time and converted to the daily dose
   For example: Fentanyl patch 50 microgram/ hour = 1.20 mg per day
5) For medications that were given orally and parenterally at the same time, the parenteral preparation was converted to the approximate oral equivalent dose and added to the oral dose using the following equation [107]:

$$\frac{parenteral\ dose}{oral\ bioavailability} + oral\ dose$$

To determine the Sed-DBI score, only medications that contributed to the Sed-DBI were included in the drug burden calculations. Refer to Appendix A for the list of medications included in the Sed-DBI calculation. Topical formulations such as dermatological and ophthalmological preparations with sedative properties but minimal systemic effects were excluded from the Sed-DBI calculations [104].

Table 5. Examples of determination of the minimum recommended daily dose based on the AMH and the TGA

Medication	Condition	AMH	TGA	Selected minimum daily dose
a. Alprazolam	Anxiety	0.25 mg 3 times daily; range: 0.5–4 mg daily	0.5 mg daily; range: 0.5-4 mg daily	0.5 mg
	Anxiety with depressive symptoms		1.5 mg daily; range:1.5-4.5 mg daily	
	Panic disorder	0.5 mg at night, increased by 0.25–1 mg every 3 days	0.5 mg	
b. Risperidone	Schizophrenia	1 mg twice a day; range: 4-6 mg daily	1 mg twice daily, increasing by 1 mg twice daily; usual range 4–6 mg	2 mg
	Bipolar mania	2 mg; range 2–6 mg daily	2 mg; range 2–6 mg daily	
	Behaviour disturbance in Alzheimer-type moderate-to-severe dementia	0.25 mg twice daily; range: 1-2 mg daily		
	Behavioural Disturbances in Dementia		0.25 mg twice daily	
	Conduct and other disruptive behaviour disorders	> 50 kg, 0.5 mg; range: 0.5–1.5 mg daily	≥ 50 kg, 0.5 mg	
		< 50 kg, 0.25 mg; range: 0.25–0.75 mg daily	< 50 kg, 0.25 mg	
	Behaviour disturbance in autism	>20 kg, 0.5 mg; range: 1–2.5 mg daily	≥20 kg, 0.5 mg; range: 1–2.5 mg daily	
		<20 kg, 0.25 mg; range: 0.5–1.5 mg daily	<20 kg, 0.25 mg; range: 0.5–1.5 mg daily	
c. Aripiprazole	Schizophrenia	10 mg daily	10 mg daily; range: 10-30 mg	10 mg
	Bipolar disorder	15 mg daily	15 mg daily	

2.2.2 Sedative load calculation

The sedative load was calculated according to the original SLM which was first developed in 2003 for prescription medications approved in Finland between 1998 to 2001 [32]. Among the group 1 and group 2 medications included in the original table, 58 medications are currently marketed in Australia. To adapt the model to contemporary clinical practice in Australia, new medications and medications that were not included in the original model were added into the original list according to their indications and adverse effects as documented in the AMH [4]. Medications that are used as primary sedatives were added to group 1 (2 medications) while medications that have sedation, drowsiness, or somnolence documented as common adverse effects were included in group 2 (36 medications). See Appendix A for all medications in groups 1 and 2.

Medications in group 1 have a sedative rating of 2, while medications in group 2 have a sedative rating of 1. Medications listed in groups 3 and 4 were given a sedative rating of 0. The medications taken by each patient at admission and discharge were determined separately by calculating the sum of all regular medications documented at the two-time points. The differences in the sedative load were then calculated to reflect the changes in sedative load between admission and discharge.

2.3 Other variables

Besides the sedative burden calculated by the Sed-DBI and SLM, additional patient variables were available in the dataset for descriptive and exploratory analyses (Table 6).

For example, there are three categories for “visit type”, inpatient and emergency department were documented in the dataset, while the third group recorded as “transferred from the emergency department to inpatient units” was derived from the patients’ information. This group of patients was identified by the overlapped emergency department discharge date and time with the inpatient admission date and time.

Another example is the length of stay. The length of hospitalisation was defined by the date and time between admission and discharge for each patient. Where differences between the two-time points were not a full day, the hours and minutes were converted to days. For example, 18 days, 23 hours, 15

minutes = 18.97 days. For descriptive and stratified analyses, the continuous variable was converted to ordinal dummy coded variables for a better explanation of the findings. It was categorised into three groups: patients hospitalised for one week or less, hospitalised for more than a week to 15 days, and more than 15 days.

Further, continuous variables such as age, and the mean number of medications were converted into ordinal variables for stratified analyses. This conversion allowed for more meaningful descriptions of the patient characteristics that are potentially associated with a higher sedative burden. According to the Australian Bureau of Statistics (ABS), there are three categories of the international age classifications, with the lowest level consisting of six groups [108]. In accordance with the ABS, patients in the present study were divided into three categories: young and middle adulthood (18-44), older adulthood (45-64), and elderly (65 and over). Additionally, using the World Health Organisation's definition of polypharmacy as the concurrent use of five or more medications [109], in the present study the number of medications was categorised into two groups, "fewer than five medications" and "five or more medications".

Table 6. Variables derived from patients' parameters for descriptive and exploratory analyses

Variables	Descriptive analysis	Exploratory analysis
Visit type	Nominal: Additional group was identified by the overlapped emergency department discharge date and time with the inpatient admission date and time, and emergency departments (n=5) was analysed as part of the "transferred from the emergency department to inpatient units" (n=129) due to the considerably smaller sample size	
Length of stay (LOS)	Ordinal: 2<LOS≤7, 7<LOS≤15, 15<LOS	Continuous: Calculated from the differences between admission and discharge dates and times
Units	Nominal: Emergency departments (n=5) was analysed as part of the acute medical units (n=61) due to the considerably smaller sample size	
Age	Ordinal: 18-44, 45-64, 65 and above	Continuous
Mean number of medications	Ordinal: Less than five regular medications, and five or more regular medications	Continuous: Average of the regular medications taken on admission and discharge

2.4 Medication data

Medication data were analysed to identify the most prevalent medications prescribed in this study population prior to admission and on discharge. For the five most frequently prescribed sedating medications, changes in dosage were measured by identifying patients who were taking the five most frequently prescribed sedating medications. The differences in dose prior to admission and on discharge were then calculated. The changes in dosage were then categorised into three categories: "remained unchanged", "increased", or "decreased". The number of patients who were taking these medications was calculated and grouped into these three categories. The total number was counted, and the results were presented as percentages.

2.5 Statistical analysis

Participants' demographics were presented as mean and standard deviations for continuous variables, such as the Sed-DBI scores and the sedative load. Categorical variables, such as gender and admission type, were presented as counts and percentages.

Descriptive analyses examined the mean Sed-DBI score and sedative load by patient characteristics and other related parameters, such as length of hospitalisation, facility, unit, visit type, and the number of medications.

To determine whether there were statistically significant differences between patients' sedative burden prior to admission and on discharge, the paired samples t-test was used. The dependent variables were the differences between the Sed-DBI score and the sedative load rating between pre-admission and discharge. The assumption of normality was checked by plotting the differences of the dependent variables on a histogram.

Univariate linear regression analyses were performed to examine the associations between patients' characteristics and other hospital-related parameters (that is, gender, age, length of hospitalisation, unit, discharge location, visit type, and the number of medications) with the changes in the sedative burden (quantified by the Sed-DBI and SLM). Variables that were found to be significant were then stratified by groups, and the mean sedative burden differences between pre-admission and discharge

were then analysed with paired samples t-test to determine whether the changes were significant among the stratified groups. All variables were also included in the baseline-adjusted models to determine the associations with the changes in the sedative burden after adjusting for the pre-admission sedative burden.

Backward selection multiple regression was performed to identify variables that were predictive of the changes in the Sed-DBI score and the sedative load. All independent variables were included in the model. In each model, the least significant variable was removed, this procedure was repeated until all the remaining variables were statistically significant. The least significant variables defined by a p-value higher than 0.05 were removed from the model one at a time, and the final model was fitted to determine the variables that predicted the changes in the Sed-DBI score and the sedative load in this study population.

To explore potential differences between patients admitted to acute mental health units and patients admitted to other units, subgroup analyses were performed in patients admitted to acute mental health units. Independent samples t-test was conducted to determine whether there were statistically significant differences in the sedative burden between these two groups of patients. Similar to the descriptive and exploratory analyses described for the whole study population, such analyses were also conducted for this subgroup.

P-values of less than 0.05 were considered statistically significant. All data analyses were conducted in IBM SPSS Statistics for Windows, version 27.0. IBM Corp., Armonk, NY: IBM Corp and StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC.

2.6 Ethics approval

Ethics approval to conduct this study was granted by the SA Department for Health and Wellbeing Human Research Ethics Committee (HREC study number: HREC/16/SAH/130), and the University of South Australia Human Research Ethics Committee (Protocol no: 204486).

3. Results

3.1 Description of the study population

The initial dataset obtained from the data custodian consisted of 3,615 individual admissions of 2,715 patients. This dataset was screened to identify patients who were taking at least one antipsychotic medication prior to their admission. Of the 2,715 patients that have been prescribed antipsychotics, 1,677 were excluded at this stage as they were patients that have been prescribed antipsychotics during hospitalisation and/or upon discharge but not before admission. This resulted in 1,038 patients being shortlisted for further screening. An additional 327 patients were excluded for various reasons (Figure 1).

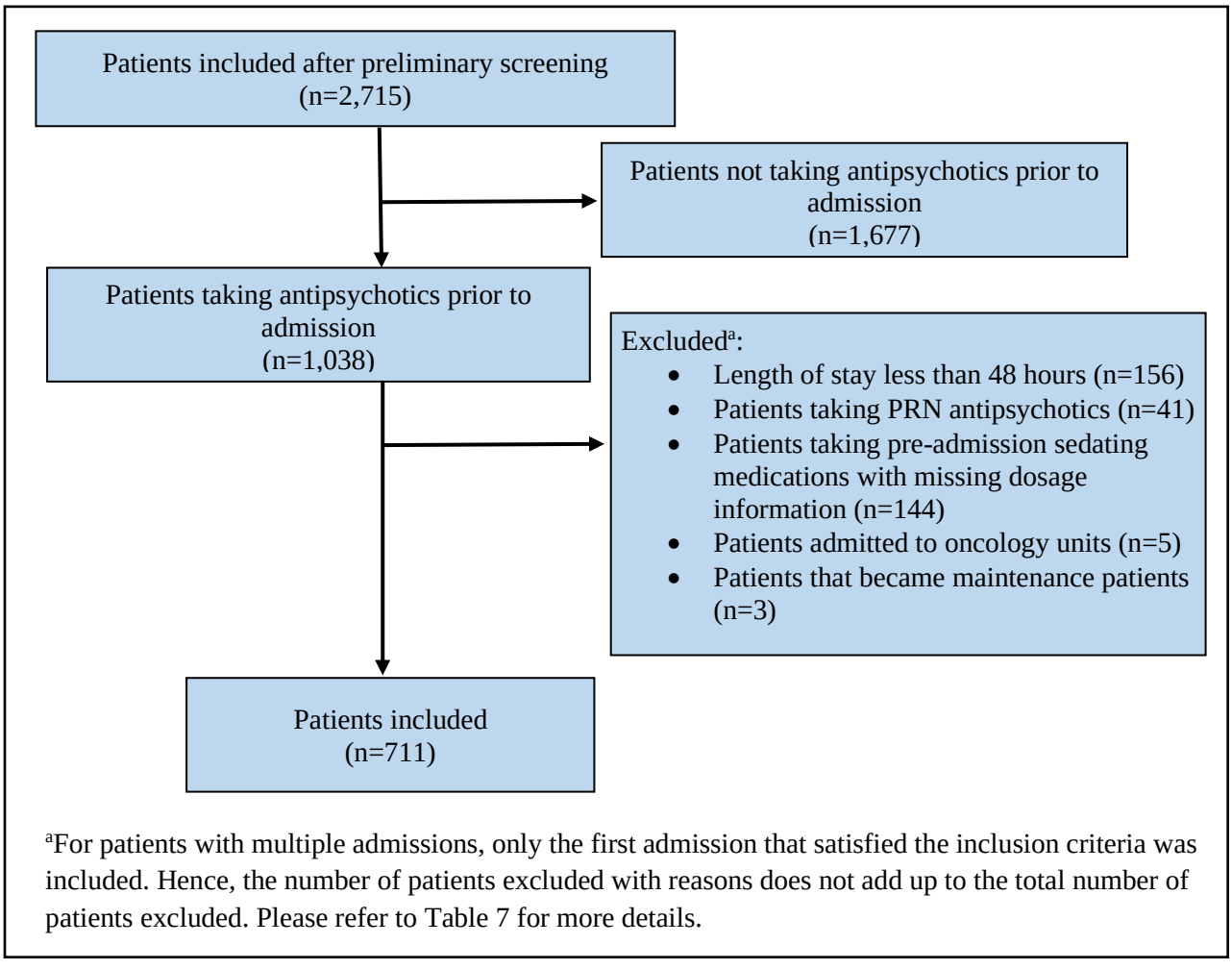


Figure 1. The process of patient selection and exclusion

In this study, multiple patients were hospitalised more than once. For these patients, each admission was considered as a separate event, and only the first admission that satisfied the inclusion criteria was included. In the examples in Table 7, patient A was hospitalised five times. However, only the fifth admission met the inclusion criteria. The reasons for exclusion for the previous four admissions were documented and these admissions were considered and excluded. Patient B was also admitted five times, and the third admission was included. As such, only the reasons for excluding the first and second admissions were documented, while the fourth and fifth admissions were not taken into account. Therefore, the number of patients excluded with reasons in Figure 1 does not add up to the total number of patients excluded.

Table 7. Examples of selection of admission data that satisfy the inclusion criteria for patients with multiple visits

Patient	Admission	Reasons of exclusion / inclusion
A	First	Less than 48 hours
	Second	Less than 48 hours
	Third	Not taking antipsychotics prior to admission
	Fourth	Less than 48 hours
	Fifth	Met the inclusion criteria- Included
B	First	Less than 48 hours
	Second	Less than 48 hours
	Third	Met the inclusion criteria- Included
	Fourth	
	Fifth	

This study population consisted of 711 patients, with the majority admitted at Facility A (73.1%) (Table 8). The mean age of the cohort was 54.65 years (SD=21.04) with 52.0% females and 37.4% in young to middle adulthood. The average length of hospitalisation was 16.87 days (SD= 25.90) while 40.1% were hospitalised for less than one week. The overall mean number of regular medications in this population was 5.99 (SD=4.04) while the mean numbers of regular medications were 5.86 (SD=4.31), and 6.10 (SD=4.15) prior to hospitalisation and on discharge, respectively. The majority were admitted to acute mental health units (57.2%), followed by general medical units (14.8%), medical subspecialty units

(9.4%), acute medical units (9.3%), and geriatric units (9.1%). Of the 711 patients, 81.2% were admitted as inpatients while 18.8% were transferred from the ED to an inpatient unit. Additionally, most patients were discharged to their homes (81.4%).

Table 8. Demographics of the study population

Characteristics	Total (n=711)
Female, n (%) [a]	370 (52.0)
Age	
Mean (SD)	54.65 (21.04)
18-44, n (%)	266 (37.4)
45-64, n (%)	197 (27.7)
65 and above, n (%)	248 (34.9)
Number of regular medications, mean (SD)	
Total	5.99 (4.04)
Pre-admission	5.86 (4.31)
Discharge	6.10 (4.15)
Length of stay	
Mean (SD)	16.87 (25.90)
2≤LOS<7, n (%)	285 (40.1)
7≤LOS<15, n (%)	207 (29.1)
15≤LOS, n (%)	219 (30.8)
Facility	
Facility A, n (%)	520 (73.1)
Facility B, n (%)	147 (20.7)
Facility C, n (%)	44 (6.2)
Unit [a]	
Acute Mental Health, n (%)	407 (57.2)
General Medical, n (%)	105 (14.8)
Medical Subspecialties, n (%)	67 (9.4)
Acute medical, n (%)	66 (9.3)
Geriatric, n (%)	65 (9.1)
Visit type	
Inpatient, n (%)	577 (81.2)
ED to inpatient, n (%)	134 (18.8)
Discharge Location [a]	
Home, n (%)	579 (81.4)
Residential Care Facility, n (%)	131 (18.4)

[a] Missing data n=1

3.2 Prevalence of prescriptions for sedating medications

A total of 92 unique sedating medications were identified in this study population. The mean number of sedating medications that this cohort was taking prior to admission and on discharge were both 2.4.

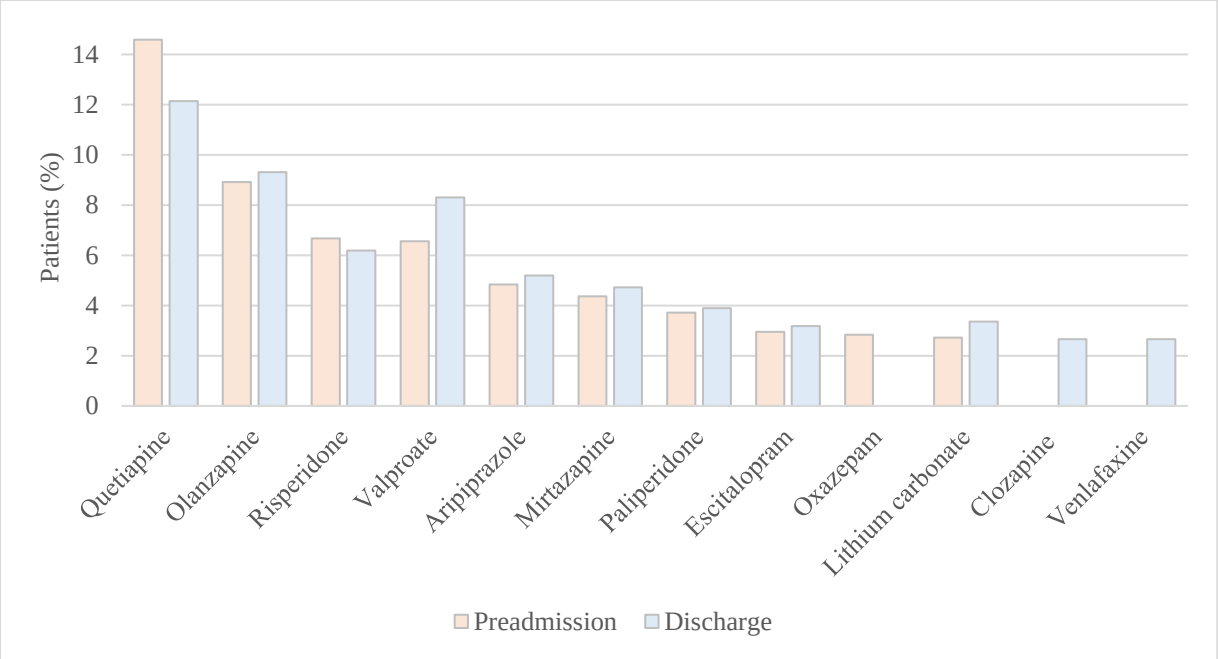
The ten most frequently documented sedating medications before admission contributed to 58.0% of all the pre-admission sedating medications (Table 9). With quetiapine (N05AH04) being the most frequently prescribed sedating medication (14.6%), followed by olanzapine (N05AH03) (8.9%), and risperidone (N05AX08) (6.7%).

Similarly, the ten most frequently prescribed sedating medications on discharge contributed to 61.8% of all the sedating medications prescribed on discharge (Table 9). Even though fewer patients were prescribed quetiapine on discharge, quetiapine remained the most frequently prescribed sedating medication taken by the patients (Figure 2). Quetiapine (12.2%) and olanzapine (9.3%) were again the two most frequently prescribed medications, followed by valproate (N03AG01) (8.3%).

Further analyses were conducted for the five most frequently prescribed sedating medications at pre-admission and discharge. Among patients taking quetiapine, risperidone, valproate, or aripiprazole, a majority had their dose remained unchanged at discharge. However, a greater percentage of patients taking olanzapine had their doses increased at discharge (Figure 3).

Table 9. Ten most frequently prescribed sedating medications prior to admission and on discharge by level 5 ATC code

Period	ATC level 5	Medication name	n	Percentages
Pre-admission				1693 sedating medications
	N05AH04	Quetiapine	247	14.6
	N05AH03	Olanzapine	151	8.9
	N05AX08	Risperidone	113	6.7
	N03AG01	Valproate	111	6.6
	N05AX12	Aripiprazole	82	4.8
	N06AX11	Mirtazapine	74	4.4
	N05AX13	Paliperidone	63	3.7
	N06AB10	Escitalopram	50	3.0
	N05BA04	Oxazepam	48	2.8
	N05AN01	Lithium carbonate	46	2.7
Discharge				1696 sedating medications
	N05AH04	Quetiapine	206	12.2
	N05AH03	Olanzapine	158	9.3
	N03AG01	Valproate	141	8.3
	N05AX08	Risperidone	105	6.2
	N05AX12	Aripiprazole	88	5.2
	N06AX11	Mirtazapine	80	4.7
	N05AX13	Paliperidone	66	3.9
	N05AN01	Lithium carbonate	57	3.4
	N06AB10	Escitalopram	54	3.2
	N05AH02	Clozapine	45	2.7
	N06AX16	Venlafaxine	45	2.7



Note. Clozapine and venlafaxine were not in the top ten most frequently prescribed sedating medications on admission, while oxazepam was not in the top ten most frequently prescribed sedating medications on discharge

Figure 2. Distribution of ten most frequently prescribed sedating medications at pre-admission and on discharge

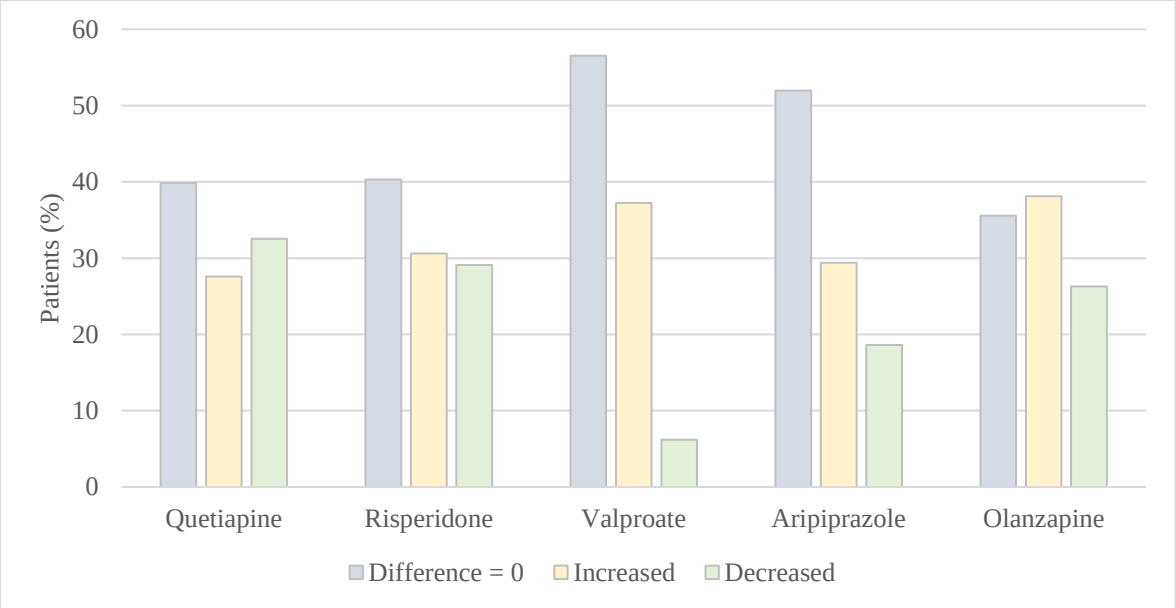


Figure 3. Changes to doses of the five most frequently prescribed sedating medications

3.3 Differences between sedative burden from pre-admission to discharge

Table 10 shows the mean Sed-DBI score and sedative load of the whole cohort stratified by the patients' characteristics.

For both Sed-DBI score and the sedative load, the paired samples t-tests showed no statistically significant differences between the mean sedative burden for both models (Sed-DBI: $t(710) = -1.835$, $p= 0.067$, $d = 0.069$; SLM: $t(710) = -0.308$, $p = 0.758$, $d= 0.012$) (Table 11).

Table 10. Sed-DBI scores and sedative load by patients' characteristics

Characteristics		Sed-DBI score				Sedative load			
		Pre-admission		Discharge		Pre-admission		Discharge	
	n	mean	SD	mean	SD	mean	SD	mean	SD
Total	711	1.38	0.81	1.42	0.79	2.71	1.61	2.73	1.58
Gender									
Female	370	1.40	0.84	1.39	0.78	2.82	1.68	2.70	1.55
Male	340	1.36	0.79	1.44	0.80	2.59	1.52	2.75	1.61
Age									
18-44	266	1.23	0.73	1.33	0.73	2.23	1.33	2.39	1.40
45-64	197	1.65	0.95	1.69	0.86	3.09	1.78	3.06	1.66
65 and above	248	1.32	0.72	1.30	0.74	2.93	1.61	2.82	1.64
Length of stay									
2<LOS≤7	285	1.43	0.83	1.34	0.82	2.77	1.60	2.54	1.55
7<LOS≤15	207	1.34	0.86	1.41	0.81	2.62	1.62	2.70	1.59
15<LOS	219	1.35	0.73	1.53	0.71	2.72	1.61	3.00	1.58
Facility									
Facility A	520	1.39	0.82	1.41	0.80	2.73	1.63	2.71	1.59
Facility B	147	1.31	0.70	1.44	0.67	2.58	1.42	2.82	1.47
Facility C	44	1.53	1.07	1.48	1.03	2.89	1.93	2.64	1.84
Unit									
Acute mental health	407	1.30	0.73	1.41	0.70	2.45	1.42	2.60	1.42
General medical	105	1.58	1.01	1.48	0.99	3.31	2.00	2.99	1.84
Medical subspecialties	67	1.30	0.64	1.21	0.65	2.51	1.35	2.31	1.37
Acute medical	66	1.62	1.03	1.53	1.03	3.11	1.81	2.80	1.83
Geriatric	65	1.40	0.78	1.51	0.80	3.15	1.66	3.40	1.80
Visit type									
Inpatient	577	1.41	0.82	1.43	0.79	2.80	1.63	2.77	1.59
ED to inpatient	134	1.26	0.77	1.37	0.78	2.34	1.46	2.55	1.53
Discharge Location									
Home	579	1.37	0.83	1.41	0.80	2.64	1.59	2.69	1.57
Residential Care Facility	131	1.44	0.74	1.46	0.75	3.02	1.68	2.90	1.62
Number of medications									
Less than five medications	330	1.08	0.54	1.16	0.57	1.97	1.00	2.05	1.09
Five or more medications	381	1.64	0.91	1.65	0.88	3.35	1.76	3.31	1.70

Table 11. Paired samples t-test between pre-admission and discharge sedative burden

Sedative burden	t-statistic	df	95 % confidence interval		effect size	p-value
			lower bound	higher bound		
Sed-DBI score	-1.835	710	-0.003	0.081	0.069	0.067
Sedative load	-0.308	710	-0.083	0.114	0.012	0.758

Between admission and discharge, 29.7% and 55.3% of the patients had no changes in their Sed-DBI scores and sedative load, respectively (Figure 4). 31.1% and 21.1% of the patients experienced a decrease in Sed-DBI score and sedative load, and 39.2% and 23.6% of the patients had an increased Sed-DBI score and sedative load, respectively.

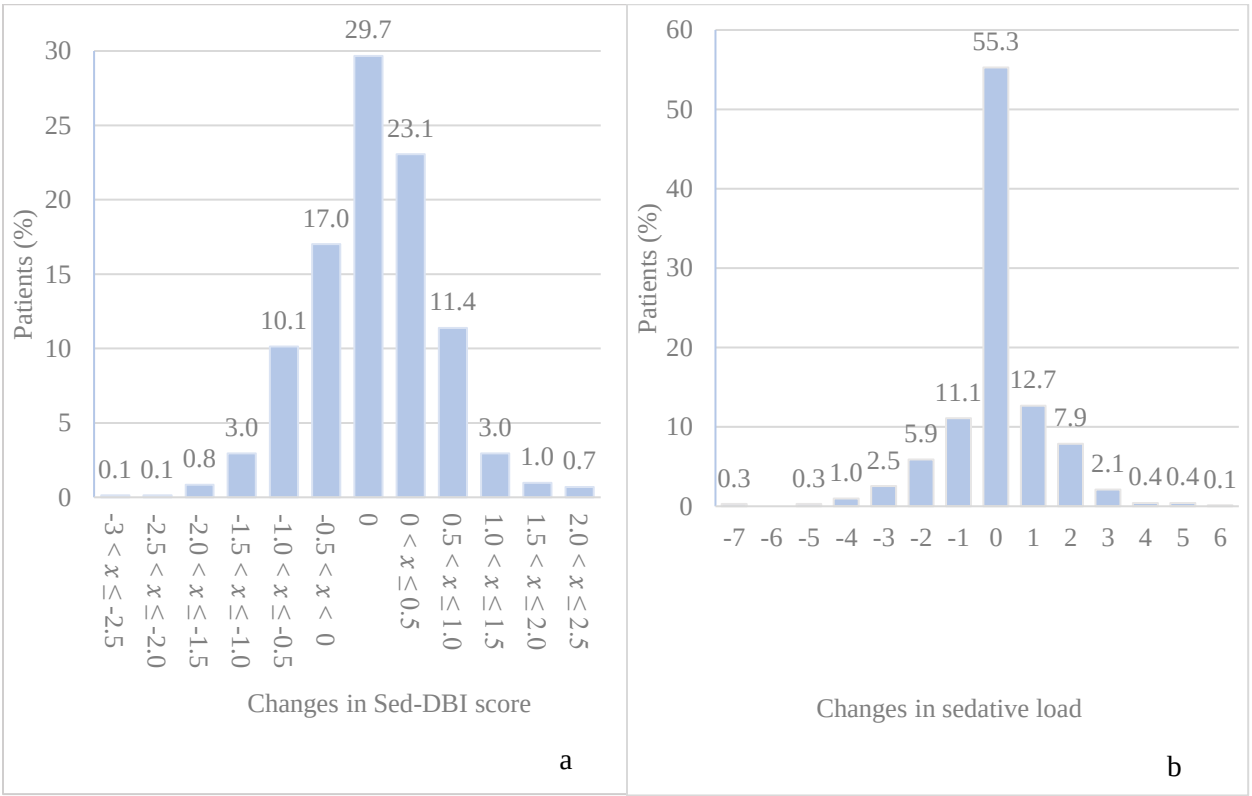


Figure 4. Frequency of the changes in Sed-DBI score (a) and sedative load (b)

3.4 Factors associated with the differences in the sedative burden

3.4.1 Univariate analyses to determine the associations of the variables with the changes in the sedative burden

Results of the univariate linear regression analyses suggested that five independent variables, namely gender, age, unit, length of stay, and the mean number of medications were associated with the changes in the Sed-DBI score and sedative load (Table 12).

In the unadjusted univariate analyses, the increase in the Sed-DBI score and sedative load were similarly significant for six variables, namely male gender (Sed-DBI: $\beta = 0.086$, $p = 0.044$; SLM: $\beta = 0.292$, $p = 0.004$), younger patients (Sed-DBI: $\beta = -0.003$, $p = 0.008$; SLM: $\beta = -0.006$, $p = 0.017$), patients admitted to geriatric or acute mental health units (Sed-DBI: $\beta = 0.210$, $p = 0.018$; SLM: $\beta = 0.570$, $p = 0.007$ and Sed-DBI: $\beta = 0.218$, $p < 0.0001$; SLM: $\beta = 0.479$, $p = 0.001$ respectively), a longer length of hospitalisation (Sed-DBI: $\beta = 0.004$, $p < 0.0001$; SLM: $\beta = 0.008$, $p < 0.0001$), and a lower mean number of medications (Sed-DBI: $\beta = -0.018$, $p = 0.001$; SLM: $\beta = -0.031$, $p = 0.012$) (Table 12). The results of the unadjusted models have been independently verified by another method (Appendix B).

Table 12. Association of patients' characteristics with the changes in Sed-DBI score and sedative load during hospitalisation in the unadjusted linear regression models

		Sed-DBI score					Sedative load				
Parameters	Reference category	coefficient	p-value	95% confident interval		adjusted R-square	coefficient	p-value	95% confident interval		adjusted R-square
				lower bound	higher bound				lower bound	higher bound	
Gender											
Male	Female	0.086	**0.044**	0.002	0.170	0.004	0.292	**0.004**	0.095	0.488	0.011
Age		-0.003	**0.008**	-0.005	-0.001	0.009	-0.006	**0.017**	-0.010	-0.001	0.007
Discharge location											
Residential Care Facility	Home	-0.029	0.596	-0.137	0.079	-0.001	-0.169	0.194	-0.424	0.086	0.001
Visit type											
Inpatient	ED to inpatient	-0.089	0.104	-0.195	0.018	0.002	-0.238	0.064	-0.490	0.014	0.003
Units											
Geriatric unit	General medical unit	0.210	**0.018**	0.036	0.384		0.570	**0.007**	0.159	0.981	
Medical subspecialty units		0.014	0.877	-0.159	0.186		0.100	0.630	-0.308	0.507	
Acute medical unit		0.024	0.783	-0.149	0.198		0.021	0.921	-0.389	0.430	
Acute mental health unit		0.218	<**0.0001**	0.098	0.339	0.024	0.479	**0.001**	0.193	0.764	0.021
Length of stay		0.004	<**0.0001**	0.002	0.006	0.031	0.008	<**0.0001**	0.005	0.012	0.025
Mean number of medications		-0.018	**0.001**	-0.029	-0.008	0.016	-0.031	**0.012**	-0.056	-0.007	0.008

3.4.2 Stratified analyses for variables with statistically significant associations with the changes in the Sed-DBI score and the sedative load

The stratified analyses using the Sed-DBI score and sedative load as dependent variables produced similar results (Table 13). Male patients (Sed-DBI: $t(339)= 2.793$, $p = 0.006$; SLM: $t(339)= 2.357$, $p = 0.019$) had a statistically significantly higher sedative burden on discharge while the decrease observed in female patients was not statistically significant.

The 18-44 age group had a statistically significant increase in their Sed-DBI score as well as their sedative load quantified by the SLM ($t(265)= 2.922$, $p = 0.004$ and $t(265)= 2.215$, $p = 0.028$ respectively).

Patients admitted to acute mental health units had an increased sedative burden on discharge (Sed-DBI: $t(406)= 3.962$, $p = 0.0001$; SLM: $t(406)= 2.369$, $p = 0.018$) while those admitted to general medical units had a significantly lower sedative burden on discharge (Sed-DBI: $t(104)= -2.007$, $p = 0.047$; SLM: $t(104)= -2.226$, $p = 0.028$).

The results of the stratified analyses for the length of stay were consistent for both the Sed-DBI score and sedative load. Significantly higher sedative burden on discharge was observed among patients admitted for more than 15 days (Sed-DBI: $t(218)= 3.724$, $p = 0.0002$; SLM: $t(218)= 2.545$, $p = 0.012$), while those admitted for 2 to 7 days had a significantly lower sedative burden upon discharge (Sed-DBI: $t(284)= -3.168$, $p = 0.002$; SLM: $t(284)= -3.634$, $p = 0.0003$).

The change in the sedative burden quantified by the Sed-DBI was only significant for patients taking an average of fewer than five medications (Sed-DBI: $t(329)= 2.739$, $p = 0.007$).

Table 13. Changes in Sed-DBI score and sedative load from admission to discharge by categories in stratified paired samples t-tests

	Sed-DBI score					Sedative load				
Parameters	t-statistic	df	p-value	95% confident interval		t-statistic	df	p-value	95% confident interval	
				lower bound	higher bound				lower bound	higher bound
Gender										
Female	-0.090	369	0.928	-0.062	0.057	-1.780	369	0.076	-0.267	0.013
Male	2.793	339	**0.006**	0.025	0.142	2.357	339	**0.019**	0.027	0.302
Age range										
18-44	2.922	265	**0.004**	0.033	0.169	2.215	265	**0.028**	0.019	0.320
45-64	0.795	196	0.428	-0.051	0.120	-0.300	196	0.764	-0.231	0.170
65 and above	-0.702	247	0.484	-0.091	0.043	-1.307	247	0.192	-0.283	0.057
Unit										
General medical unit	-2.007	104	**0.047**	-0.215	-0.001	-2.226	104	**0.028**	-0.612	-0.035
Geriatric unit	1.202	64	0.234	-0.067	0.269	1.351	64	0.181	-0.118	0.610
Medical subspecialty units	-1.623	66	0.109	-0.211	0.022	-1.961	66	0.054	-0.452	0.004
Acute medical unit	-1.270	65	0.209	-0.216	0.048	-1.893	65	0.063	-0.623	0.017
Acute mental health unit	3.962	406	**0.0001**	0.055	0.164	2.369	406	**0.018**	0.026	0.283
Length of stay										
2<LOS≤7	-3.168	284	**0.002**	-0.133	-0.031	-3.634	284	**0.0003**	-0.357	-0.106
7<LOS≤15	1.663	206	0.098	-0.012	0.143	0.862	206	0.390	-0.099	0.254
15<LOS	3.724	218	**0.0002**	0.081	0.262	2.545	218	**0.012**	0.063	0.494
Number of medications										
Less than five	2.739	329	**0.007**	0.023	0.139	1.308	329	0.192	-0.040	0.197
Five or more	0.100	380	0.920	-0.057	0.063	-0.505	380	0.614	-0.193	0.114

3.4.3 Baseline-adjusted linear regression analyses

The baseline adjusted linear regression analyses revealed the significance of the effect of the pre-admission sedative burden (Table 14). For both the Sed-DBI score and the sedative load, a higher pre-admission sedative burden was associated with the decreased sedative burden on discharge (Sed-DBI: β = -0.274, $p < 0.0001$; SLM: β = -0.365, $p < 0.0001$).

Compared with the unadjusted linear regression models presented in Table 12, younger patients (β = -0.002, $p = 0.013$), admitted to geriatric units ($\beta = 0.162$, $p = 0.049$) or acute mental health units (β = 0.142, $p = 0.013$), and a longer length of hospitalisation ($\beta = 0.004$, $p < 0.0001$) remained significantly associated with the increased Sed-DBI score on discharge after adjusting for the pre-admission Sed-DBI score.

For the differences in the sedative load during hospitalisation, male gender ($\beta = 0.205$, $p = 0.023$), admitted to geriatric units ($\beta = 0.512$, $p = 0.007$), a longer length of stay ($\beta = 0.008$, $p < 0.0001$), and the mean number of medications ($\beta = 0.064$, $p < 0.0001$) were significantly associated with the increase in the sedative load after adjusting for the pre-admission sedative load.

In comparison to the univariate analyses (Table 12), these baseline-adjusted models fit the observations better as suggested by the higher R-squared statistics. For example, in the unadjusted analysis, the adjusted R-squared statistic suggested that only 3.1% of the changes in the Sed-DBI score can be predicted by the length of stay. After adjusting for the pre-admission sedative burden, the length of stay was able to explain 17.8% of the changes in the Sed-DBI score. An adjusted R-squared statistic of 0.178 indicates that the length of hospitalisation only accounts for a small proportion of the variance of the changes in the Sed-DBI score during hospitalisation, however, it is a much greater R-squared statistic in comparison to the unadjusted model.

Table 14. Association of patients' characteristics with the changes in Sed-DBI score and sedative load during hospitalisation in baseline adjusted linear regression models

		Sed-DBI score					Sedative load				
Parameters	Reference category	coefficient	p-value	95% confident interval		adjusted R-square	coefficient	p-value	95% confident interval		adjusted R-square
				lower bound	higher bound				lower bound	higher bound	
Pre-admission sedative burden		-0.274	**<0.0001**	-0.321	-0.226	0.152	-0.365	**<0.0001**	-0.421	-0.310	0.191
Gender											
Male	Female	0.077	0.051	0.000	0.154	0.156	0.205	**0.023**	0.028	0.383	0.196
Age		-0.002	**0.013**	-0.004	0.000	0.158	-0.001	0.767	-0.005	0.004	0.190
Discharge location											
Residential Care Facility	Home	-0.009	0.856	-0.109	0.091	0.149	-0.032	0.786	-0.260	0.201	0.190
Visit type											
Inpatient	ED to inpatient	-0.047	0.353	-0.146	0.052	0.152	-0.074	0.525	-0.303	0.154	0.190
Unit											
Geriatric unit	General medical unit	0.162	**0.049**	0.001	0.323		0.512	**0.007**	0.140	0.883	
Medical subspecialty units		-0.062	0.449	-0.222	0.098		-0.183	0.333	-0.553	0.188	
Acute medical unit		0.033	0.685	-0.127	0.193		-0.055	0.770	-0.425	0.315	
Acute mental health unit		0.142	**0.013**	0.030	0.255	0.165	0.164	0.220	-0.098	0.426	0.202
Length of stay		0.004	**<0.0001**	0.002	0.005	0.178	0.008	**<0.0001**	0.005	0.011	0.214
Mean number of medications		0.009	0.098	-0.002	0.020	0.154	0.064	**<0.0001**	0.038	0.090	0.216

3.4.4 Stepwise multiple regression analyses

A backward linear regression analysis was employed to adjust for and determine the possible variables that would independently predict the changes in the Sed-DBI score and the sedative load during hospitalisation. Predictor variables included in this analysis were pre-admission sedative burden, age, gender, discharge location, visit type, unit, length of stay, and the mean number of medications. To predict the changes in the Sed-DBI score between pre-admission and discharge, the backward stepwise linear regression analysis eliminated gender, discharge location, visit type, and unit in the final model (Table 15). The stepwise selection of the variables can be found in Appendix C. After adjusting for other variables in the model, a greater pre-admission sedative burden ($\beta = -0.322$, $p < 0.0001$) and older age ($\beta = -0.005$, $p < 0.0001$) were found to be significantly associated with the decreased Sed-DBI score, while the longer length of hospitalisation ($\beta = 0.004$, $p < 0.0001$) and a greater mean number of medications ($\beta = 0.025$, $p < 0.0001$) were significantly associated with the increased Sed-DBI score from pre-admission to discharge. The adjusted R-squared statistic for this model was 0.205, suggesting that 20.5% of the data fit this model.

The predictor variables that were found to be significantly associated with the changes in the sedative load included the pre-admission sedative load ($\beta = -0.460$, $p < 0.0001$), male gender ($\beta = 0.227$, $p = 0.009$), age ($\beta = -0.010$, $p < 0.0001$), acute mental health units ($\beta = 0.236$, $p = 0.026$) or geriatric units ($\beta = 0.498$, $p = 0.003$), length of hospitalisation ($\beta = 0.007$, $p < 0.0001$) and the mean number of medications ($\beta = 0.098$, $p < 0.0001$) (Table 16). This model could explain 26.8% of the variation in the changes in the sedative load from pre-admission to discharge.

Table 15. Backward selection of predictor variables that predict the changes in Sed-DBI score during hospitalisation

Predictor variables	Reference category	coefficient	p-value	95% confident interval	
				lower bound	higher bound
Constant		0.563	**<0.0001**	0.439	0.688
Pre-admission Sed-DBI score		-0.322	**<0.0001**	-0.376	-0.268
Gender					
Male	Female				
Age		-0.005	**<0.0001**	-0.008	-0.003
Discharge location					
Residential Care Facility	Home				
Visit type					
Inpatient	ED to inpatient				
Unit					
Acute mental health unit	General medical unit				
Acute medical unit					
Medical subspecialty units					
Geriatric unit					
Length of stay		0.004	**<0.0001**	0.003	0.005
Mean number of medications		0.025	**<0.0001**	0.013	0.038
R-square		0.209			
Adjusted R-square		0.205			
n		711			

Table 16. Backward selection of predictor variables that predict the changes in sedative load during hospitalisation

Predictor variables	Reference category	coefficient	p-value	95% confident interval	
				lower bound	higher bound
Constant		0.805	<**0.0001**	0.435	1.174
Pre-admission sedative load		-0.460	<**0.0001**	-0.522	-0.397
Gender					
Male	Female	0.227	**0.009**	0.056	0.399
Age		-0.010	<**0.0001**	-0.015	-0.005
Discharge location					
Residential Care Facility	Home				
Visit type					
Inpatient	ED to inpatient				
Unit					
Acute mental health unit	General medical unit	0.236	**0.026**	0.028	0.444
Acute medical unit					
Medical subspecialty units					
Geriatric unit		0.498	**0.003**	0.168	0.829
Length of stay		0.007	<**0.0001**	0.003	0.010
Mean number of medications		0.098	<**0.0001**	0.068	0.127
R-square		0.275			
Adjusted R-square		0.268			
n		709			

3.5 Subgroup analyses: Patients admitted to acute mental health units

3.5.1 Description of patients admitted to acute mental health units

Subgroup analysis was performed to investigate the potential differences between patients admitted to acute mental health units in comparison to other units, as this group represented the largest unit within the population. A total of 407 patients (57.2%) of the total number of patients were admitted to acute mental health units (Table 17).

Among patients admitted to acute mental health units and non-acute mental health units, the gender distribution was approximately equal (acute mental health units: M 50.1%, F 49.9% and non-acute mental health units: M 45.2%, F 54.8%) (Table 17). The mean age of patients admitted to acute mental health units was 46.25 years (SD=17.79) and over half (53.3%) of the cohort were aged between 18 to 44 years. In contrast, patients admitted to non-acute mental health units had a mean age of 65.94 years (SD= 19.77) and approximately 60% of the patients were aged 65 and above. Patients admitted to acute mental health units had a mean number of medications of 4.40 (SD=3.55) prior to admission, and 4.75 (SD=3.50) on discharge, an increase of 0.35. In comparison, patients admitted to other units had a mean number of regular medications that was greater than patients admitted to acute mental health units (pre-admission: 7.82 (SD=4.46), discharge: 7.91 (SD=4.28)). Additionally, patients admitted to non-acute mental health units had a shorter length of hospitalisation with more than half (56.4%) admitted for less than 7 days while 40.1% of the patients admitted to acute mental health units were admitted for 15 days or longer.

Table 17. Demographics of patients admitted to acute mental health units and other units

Characteristics	Acute mental health units (n=407)	Other units (n=303)
Female, n (%) [a]	203 (49.9)	166 (54.8)
Age		
Mean (SD)	46.25 (17.79)	65.94 (19.77)
18-44, n (%)	217 (53.3)	49 (16.2)
45-64, n (%)	124 (30.5)	73 (24.1)
65 and above, n (%)	66 (16.2)	181 (59.7)
Number of regular medications, mean (SD)		
Total	4.57 (3.39)	7.88 (4.07)
Pre-admission	4.40 (3.55)	7.82 (4.46)
Discharge	4.75 (3.50)	7.91 (4.28)
Length of stay		
Mean (SD)	19.00 (21.70)	13.93 (30.41)
2≤LOS<7, n (%)	114 (28.0)	171 (56.4)
7≤LOS<15, n (%)	130 (31.9)	76 (25.1)
15≤LOS, n (%)	163 (40.1)	56 (18.5)
Facility		
Facility A, n (%)	307 (75.4)	213 (70.3)
Facility B, n (%)	97 (23.8)	49 (16.2)
Facility C, n (%)	3 (0.7)	41 (13.5)
Visit type		
Inpatient, n (%)	302 (74.2)	274 (90.4)
ED to inpatient, n (%)	105 (25.8)	29 (9.6)
Discharge Location [a]		
Home, n (%)	338 (83.0)	240 (79.2)
Residential Care Facility, n (%)	69 (17.0)	62 (20.5)

[a] Missing data n=1

3.5.2 Prevalence of prescriptions for sedating medications among patients admitted to acute mental health units

The ten most frequently prescribed sedating medications contributed to 65.6% and 66.7% of all the sedating medications prescribed to patients admitted to acute mental health units prior to admission and on discharge, respectively. The five most frequently prescribed medications were quetiapine (N05AH04), olanzapine (N05AH03), valproate (N03AG01), aripiprazole (N05AX12), and paliperidone (N05AX13) in the acute mental health units (Table 18). Of the ten most frequently prescribed sedating medications, 16.1% were quetiapine at pre-admission, with this dropping to 11.8% on discharge (Figure 5).

Table 18. Ten most frequently prescribed sedating medications at pre-admission and discharge by level 5 ATC code among patients admitted to acute mental health units

Period	ATC level 5	Medication name	n	Percentages
Pre-admission				865 sedating medications
	N05AH04	Quetiapine	139	16.1
	N05AH03	Olanzapine	88	10.3
	N03AG01	Valproate	64	7.4
	N05AX12	Aripiprazole	57	6.6
	N05AX13	Paliperidone	48	5.6
	N06AX11	Mirtazapine	39	4.6
	N05AN01	Lithium carbonate	36	4.2
	N05AX08	Risperidone	35	4.1
	N05AH02	Clozapine	30	3.5
	N05AF05	Zuclopenthixol	29	3.4
Discharge				914 sedating medications
	N05AH04	Quetiapine	108	11.8
	N05AH03	Olanzapine	103	11.3
	N03AG01	Valproate	89	9.7
	N05AX12	Aripiprazole	62	6.8
	N05AX13	Paliperidone	52	5.7
	N05AN01	Lithium carbonate	47	5.1
	N06AX11	Mirtazapine	45	5.0
	N05AX08	Risperidone	37	4.2
	N05AH02	Clozapine	34	3.7
	N05AF05	Zuclopenthixol	31	3.4

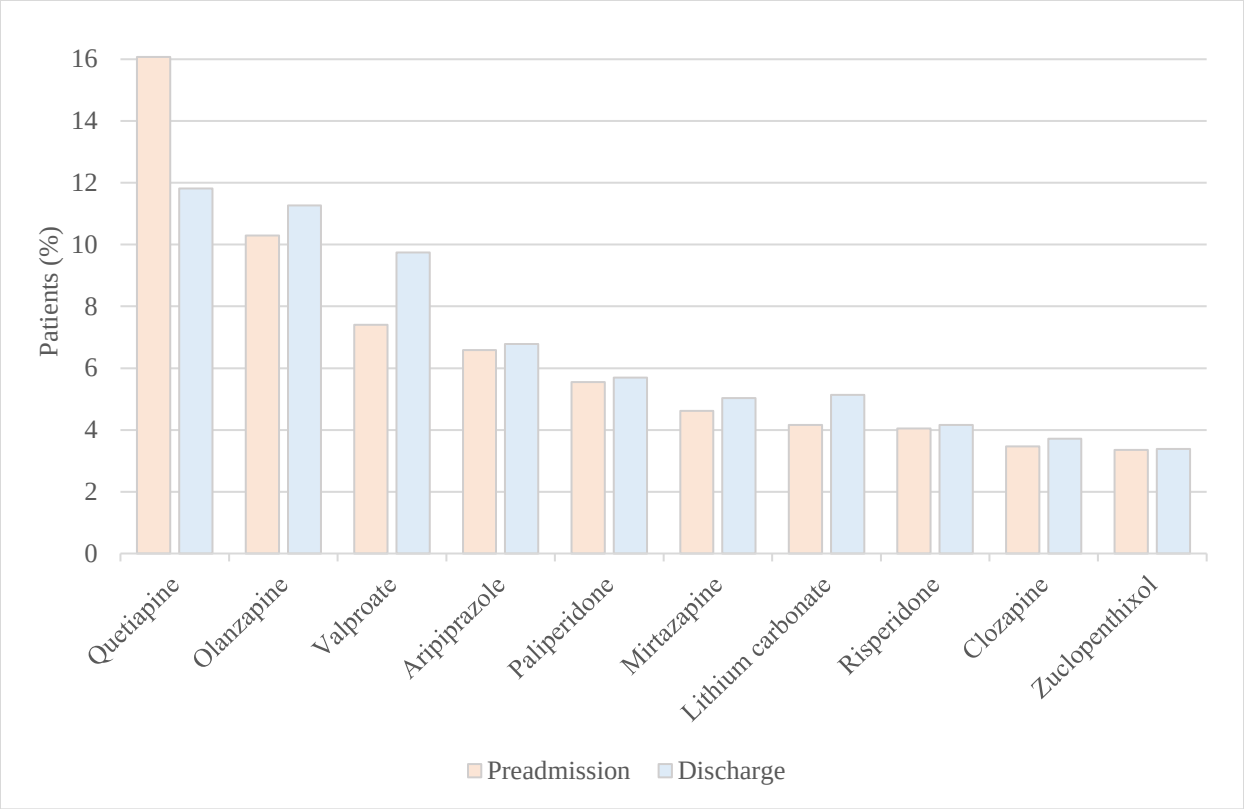


Figure 5. Distribution of ten most frequently prescribed sedating medications among patients admitted to acute mental health units prior to admission and upon discharge

3.5.3 Differences between sedative burden from pre-admission to discharge between patients admitted to acute mental health units and patients admitted to other units

Figure 6a shows that 21.1% of the patients had a stable Sed-DBI score between pre-admission and discharge, 28.3% of the patients had an increased Sed-DBI score of 0.5 or less, with a total of 48.7% of the patients experienced an increased Sed-DBI score, and 30.1% of the patients had a decreased Sed-DBI score. In comparison, when the sedative burden was measured by the SLM, over half (52.1%) of the patients had their sedative load remain unchanged, 28.5% and 19.3% of the patients experienced an increase and reduction in their sedative load, respectively (Figure 6b).

Among patients admitted to acute mental health units, the mean pre-admission Sed-DBI score was 1.30 (SD=0.73), and 1.41 (SD=0.70) on discharge (Table 19), the sedative load was found to be 2.45 (SD=1.42) and 2.60 (SD=1.42) prior to admission and on discharge, respectively (Table 20). An increased

mean sedative burden can be observed from both models. In contrast, patients admitted to other units had a higher sedative burden but experienced a decrease in the mean Sed-DBI score (pre-admission: 1.49 (SD=0.90); discharge: 1.43 (SD=0.90)) and sedative load on discharge (pre-admission: 3.06 (SD=1.77); discharge: 2.89 (SD=1.77)).

The independent samples t-test revealed that the changes in Sed-DBI score and sedative load from pre-admission to discharge were statistically significantly different for patients admitted to acute mental health units and patients admitted to units other than the acute mental health units (Table 21). The mean difference of the Sed-DBI score for patients admitted to acute mental health units (mean=0.11 (SD=0.56)) was statistically significantly greater compared to the mean difference of the Sed-DBI score for patients admitted to other units (mean= -0.05 (SD=0.57); $t(708)=3.834$, $p<0.0001$, $d=0.291$). Similar results can be observed for the mean changes in the sedative load for patients admitted to acute mental health units (mean=0.16 (SD=1.32)) and other units (mean= -0.18 (SD=1.35), $t(708)=3.249$, $p=0.001$, $d=0.247$).

The paired samples t-test suggested that among patients admitted to acute mental health units, the mean differences of the sedative burden between pre-admission and discharge were statistically significant for both the Sed-DBI score ($t(406) = 3.962$, $p<0.0001$, $d = 0.196$) and the sedative load ($t(406) = 2.369$, $p= 0.018$, $d = 0.117$) (Table 22).

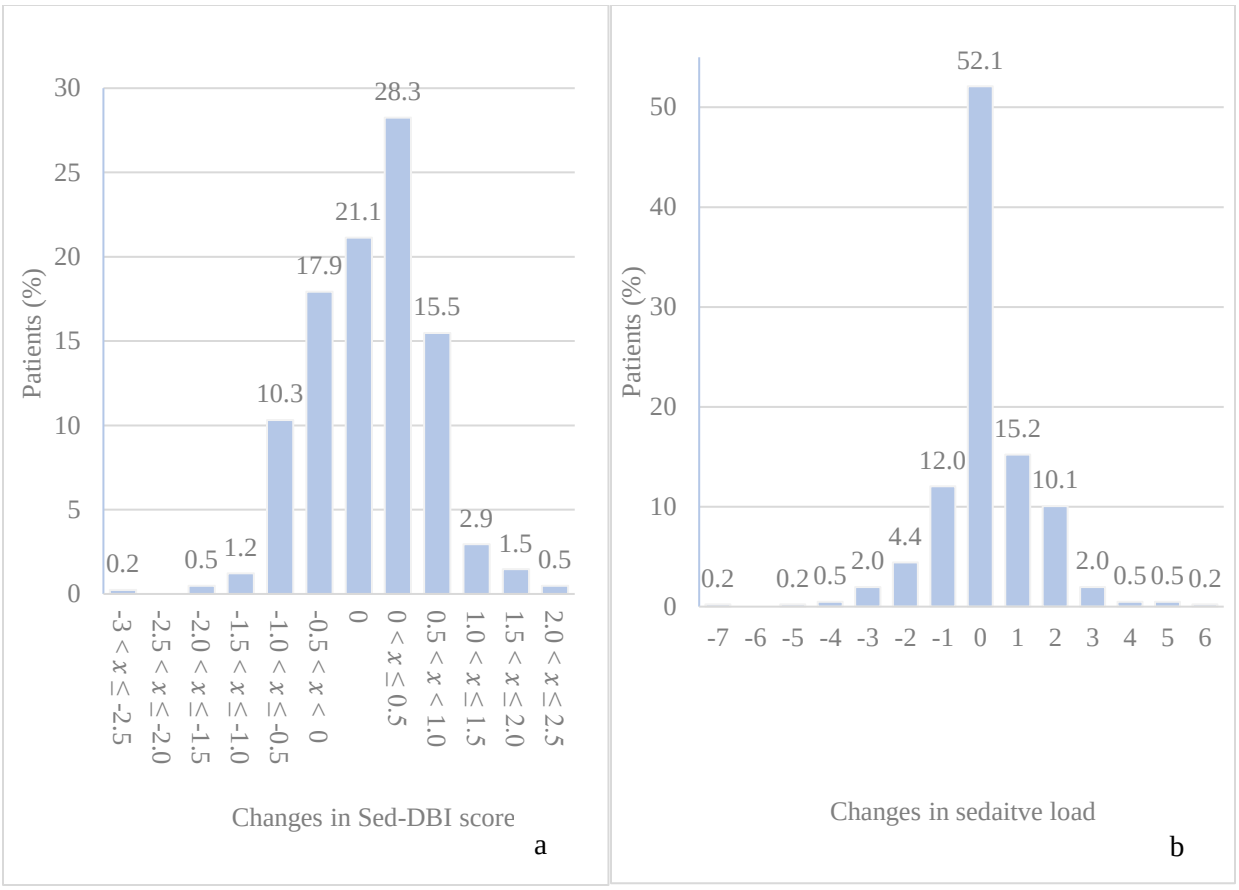


Figure 6. Frequency of the changes in Sed-DBI score (a) and sedative load (b) among patients admitted to acute mental health units

Table 19. Sed-DBI score by patients' characteristics between patients admitted to acute mental health units and patients admitted to other units

	Patients admitted to acute mental health units					Patients admitted to non-acute mental health units				
		Pre-admission		Discharge			Pre-admission		Discharge	
Characteristics	n	mean	SD	mean	SD	n	mean	SD	mean	SD
Total	407	1.30	0.73	1.41	0.70	303	1.49	0.90	1.43	0.90
Gender										
Female	203	1.26	0.72	1.32	0.63	166	1.56	0.94	1.48	0.92
Male	203	1.33	0.74	1.49	0.75	137	1.41	0.85	1.38	0.87
Age										
18-44	217	1.23	0.73	1.36	0.74	49	1.24	0.71	1.21	0.66
45-64	124	1.42	0.75	1.51	0.65	73	2.05	1.12	1.99	1.06
65 and above	66	1.29	0.66	1.37	0.60	181	1.33	0.75	1.33	0.75
Length of stay										
2<LOS≤7	114	1.26	0.74	1.31	0.76	171	1.54	0.87	1.37	0.87
7<LOS≤15	130	1.29	0.73	1.38	0.66	76	1.44	1.06	1.46	1.02
15<LOS	163	1.33	0.72	1.50	0.67	56	1.41	0.76	1.60	0.80
Facility										
Facility A	307	1.32	0.68	1.41	0.72	213	1.51	0.90	1.41	0.90
Facility B	97	1.30	0.69	1.41	0.62	49	1.33	0.73	1.52	0.76
Facility C	3	1.15	0.77	1.48	0.7	41	1.56	1.09	1.47	1.05
Visit type										
Inpatient	302	1.32	0.74	1.43	0.7	274	1.51	0.89	1.44	0.89
ED to inpatient	105	1.24	0.70	1.36	0.71	29	1.32	1.01	1.40	0.99
Discharge Location										
Home	338	1.27	0.72	1.39	0.70	240	1.50	0.94	1.44	0.92
Residential Care Facility	69	1.45	0.75	1.51	0.67	62	1.43	0.75	1.40	0.84

Table 20. Sedative load by patients' characteristics between patients admitted to acute mental health units and patients admitted to other units

	Patients admitted to acute mental health units					Patients admitted to non-acute mental health units				
		Pre-admission		Discharge			Pre-admission		Discharge	
Characteristics	n	mean	SD	mean	SD	n	mean	SD	mean	SD
Total	407	2.45	1.42	2.60	1.42	303	3.06	1.77	2.89	1.77
Gender										
Female	203	2.56	1.53	2.52	1.34	166	3.16	1.8	2.92	1.75
Male	203	2.34	1.3	2.68	1.48	137	2.95	1.74	2.85	1.79
Age										
18-44	217	2.20	1.27	2.44	1.4	49	2.35	1.56	2.18	1.39
45-64	124	2.69	1.47	2.75	1.35	73	3.75	2.05	3.58	1.99
65 and above	66	2.82	1.64	2.86	1.56	181	2.98	1.61	2.80	1.67
Length of stay										
2<LOS≤7	114	2.31	1.3	2.37	1.39	171	3.08	1.71	2.65	1.64
7<LOS≤15	130	2.41	1.37	2.50	1.31	76	2.99	1.94	3.03	1.94
15<LOS	163	2.58	1.53	2.85	1.48	56	3.13	1.76	3.43	1.78
Facility										
Facility A	307	2.50	1.49	2.65	1.5	213	3.08	1.76	2.79	1.70
Facility B	97	2.30	1.19	2.46	1.12	49	3.14	1.68	3.53	1.83
Facility C	3	2.67	1.15	2.67	1.15	41	2.9	1.99	2.63	1.89
Visit type										
Inpatient	302	2.52	1.46	2.65	1.41	274	3.1	1.76	2.9	1.76
ED to inpatient	105	2.25	1.31	2.49	1.44	29	2.69	1.89	2.79	1.84
Discharge Location										
Home	338	2.34	1.37	2.55	1.40	240	3.06	1.77	2.88	1.77
Residential Care Facility	69	2.97	1.58	2.87	1.46	62	3.08	1.80	2.94	1.78

Table 21. Independent samples t-tests between the changes in Sed-DBI score and sedative load among patients admitted to acute mental health units and patients admitted to other units

Sedative Burden	mean difference (SD)		t-statistic	df	95 % confidence interval		effect size	p-value
	Acute mental health units	Other units			lower bound	higher bound		
Sed-DBI score	0.11 (0.56)	-0.05 (0.57)	3.834	708	0.080	0.248	0.291	**<0.0001**
Sedative load	0.16 (1.32)	-0.18 (1.35)	3.249	708	0.130	0.529	0.247	**0.001**

Table 22. Paired samples t-tests between pre-admission and discharge sedative burden among patients admitted to acute mental health units

Sedative burden	t-statistic	df	95 % confidence interval		effect size	p-value
			lower bound	higher bound		
Sed-DBI score	3.962	406	0.055	0.164	0.196	**<0.0001**
Sedative load	2.369	406	0.026	0.283	0.117	**0.018**

3.5.4 Parameters associated with the differences in the sedative burden among patients admitted to acute mental health units

Unadjusted univariate regression analyses were performed to identify variables that predicted the changes of Sed-DBI score and sedative load (Table 23). A lower mean number of medications was found to be associated with a greater Sed-DBI score ($\beta = -0.019$, $p = 0.018$), and male gender was associated with a higher sedative load in comparison to female gender ($\beta = 0.379$, $p = 0.004$).

Stratified analyses (Table 24) were conducted for these two variables which were found to be significantly associated with the changes in Sed-DBI score and sedative load in the univariate analyses. The stratified paired samples t-test reported that patients taking fewer than five medications had a significantly higher sedative burden on discharge ($t(256)= 4.003$, $p = 0.0001$). The stratified analysis also suggested that male patients had a significantly greater sedative load on discharge ($t(202)= 4.017$, $p = 0.0001$).

The results of the unadjusted models of this subgroup had also been independently verified by another method (Appendix B).

Table 23. Associations of patients' characteristics with the changes in Sed-DBI score and sedative load during hospitalisation in unadjusted linear regression model among patients admitted to acute mental health units

		Sed-DBI score					Sedative load				
Parameters	Reference category	coefficient	p-value	95% confident interval		adjusted R-square	coefficient	p-value	95% confident interval		adjusted R-square
Gender				lower bound	higher bound				lower bound	higher bound	
Male	Female	0.101	0.069	-0.008	0.210	0.006	0.379	**0.004**	0.125	0.634	0.018
Age		-0.001	0.500	-0.004	0.002	-0.001	-0.004	0.306	-0.011	0.003	0.000
Discharge location											
Residential Care Facility	Home	-0.061	0.411	-0.206	0.085	-0.001	-0.309	0.076	-0.650	0.033	0.005
Visit type											
Inpatient	ED to inpatient	-0.012	0.853	-0.137	0.113	-0.002	-0.112	0.453	-0.406	0.181	-0.001
Length of stay		0.002	0.093	0.000	0.005	0.005	0.003	0.387	-0.003	0.009	-0.001
Mean number of medications		-0.019	**0.018**	-0.035	-0.003	0.011	-0.035	0.069	-0.073	0.003	0.006

Table 24. Changes in Sed-DBI score and sedative load from admission to discharge by the number of medication and gender in stratified paired samples t-tests

	Sed-DBI score					Sedative load				
Parameters	t-statistic	df	p-value	95% confident interval		t-statistic	df	p-value	95% confident interval	
				lower bound	higher bound				lower bound	higher bound
Gender										
Female						-0.402	202	0.688	-0.233	0.154
Male						4.017	202	**0.0001**	0.173	0.507
Number of medications										
Less than five	4.003	256	**0.0001**	0.065	0.191					
Five or more	1.530	149	0.128	-0.023	0.181					

The baseline-adjusted models suggested that the pre-admission sedative burden was negatively associated with the changes in the sedative burden (Sed-DBI: $\beta = -0.337$, $p < 0.0001$; SLM: $\beta = -0.433$, $p < 0.0001$).

After adjusting for baseline pre-admission Sed-DBI score, the mean number of medications remained significantly associated with the changes of sedative burden between pre-admission and discharge (Table 25). A greater mean number of medications was significantly associated with increased Sed-DBI score after adjusting for the pre-admission Sed-DBI score ($\beta = 0.025$, $p = 0.004$). Additionally, in the adjusted models, male gender ($\beta = 0.125$, $p = 0.012$) and longer length of hospitalisation ($\beta = 0.003$, $p = 0.027$) were also significantly associated with the increased Sed-DBI score.

For the baseline sedative load adjusted models, gender remained significantly associated with the changes in the sedative load ($\beta = 0.287$, $p = 0.013$), while the mean number of medications also became significantly associated with the changes in sedative load ($\beta = 0.101$, $p < 0.0001$). After adjusting for the pre-admission sedative burden, a greater R-squared statistic can be observed compared to the unadjusted univariate models, suggesting that the pre-admission sedative burden is highly correlated to the changes in the Sed-DBI score and the sedative load.

Table 25. Association of patients' characteristics with the changes in Sed-DBI score and sedative load during hospitalisation in baseline adjusted linear regression models among patients admitted to acute mental health units

		Sed-DBI score					Sedative load				
Parameters	Reference category	coefficient	p-value	95% confident interval		adjusted R-square	coefficient	p-value	95% confident interval		adjusted R-square
				lower bound	higher bound				lower bound	higher bound	
Pre-admission sedative burden		-0.337	**<0.0001**	-0.405	-0.270	0.191	-0.433	**<0.0001**	-0.513	-0.353	0.216
Gender											
Male	Female	0.125	**0.012**	0.027	0.222	0.205	0.287	**0.013**	0.061	0.513	0.229
Age		0.000	0.972	-0.003	0.003	0.189	0.003	0.353	-0.003	0.010	0.216
Discharge location											
Residential Care Facility	Home	-0.001	0.989	-0.132	0.130	0.189	-0.038	0.809	-0.345	0.270	0.214
Visit type											
Inpatient	ED to inpatient	0.015	0.787	-0.097	0.128	0.189	0.006	0.966	-0.255	0.267	0.214
Length of stay		0.003	**0.027**	0.000	0.005	0.199	0.005	0.059	0.000	0.010	0.221
Mean number of medications		0.025	**0.004**	0.008	0.041	0.206	0.101	**<0.0001**	0.061	0.141	0.260

Backward selection multiple regression analyses were performed to develop models that predict the changes in Sed-DBI score and sedative load among patients admitted to acute mental health units. Greater pre-admission Sed-DBI score ($\beta = -0.432$, $p < 0.0001$) and older age ($\beta = -0.003$, $p = 0.040$) were found to be independently associated with the decreased Sed-DBI score (Table 26). Additionally, male gender was found to be significantly associated with the increased Sed-DBI score ($\beta = 0.160$, $p = 0.002$), a longer length of hospitalisation ($\beta = 0.002$, $p = 0.046$) and a greater mean number of medications ($\beta = 0.038$, $p < 0.0001$) were also significantly associated with the increased Sed-DBI score. This model suggested that 23.7% of the changes in the Sed-DBI score between pre-admission and discharge among patients that were admitted to an acute mental health unit fit this regression model.

In comparison, the changes in the sedative load can be independently predicted by the lower pre-admission sedative load ($\beta = -0.576$, $p < 0.0001$), male gender ($\beta = 0.386$, $p = 0.001$), and a greater mean number of medications ($\beta = 0.112$, $p < 0.0001$) (Table 27). The adjusted R-squared statistic of 0.282 indicated that 28.2% of the variation in the changes in sedative load between pre-admission and discharge for this subgroup of patients can be explained by this model.

Additional information on the backward selection multiple regression models can be found in Appendix C.

Table 26. Backward selection of predictor variables that predict the changes in Sed-DBI score during hospitalisation for patients admitted to acute mental health units

Predictor variables	Reference category	coefficient	p-value	95% confident interval	
				lower bound	higher bound
Constant		0.529	**<0.0001**	0.360	0.697
Pre-admission Sed-DBI score		-0.432	**<0.0001**	-0.512	-0.353
Gender					
Male	Female	0.160	**0.002**	0.061	0.258
Age		-0.003	**0.040**	-0.007	0.000
Discharge location					
Residential Care Facility	Home				
Visit type					
Inpatient	ED to inpatient				
Length of stay		0.002	**0.046**	0.000	0.005
Mean number of medications		0.038	**<0.0001**	0.018	0.057
R-square		0.246			
Adjusted R-square		0.237			
n		406			

Table 27. Backward selection of predictor variables that predict the changes in sedative load during hospitalisation for patients admitted to acute mental health units

Predictor variables	Reference category	coefficient	p-value	95% confident interval	
				lower bound	higher bound
Constant		0.855	**<0.0001**	0.597	1.114
Pre-admission sedative load		-0.576	**<0.0001**	-0.669	-0.483
Gender					
Male	Female	0.386	**0.001**	0.165	0.607
Age					
Discharge location					
Residential Care Facility	Home				
Visit type					
Inpatient	ED to inpatient				
Length of stay					
Mean number of medications		0.112	**<0.0001**	0.073	0.152
R-square		0.287			
Adjusted R-square		0.282			
n		406			

4. Discussion

The primary objective of the present study was to determine the changes in the sedative burden, as quantified by both the Sed-DBI and the SLM, among hospitalised patients taking at least one antipsychotic medication prior to admission. Secondary objectives were to determine the patient characteristics associated with changes in the sedative burden, and the differences between patients admitted to acute mental health units and other units. To this researcher's knowledge, this was the first study to explore the changes in the sedative burden among this specific group of patients in an overall hospital population.

4.1 Changes in sedative burden between admission and discharge

4.1.1 Comparison with prior studies that calculated the changes in Sed-DBI score in hospitals

In the total study cohort, there were no significant changes in the mean Sed-DBI scores and sedative load between pre-admission and discharge. Compared to previous studies that investigated the changes in DBI scores in hospital inpatients [41, 45, 95], the mean DBI scores in the present study were greater (pre-admission=1.38 (SD=0.81); discharge=1.42 (SD=0.79)). One earlier study reported a mean DBI score of 0.41 at admission, and 0.36 on discharge [45] and another reported changes in the DBI scores between admission and discharge at three geriatric hospitals: the DBI scores at admission and on discharge were found to be 0.58 and 0.58; 0.53 and 0.64; 0.60 and 0.62, respectively [95]. No statistically significant differences between admission and discharge were reported in these two studies [45, 95]. A further study also reported changes in sedative drug burden in hospitals, the DBI score was reported to be 0.40 prior to admission and 0.41 during hospitalisation, but the authors did not report the significance of the difference [41].

Similar to the present study, these studies reported the changes in the drug burden during hospitalisation in their patient cohorts. The higher mean Sed-DBI scores in the present study were primarily due to the inclusion criteria, while earlier studies only had 52% [41] and 49% [45] of their study populations taking

medications that contributed to the DBI score, all patients included in the present study were taking at least one antipsychotic medication prior to admission. Additionally, the three earlier studies restricted their study populations to older patients (aged 65 and above [45, 95], and 70 and above [41]), while the present study included all adults aged 18 and above, this difference may also contribute to the higher sedative burden.

4.1.2 Comparison with prior studies that calculated the sedative load

To this researcher's knowledge, changes in the sedative load between hospital admission and discharge have not been previously explored. Most prior studies that employed the SLM have reported a mean sedative load of lower than 1 and mainly focused on community-dwelling older individuals aged 65 years [84] or 75 years and above [63, 64, 69, 89]. However, the majority of the participants in these studies had a sedative load of zero (81% [84], 71% [63, 64, 69], and 64-71% [89]) indicative of study participants not taking any sedating medications [63, 64, 69, 84, 89].

Further, differences in the sedative load between the present study and these prior studies were likely due to the inclusion of patients aged 18 and above and specifically including patients taking at least one antipsychotic medication prior to hospitalisation.

4.2 Associations between sedative burden and patients' characteristics

4.2.1 Parameters associated with the increased Sed-DBI scores and sedative load: Results from univariate and baseline-adjusted linear regressions

Male gender, younger age, patients admitted to geriatric or acute mental health units, a longer length of stay, and a lower mean number of medications were associated with the increase in both the Sed-DBI score and the sedative load on discharge. However, the expected changes in the sedative burden varied for these independent variables as suggested by the magnitude of their coefficients. The results of the present study are consistent with previous studies which suggested that male gender [41, 95], and longer length of hospitalisation [41] predicted changes in the drug burden among hospitalised patients. Additionally, the results of the baseline adjusted models are in line with the results of a previous study which also reported

a significant relationship between a greater sedative burden on admission and a decrease in the sedative burden [41].

4.2.2 Independent predictors of the increased Sed-DBI score: Results from backward selection multiple regression

In this study, the increase in the Sed-DBI score can be independently predicted by a lower pre-admission sedative score, younger age, a longer length of stay and a greater mean number of medications.

Two prior studies had also investigated factors that were associated with an increase in the DBI score in their study cohort. One study reported that increased DBI score during hospitalisation was associated with of male gender, hospitalisation due to stroke, or patients who were unable to stay home, patients with diabetes mellitus, and a greater number of medications at admission [95]. Another study suggested that cognitive decline, comorbidity, cognitive status on admission, depressive symptoms, and years of education were associated with an increase in DBI scores [41].

However, most findings were not comparable with the present study as these parameters were not routinely collected at South Australian public hospitals. Nevertheless, Smichenko et al. [41] suggested that a greater pre-admission burden and other parameters indicative of poorer health at the time of admission (i.e. severity of illness, higher comorbidities score, and poorer cognitive status on admission which were also not considered in the present study) were associated with a decrease in the DBI score during hospitalisation. These factors were highlighted as potential reasons for the removal and/or reduction of unnecessary medications and doses during hospitalisation, resulting in the observed reduction in the sedative burden [41]. This has also been observed in the present study. The sedative burden prior to admission was a possible marker of severity of illness prior to admission, and it was found to be associated with the changes in the Sed-DBI score upon discharge. In addition, a longer duration of hospital stay and a greater number of medications were possible markers of severe illness during hospitalisation, hence, requiring additional medications, and thus contributing to a greater Sed-DBI score

on discharge. Additional markers for the severity of illness would be the reasons for admission. However, in the present study, reasons for hospital admission were not available to be included in the analyses.

Further, in the present study, younger age was one of the significant factors associated with an increase in the Sed-DBI score. This finding was in concordance with treatment guidelines recommending dose reductions for the elderly for psychotropic medications (such as quetiapine). The TGA recommends that the dose of quetiapine, which is the most frequently prescribed sedating medication in this cohort, be lower for older individuals [5]. The AMH also states that older individuals are more susceptible to the risks of the adverse effects associated with antipsychotics. In particular, the risk of stroke and death increases when older individuals take higher doses of antipsychotics [4]. Hence, when prescribed the same medications, the sedative burden would be greater for younger patients when compared to older patients.

4.2.3 Independent predictors of the increased sedative load: Results from backward selection multiple regression

Factors that independently predicted the increase in sedative load were the same as those predicted the changes in the Sed-DBI score, with an additional three factors: male gender and patients admitted to either acute mental health or geriatric units. These additional factors can be explained by the inherent differences in how the Sed-DBI score and the sedative load are calculated. While the DBI takes into account the daily dose of medications taken by the patients and the minimum recommended daily dose, the sedative load is solely dependent on a sedative rating assigned to the medications taken by study participants. Upon discharge, patients with these characteristics (that is, male gender, admitted to either acute mental health or geriatric units) were possibly given additional sedating medications, or the medication was changed into a sedating medication with a greater sedative rating, but at a lower dose.

As prior studies have not explored the changes in sedative load in hospitalised patients, results of the present study could not be compared to previous studies. In comparison to the SLM, the DBI had been widely used as a validated method of measuring medication burden. The researcher is hypothesising that

more studies have utilised the DBI due to the SLM's lack of consideration for the medication dosage and the frequency of administration. For example, a sedating medication given towards the upper end of the dose range and multiple times during the day would be more sedating than the same medication given at the lower end of the dose range once a day. The SLM also does not account for the different sedating properties of SGAs. Instead, they have been placed in the same group and assigned the same sedative rating. For example, even though quetiapine is more sedating compared to risperidone [8], both had been given the same sedative rating of 2 in the SLM.

4.3 Subgroup analyses: Patients admitted to acute mental health units

To the researcher's knowledge, prior studies had not explored the changes in DBI score and sedative load among patients admitted to acute mental health units. In the present study, over half of the patients (57.2%) were admitted to acute mental health units and the mean Sed-DBI score and sedative load were observed to be significantly greater at discharge. Compared to the patients who were admitted to non-acute mental health units, the mean differences between pre-admission and discharge were found to be significantly different.

In this subgroup, the differences in the mean Sed-DBI score between admission and discharge for male patients was 0.160 higher than for female patients. Additionally, for every unit increase in the pre-admission Sed-DBI score and age, the Sed-DBI score decreased by 0.432, and 0.003 respectively. The Sed-DBI score increased by 0.002 for every unit increase in the length of hospitalisation, and by 0.038 for every unit increase in the mean number of medications.

Similar to the whole study population, those admitted to acute mental health units also showed significant associations between lower pre-admission sedative burden, younger age, a longer length of stay and a greater mean number of medications, and an increase in Sed-DBI scores between admission and discharge. This confirmed that admission to an acute mental health unit was not an independent predictor of the changes observed in the Sed-DBI score. Additionally, being of male gender was found to be associated with an increased Sed-DBI score among patients admitted to acute mental health units. It is

possible that the homogeneity of this subgroup could explain male gender being significantly associated in the subgroup analyses. In the multiple regression analyses of the whole study population, the increased sedative burden on discharge was negatively associated with age (younger age was associated with increased sedative burden) and positively associated with the length of hospitalisation (longer length of hospitalisation was associated with increased sedative burden). Therefore, as most patients were younger and had a longer length of stay in this subgroup, male gender was picked up as a significant predictor even though it was originally not significant in the whole study population.

For the changes in the sedative load, male patients are more likely to have a greater sedative load on discharge, which was on average higher by 0.386 compared to female patients. In addition to gender, for every unit decrease in the pre-admission sedative load, the sedative load increased by 0.576 on discharge, and for every unit increase in the overall mean number of medications, the sedative load increased by 0.112.

Once again, the different findings of parameters associated with the increased Sed-DBI score and sedative load may be explained by the differences between the DBI and the SLM. Younger patients and patients with a longer length of hospital stay were prescribed sedating medications at a higher dose, and hence, their Sed-DBI scores increased upon discharge. However, the number of sedating medications had decreased, or the sedating medication prescribed on discharge had a lower sedative rating. Hence these parameters did not contribute to the increase in the sedative load.

This study was the first to identify parameters associated with the changes in Sed-DBI score and sedative load among patients admitted to acute mental health units. The present study has highlighted that patients admitted to acute mental health units had a significantly greater Sed-DBI score and sedative load on discharge when compared to those admitted to other units. The lower pre-admission sedative burden was the strongest predictor for an increase in the Sed-DBI score, followed by being of male gender, higher mean number of medications, decreasing age and longer length of hospitalisation. For the increased

sedative load, the pre-admission sedative load had the greatest effect on the changes in sedative load, followed by gender, and the mean number of medications.

4.4 Comparison of DBI and SLM

The present study utilised the Sed-DBI and SLM to qualify the changes in sedative burden in the study population. In particular, significant differences were observed among patients taking at least one antipsychotic medication prior to admission and admitted to an acute mental health unit. Additionally, this study was also able to identify parameters that were associated with the increase in the Sed-DBI score and sedative load. This provides a valuable comparison between the two models. As previously discussed, the calculation of the DBI score takes dosages into account, and the DBI has been more widely validated in comparison to the SLM. While acknowledging that the DBI is a superior model, the SLM would be easier to employ in a clinical setting, such as within the hospital or other acute care settings. This study was able to determine whether the two models were comparable and can be used interchangeably in identifying patients with a high risk of being discharged with a greater sedative burden. However, the differences in the results are suggestive of the dose of medication being an important component and it should be considered when quantifying the overall sedative burden.

4.5 Prevalence of sedating medications

Quetiapine and olanzapine were the most prescribed sedating medications at both time points in this study cohort. This is concordant with a previous Australian study [13]. Followed by quetiapine and olanzapine, the most prevalent sedating medications in this study cohort were risperidone at admission and valproate on discharge respectively. The Australian national survey of psychosis which included individuals with psychosis aged 18-64, reported quetiapine, clozapine, olanzapine and risperidone as the four most frequently used antipsychotics, while sodium valproate was the most frequently used mood stabiliser [110]. The results of the present study validate these findings.

4.6 Applications of findings from previous studies to the present study population

4.6.1 Age and sedative burden

In the present study, younger age was one of the variables found to be significantly associated with an increase in the sedative burden on discharge among hospitalised patients. In this relationship, younger age referred to patients who were relatively younger in comparison to other patients. In the multiple regression analyses, age was a continuous variable. Hence, "younger age" was not defined by a specific age range. Additionally, it is important to emphasise that although younger patients were more likely to have a higher sedative burden upon discharge, this did not equate to younger patients having a higher mean sedative burden in comparison to older patients.

Previous findings suggested that the dosages of lamotrigine, olanzapine, quetiapine, risperidone and valproate were significantly lower among older patients during hospitalisation [24, 97]. These findings are possible explanations for the increased sedative burden during hospitalisation observed in younger patients in the present study.

The negative relationship between age and the changes in sedative burden may raise safety concerns as prior studies have found significant relationships between age and adverse reactions of psychotropic medications. One study observed that patients aged 60 years or younger had a significantly higher frequency of experiencing adverse drug reactions compared to older patients [97]. Another study reported an increased risk of reduction in sleep duration and a decreased likelihood of experiencing sedation with increasing age [36]. As such, the increased sedative burden on discharge is problematic as the patients will be continuing on these sedating medications after discharge.

4.6.2 Physical and cognitive impairments significantly associated with the DBI score and the sedative load

In addition to the findings of the present study, previous studies have shown significant associations between a greater DBI score or sedative load and impaired physical [31, 39, 40, 44, 51, 63, 66-69], and cognitive functions [31, 50, 70]. However, these associations had been mainly investigated in older community-dwelling populations. While there are limited studies that explored the changes in sedative

burden in hospitals, other studies had reported that a higher drug burden and sedative load were associated with an increased risk of hospitalisation [74, 80], falls [78, 79], readmission after discharge [75, 76], and poorer quality of life [54, 72, 73]. Additionally, one recent study reported that diagnoses of psychosis are one of the strongest predictors of a higher DBI score [85]. In the present study, increasing age was found to be associated with a decreased sedative burden on discharge. However, although older patients on average had experienced a decrease in the sedative burden in the present study, their mean sedative burden remained greater or similar to younger patients (patients aged 18-44, as shown in tables 10, 19 and 20) between admission and discharge. As established by previous studies, older patients in this study were also susceptible to the risks associated with a high sedative burden.

Sedating medications can also impact younger individuals in several ways. In the present study, younger patients were found to be more likely to experience an increase in their sedative burden during hospitalisation, which would increase their likelihood of being discharged with a sedative burden that was greater than prior to their hospitalisation. Individuals discharged back to the community with a higher sedative burden may experience impairment in their ability to drive due to drowsiness and increased sedation [111]. Additionally, the use of multiple medications with sedating properties can exacerbate this impairment and increase the risk of traffic accidents [111]. One study that included individuals aged 18 to 65, reported that among patients diagnosed with schizophrenia and taking SGAs, 83.5% of the participants reported feeling drowsy during the day, and the sedative effect of antipsychotics had a negative impact on their daily functioning [112]. In particular, employment was one of the areas that were greatly affected [112]. The study reported that impacts of side effects such as “feeling sleepy during daytime” and “feeling drugged or like a zombie” highly impacted the participants’ ability to gain employment and to continue working if they were employed [112]. These issues would be especially problematic for patients discharged with long-acting antipsychotics.

4.7 Implications for future research

The present study investigated the changes in the sedative burden of hospitalised patients taking at least one antipsychotic medication prior to admission and identified factors that predicted an increase in sedative burden at discharge. With significant findings observed in patients admitted to acute mental health units, this study raises several opportunities for future research.

Firstly, the data utilised in this study were drawn from Sunrise EMR and the potential of using the Sed-DBI (or to a lesser extent the SLM) to automatically quantify the pre-admission sedative burden should be investigated. In addition to the pre-admission burden, several other factors had been identified as predictors of increased sedative burden at discharge. Future research should focus on patients admitted to acute mental health units, as a significantly higher sedative burden was observed at discharge in this cohort. To ensure that the increased sedative burden during hospitalisation was necessary and appropriate, a pilot study could be conducted to investigate whether the indications for the prescribed sedating medications are in accordance with clinical guidelines and appropriately prescribed. The feasibility of incorporating an alert system on Sunrise EMR for patients with parameters that were found to be significantly associated with an increased sedative burden should also be investigated whereby prescribers can be alerted to the sedative burden of the medications that they intend to prescribe. The DBI, and to a lesser extent the SLM, would be able to individualise treatment, as a patient's individual sedative burden can be calculated and hence provide patient-centred care. However, it is important to note that the usefulness of these models is limited for patients with limited treatment options. For patients without safer alternative treatment options, ceasing or not prescribing sedating medications that can contribute to a greater sedative burden may be impracticable. While it is important to consider the sedative burden, there is also the possibility of introducing the risk of under-prescribing due to overcautiousness induced by these models.

Secondly, future research should also be undertaken to determine other parameters that can predict an increase in the sedative burden in hospitals. Reasons for admission and comorbidities are possible predictors of changes in the sedative burden. Examining additional factors would allow for a better

understanding of the changes in the sedative burden in this study population, particularly those admitted to acute mental health units. Additionally, this study was able to identify patients that were at risk of leaving the hospital with a higher sedative burden. As such, the possible functional impairments associated with the increased sedative burden among this group of patients could be investigated. Further studies are needed to validate the DBI and SLM as measures of functional impairments in the present study population and it would be worthwhile to determine whether physical impairments and other factors that were found to be associated with a higher Sed-DBI score and sedative load in prior studies are also associated with the present study population.

Lastly, another possible area of future research would be to determine whether patients discharged with an increased sedative burden receive any ongoing medication reviews, home medicines reviews, and any other forms of follow ups after their hospital discharge. As reviews in hospitals are often difficult for individuals that are acutely unwell, it is vital that patients are followed up regularly to determine the impact of sedation on their safety and daily activities. This is particularly important for patients discharged with sedating medications with long half-lives.

These could be some important areas of research with recent reports highlighting the negative impacts of the COVID-19 pandemic on the mental health of the general population in Australia [12, 113]. It can be assumed that more individuals will fit the profile of the patients in acute mental health units in the present study population, and hence it is important to gain a better understanding of the potential risks of sedation that may negatively impact this population.

4.8 Strengths and limitations

The major strengths of this study were the breadth of data from three public hospitals in South Australia and the validated measures used to quantify the sedative burden. The present study included all patients aged 18 years and older derived from ‘a real world’ hospital cohort. Relatively few studies have explored the drug burden and sedative load in patients below the age of 65 years. Additionally, only limited studies have explored changes in the sedative burden in hospitalised patients. In particular, this study focused

specifically on patients who were taking at least one antipsychotic medication prior to admission, including patients admitted to acute mental health units. To the researcher's knowledge, the present study was the first study to quantify the changes in the sedative burden between admission and discharge among patients admitted to acute mental health units.

The quantification of the sedative burden using the DBI and SLM, two widely validated measures for the medication burden was also a major strength. Functional impairments and parameters associated with a greater DBI score and sedative load have been widely investigated among the elderly in many studies. This allowed the present study to use these validated measures in a wider hospitalised population. Additionally, the Sed-DBI was one of the measures used to determine the sedative burden in this study. The recommended minimum daily dose for the sedating medications was determined in consultation with the TGA and AMH in order to maintain relevance to the Australian context.

There were also some limitations. Due to the limited demographic data available, variables such as ethnicity, marital status, income, and education were unavailable to be incorporated into the analyses. These parameters have been analysed in prior studies to identify potential associations with the sedative burden. However, the associations of these parameters cannot be validated in the present study.

Additionally, as data on discharge medications were not extracted from patients' discharge summaries (which are often inaccurate or not documented), additional assumptions had to be made in relation to the medications prescribed on discharge. Therefore, it is possible that these assumptions may have impacted the sedative burden calculations. Depending on the dose and frequency of the medication, and whether the medication was actually prescribed on discharge, the assumptions made for the discharge medications could possibly result in an overestimation or underestimation of the changes in the sedative burden.

Further, as previously mentioned, the Sed-DBI was used to determine the sedative burden in this study. Although the DBI was validated by many studies, most studies focused on older populations (aged 65 and years and above). Therefore, the relationships between a higher DBI score and the functional impairments

and risks that have been previously established have not been widely investigated in the younger cohorts. Moreover, due to the lack of standardisation of the minimum recommended daily dose, the selected minimum recommended daily dose in the present study may be different to other Australian studies. Additionally, the present study also included additional sedating medications to the original SLM. The differences in comparison to the original DBI and SLM are also important limitations that should be taken into account when interpreting the findings of the present study.

Patients included in the present study were all taking at least one regular antipsychotic medication prior to admission and were acutely unwell being hospitalised for more than 48 hours. Therefore, the findings of the present study may not be generalisable to a wider population.

PRN medications were not included in the calculations in the present study as it was difficult to ascertain whether patients were actually administered their PRN medications. Including PRN medications in the calculations would likely result in overestimations of the sedative burden. Alternatively, excluding PRN medication in the calculations may have resulted in underestimations of the overall sedative burden.

Another limitation of the present study was the low R-squared statistics reported in the multiple regression analyses. Although all the variables included in the final models were statistically significant, low R-squared statistics indicated that the significant predictor variables identified in the present study only account for a small variation of the changes in the sedative burden between admission and discharge. A possible explanation may be the limited number of independent variables included in the analyses. Factors such as comorbidities, reasons for admission, and indications of use for the sedating medications could not be included in the present study. Hence, it may well be that the changes in the sedative burden during hospitalisation might be related to factors that were not able to be accounted for in this study.

5. Conclusion

The objective of the present study was to determine the changes in the sedative burden quantified by the Sed-DBI and SLM among patients taking at least one antipsychotic medication prior to admission. Even though no significant differences between the sedative burden at admission and discharge were observed in the total cohort, significant changes in the sedative burden among patients admitted to acute mental health units were observed. To the researcher's knowledge, this was the first study to report changes in the sedative burden among patients admitted to acute mental health units. The increase in the Sed-DBI score was predicted by male gender, a greater mean number of medications, longer length of hospitalisation, lower pre-admission Sed-DBI score and younger age, while the increase in the sedative load was predicted by male gender, greater mean number of medications and lower pre-admission sedative load. The present study identified this group of patients as a population at a higher risk of being discharged with a significantly higher sedative burden. Due to the current lack of research in this patient group, more research could strengthen and validate the findings of this study.

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7. Appendices

7.1 Appendix A

Supplementary Table 1. List of medications included in the present study

Medications from the original SLM[a]	Additional medications from the present study	Sedative group	Sedative rating	ATC code level 5	Selected minimum daily dose for Sed-DBI calculation
Alprazolam		1	2	N05BA12	0.5 mg
Amitriptyline		1	2	N06AA09	75 mg
Chlorpromazine		1	2	N05AA01	75 mg
Clomipramine		1	2	N06AA04	50 mg
Diazepam		1	2	N05BA01	2 mg
Doxepin		1	2	N06AA12	25 mg
	Doxylamine	1	2	R06AA09	25 mg
Droperidol		1	2	N05AD08	2.5 mg
Flupentixol injection		1	2	N05AF01	0.714 mg
Haloperidol		1	2	N05AD01	1 mg
	Haloperidol injection [d]	1	2	N05AD01	1.786 mg
Lithium carbonate		1	2	N05AN01	750 mg
Lorazepam		1	2	N05BA06	2 mg
	Melatonin	1	2	N05CH01	2 mg
Midazolam		1	2	N05CD08	2.5 mg
Nitrazepam		1	2	N05CD02	5 mg
Nortriptyline		1	2	N06AA10	25 mg
Oxazepam		1	2	N05BA04	22.5 mg
Periciazine		1	2	N05AC01	15 mg
Prochlorperazine		1	2	N05AB04	20 mg
	Prochlorperazine injection [d]	1	2	N05AB04	12.5 mg
Temazepam		1	2	N05CD07	10 mg
Zolpidem		1	2	N05CF02	5 mg
Zopiclone		1	2	N05CF01	7.5 mg

Zuclopenthixol		1	2	N05AF05	10 mg
	Zuclopenthixol injection [d]	1	2	N05AF05	7.143 mg
	Amisulpride	2	1	N05AL05	400 mg
	Aripiprazole	2	1	N05AX12	10 mg
	Aripiprazole injection	2	1	N05AX12	14.29 mg
	Asenapine	2	1	N05AH05	10 mg
	Baclofen	2	1	M03BX01	15 mg
	Benzatropine	2	1	N04AC01	1 mg
Bromhexine		2	1	R05CB02	24 mg
Buprenorphine	Buprenorphine patch [d]	2	1	N02AE01	0.12 mg
	Buprenorphine, combinations (sublingual)	2	1	N07BC51	2 mg
Carbamazepine		2	1	N03AF01	400 mg
Citalopram		2	1	N06AB04	20 mg
	Clonazepam	2	1	N03AE01	1 mg
	Clonidine	2	1	C02AC01	0.1 mg
Clozapine		2	1	N05AH02	12.5 mg
Codeine		2	1	R05DA04	30 mg
	Codeine and ibuprofen	2	1	N02AJ08	30 mg
	Cyproheptadine	2	1	R06AX02	12 mg
	Desvenlafaxine	2	1	N06AX23	50 mg
	Dexchlorpheniramine	2	1	R06AB02	8 mg
	Digoxin	2	1	C01AA05	0.25 mg
	Disulfiram	2	1	N07BB01	100 mg
	Dosulepin	2	1	N06AA16	75 mg
	Duloxetine	2	1	N06AX21	60 mg
	Escitalopram	2	1	N06AB10	10 mg
Fentanyl	Fentanyl patch [d]	2	1	N02AB03	0.288 mg
	Fexofenadine	2	1	R06AX26	120 mg
Fluoxetine		2	1	N06AB03	20 mg
Fluvoxamine		2	1	N06AB08	50 mg
Gabapentin		2	1	N03AX12	900 mg

	Hydromorphone	2	1	N02AA03	3 mg
	Hydromorphone injection [d]	2	1	N02AA03	4 mg
	Lacosamide	2	1	N03AX18	200 mg
	Lamotrigine	2	1	N03AX09	25 mg
	Levetiracetam	2	1	N03AX14	500 mg
	Lurasidone	2	1	N05AE05	40 mg
	Memantine	2	1	N06DX01	5 mg
	Methadone	2	1	N07BC02	20 mg
	Methyldopa	2	1	C02AB01	250 mg
Metoclopramide		2	1	A03FA01	30 mg
Mirtazapine		2	1	N06AX11	15 mg
Morphine	Morphine hydrochloride oral liquid [d]	2	1	N02AA01	30 mg
	Morphine injection [d]	2	1	N02AA01	60 mg
	Morphine sulfate controlled release tablet [d]	2	1	N02AA01	10 mg
Olanzapine		2	1	N05AH03	5 mg
	Olanzapine modified release injection [d]	2	1	N05AH03	10.714 mg
Oxycodone		2	1	N02AA05	30 mg
	Oxycodone and naloxone [d]	2	1	N02AA55	10 mg
	Paliperidone	2	1	N05AX13	3 mg
	Paliperidone modified release injection [d]	2	1	N05AX13	2.679 mg
Paroxetine		2	1	N06AB05	20 mg
	Pizotifen	2	1	N02CX01	1.5 mg
	Pramipexole	2	1	N04BC05	0.375 mg
	Promethazine hydrochloride	2	1	R06AD02	25 mg
Quetiapine		2	1	N05AH04	50 mg
	Quetiapine controlled release tablet [d]	2	1	N05AH04	300 mg
Risperidone		2	1	N05AX08	2 mg

	Risperidone modified release injection [d]	2	1	N05AX08	1.786 mg
Rizatriptan		2	1	N02CC04	10 mg
	Rotigotine patch	2	1	N04BC09	2 mg
Sertraline		2	1	N06AB06	50 mg
Sumatriptan		2	1	N02CC01	50 mg
	Tapentadol	2	1	N02AX06	200 mg
Theophylline [b]		2	1	R03DA04	No sedative effect according to the AMH
	Topiramate	2	1	N03AX11	25 mg
Tramadol		2	1	N02AX02	100 mg
	Trihexyphenidyl	2	1	N04AA01	1 mg
Valproate		2	1	N03AG01	600 mg
Venlafaxine		2	1	N06AX16	75 mg
	Ziprasidone	2	1	N05AE04	80 mg
Zolmitriptan		2	1	N02CC03	2.5 mg
Sotalol [c]		3	0	C07AA07	80 mg
Donepezil [c]		3	0	N06DA02	5 mg
Rivastigmine [c]		3	0	N06DA03	9.5 mg
Galantamine [c]		3	0	N06DA04	8 mg
Cetirizine [c]		3	0	R06AE07	10 mg
Loratadine [c]		3	0	R06AX13	10 mg
Levodopa [c]		3	0	N04BA02	150 mg

ATC: Anatomical Therapeutic Chemical; AMH: Australian Medicines Handbook; Sed-DBI: Sedative component of the Drug burden index; SLM: Sedative load model

[a] Only included medications that were also included in the present study
[b] Theophylline is included in the original sedative load model table in group 2, however, according to the AMH theophylline has no sedative effect, hence, not included for the Sed-DBI calculation
[c] Seven medications in group 3 have drowsiness reported as a common adverse effect according to the AMH
[d] Not an additional medication added to the SLM, included as the minimum recommended dose varies for different formulations

7.2 Appendix B

The linear mixed-effects models were performed using SPSS Statistics, while the results reported in Chapter 3 were conducted with STATA. Results of the linear mixed-effects models were not presented in Chapter 3 as the findings overlapped with the results of the unadjusted linear regression models. Additionally, due to the researcher's limited knowledge of the linear mixed-effects model, the methods for additional analyses to adjust for other factors were unknown to this researcher.

Data utilised for the linear mixed-effects models were organised into a wide format for analyses, where the sedative burden was categorised into two groups, period 0 and period 1, with 0 indicating pre-admission sedative burden and 1 as discharge sedative burden. The Linear mixed-effects model considers period and independent variables as fixed effects and patients as a random effect. Interaction terms between period referred to the independent variables and the sedative burden at period 0 and period 1, these variables were included in the models to determine whether the independent variables have different effects on the sedative burden.

In comparison to STATA, by default, SPSS employed the last category of a variable as the reference category, and the differences between the sedative burden between admission and discharge were tabulated automatically (Differences = period 0 sedative burden – period 1 sedative burden). Consequently, a positive coefficient in the outputs of the linear mixed-effects models indicated that the variable had a lower sedative burden compared to the reference category, and a negative coefficient suggested a higher sedative burden. In comparison, the opposite was observed for the linear regression models, the dependent variable was the differences calculated from the pre-admission sedative burden and the discharge sedative burden (Difference = discharge sedative burden – pre-admission sedative burden). As such, a positive coefficient can be interpreted as a higher sedative burden compared to the reference category, while a negative coefficient indicated a lower sedative burden. This also explains the differences in the confidence intervals.

Taking into account the differences in the reference categories and the calculated differences in the sedative burden, both models produced identical results (for gender, discharge location, and visit type) or matching results with opposite signs (for units). Additionally, the results for age, length of hospitalisation, and the number of medications were not comparable to the results of the unadjusted linear regression models, as these variables were analysed as ordinal variables in the linear mixed-effects models and as continuous variables in the unadjusted linear regression models.

The following tables are the results from the linear mixed-effects models which independently verified the results of the unadjusted linear regression models.

Supplementary Table 2. Estimates of Fixed Effects coefficients for interaction terms with period

		Sed-DBI score					Sedative load				
Interaction terms with period	Reference category	estimated coefficient	standard error	p-value	95 % confidence interval		estimated coefficient	standard error	p-value	95 % confidence interval	
					lower bound	higher bound				lower bound	higher bound
Gender				**0.044**					**0.004**		
Female	Male	0.086	0.043	**0.044**	0.003	0.170	0.292	0.100	**0.004**	0.095	0.488
Age				**0.044**					**0.050**		
18-44	≥65	-0.126	0.050	**0.013**	-0.223	-0.027	-0.282	0.118	**0.017**	-0.514	-0.050
45-64		-0.058	0.054	0.283	-0.164	0.048	-0.082	0.128	0.518	-0.333	0.168
Unit				**<0.0001**					**0.001**		
Acute mental health unit	General medical unit	-0.218	0.061	**<0.0001**	-0.339	-0.098	-0.479	0.145	**0.001**	-0.764	-0.193
Geriatric unit		-0.210	0.089	**0.018**	-0.384	-0.036	-0.570	0.209	**0.007**	-0.981	-0.159
Medical subspecialty units		-0.014	0.088	0.877	-0.186	0.159	-0.100	0.208	0.630	-0.507	0.308
Acute medical unit		-0.024	0.088	0.783	-0.198	0.149	-0.021	0.208	0.921	-0.430	0.389
Length of stay				**<0.0001**					**<0.0001**		
7<LOS≤15	2<LOS≤7	-0.147	0.051	**0.004**	-0.247	-0.047	-0.309	0.121	**0.011**	-0.546	-0.071
15<LOS		-0.253	0.050	**<0.0001**	-0.352	-0.155	-0.510	0.119	**<0.0001**	-0.744	-0.276
Discharge location				0.596					0.194		
Home	Residential care facility	-0.029	0.055	0.596	-0.137	0.079	-0.169	0.130	0.194	-0.424	0.086
Visit type				0.104					0.064		
ED to inpatient	Inpatient	-0.089	0.054	0.104	-0.196	0.018	-0.238	0.128	0.064	-0.490	0.014
Number of medications				0.054					0.181		
Less than five	Five or more	-0.082	0.043	0.054	-0.166	0.001	-0.135	0.101	0.181	-0.333	0.063

Supplementary Table 3. Estimate of fixed effects coefficients for interaction terms with period for patients admitted to acute mental health units

		Sed-DBI score					Sedative load				
Interaction terms with period	Reference category	estimated coefficient	standard error	p-value	95 % confidence interval		estimated coefficient	standard error	p-value	95 % confidence interval	
					lower bound	higher bound				lower bound	higher bound
Gender				0.069					**0.004**		
Female	Male	0.101	0.055	0.069	-0.008	0.210	0.379	0.129	**0.004**	0.125	0.634
Age				0.710					0.343		
18-44	≥65	-0.054	0.079	0.497	-0.209	0.101	-0.199	0.185	0.284	-0.563	0.165
45-64		-0.013	0.085	0.883	-0.181	0.155	-0.011	0.201	0.956	-0.406	0.384
Length of stay				0.250					0.349		
7<LOS≤15	2<LOS≤7	-0.034	0.072	0.633	-0.175	0.107	-0.031	0.169	0.855	-0.363	0.302
15<LOS		-0.109	0.068	0.112	-0.243	0.026	-0.209	0.161	0.196	-0.525	0.108
Discharge location				0.411					0.076		
Home	Residential care facility	-0.061	0.074	0.411	-0.206	0.085	-0.309	0.174	0.076	-0.650	0.033
Visit type				0.853					0.453		
ED to inpatient	Inpatient	-0.012	0.063	0.853	-0.137	0.113	-0.112	0.149	0.453	-0.406	0.181
Number of medications				0.312					0.530		
Less than five	Five or more	-0.058	0.058	0.312	-0.171	0.055	-0.085	0.136	0.530	-0.352	0.181

7.3 Appendix C

Supplementary Table 4. Stepwise backward selection multiple regression models for the changes in Sed-DBI score

		Model 1				Model 2				Model 3			
Predictor variables	Reference category	coefficient	p-value	95% confident interval		coefficient	p-value	95% confident interval		coefficient	p-value	95% confident interval	
				lower bound	higher bound			lower bound	higher bound			lower bound	higher bound
Constant		0.480	<**0.0001**	0.276	0.684	0.480	<**0.0001**	0.277	0.684	0.492	<**0.0001**	0.300	0.684
Pre-admission Sed-DBI score		-0.328	<**0.0001**	-0.382	-0.274	-0.327	<**0.0001**	-0.381	-0.273	-0.327	<**0.0001**	-0.381	-0.273
Gender													
Male	Female	0.072	0.062	-0.004	0.148	0.071	0.064	-0.004	0.147	0.071	0.064	-0.004	0.146
Age		-0.005	<**0.0001**	-0.008	-0.003	-0.005	<**0.0001**	-0.008	-0.003	-0.005	<**0.0001**	-0.008	-0.003
Discharge location													
Residential Care Facility	Home	0.005	0.928	-0.097	0.106								
Visit type													
Inpatient	ED to inpatient	-0.031	0.541	-0.130	0.068	-0.031	0.538	-0.130	0.068	-0.031	0.535	-0.130	0.068
Unit													
Acute mental health unit	General medical unit	0.085	0.164	-0.035	0.205	0.085	0.165	-0.035	0.205	0.074	0.160	-0.029	0.177
Acute medical unit		0.031	0.700	-0.126	0.187	0.028	0.727	-0.128	0.183				
Medical subspecialty units		-0.085	0.292	-0.244	0.073	-0.086	0.285	-0.243	0.072	-0.097	0.192	-0.242	0.049
Geriatric unit		0.134	0.107	-0.029	0.297	0.133	0.105	-0.028	0.294	0.122	0.109	-0.027	0.272
Length of stay		0.003	<**0.0001**	0.016	0.042	0.003	<**0.0001**	0.002	0.005	0.003	<**0.0001**	0.002	0.005
Mean number of medications		0.029	<**0.0001**	0.016	0.042	0.029	<**0.0001**	0.016	0.042	0.029	<**0.0001**	0.016	0.042
R-square		0.225				0.225				0.225			
Adjusted R-square		0.213				0.214				0.215			
n		708				709				709			

Supplementary Table 4. Continued

		Model 4				Model 5				Model 6			
Predictor variables	Reference category	coefficient	p-value	95% confident interval		coefficient	p-value	95% confident interval		coefficient	p-value	95% confident interval	
				lower bound	higher bound			lower bound	higher bound			lower bound	higher bound
Constant		0.472	**<0.0001**	0.291	0.653	0.424	**<0.0001**	0.257	0.592	0.466	**<0.0001**	0.306	0.626
Pre-admission Sed-DBI score		-0.327	**<0.0001**	-0.381	-0.273	-0.325	**<0.0001**	-0.378	-0.271	-0.321	**<0.0001**	-0.375	-0.267
Gender													
Male	Female	0.072	0.061	-0.003	0.147	0.073	0.058	-0.002	0.148				
Age		-0.005	**<0.0001**	-0.008	-0.003	-0.005	**<0.0001**	-0.007	-0.003	-0.005	**<0.0001**	-0.007	-0.003
Discharge location													
Residential Care Facility	Home												
Visit type													
Inpatient	ED to inpatient												
Unit													
Acute mental health unit	General medical unit	0.076	0.150	-0.027	0.179	0.108	**0.020**	0.017	0.200	0.107	**0.021**	0.016	0.199
Acute medical unit													
Medical subspecialty units		-0.099	0.181	-0.244	0.046								
Geriatric unit		0.121	0.113	-0.029	0.270	0.146	**0.049**	0.000	0.291	0.143	0.054	-0.002	0.289
Length of stay		0.003	**<0.0001**	0.002	0.005	0.003	**<0.0001**	0.002	0.005	0.003	**<0.0001**	0.002	0.005
Mean number of medications		0.029	**<0.0001**	0.016	0.042	0.029	**<0.0001**	0.016	0.042	0.028	**<0.0001**	0.015	0.040
R-square		0.224				0.222				0.217			
Adjusted R-square		0.215				0.214				0.210			
n		709				709				710			

Supplementary Table 4. Continued

		Model 7				Model 8			
Predictor variables	Reference category	coefficient	p-value	95% confident interval		coefficient	p-value	95% confident interval	
				lower bound	higher bound			lower bound	higher bound
Constant		0.467	**<0.0001**	0.307	0.628	0.563	**<0.0001**	0.439	0.688
Pre-admission Sed-DBI score		-0.322	**<0.0001**	-0.376	-0.268	-0.322	**<0.0001**	-0.376	-0.268
Gender									
Male	Female								
Age		-0.005	**<0.0001**	-0.007	-0.002	-0.005	**<0.0001**	-0.008	-0.003
Discharge location									
Residential Care Facility	Home								
Visit type									
Inpatient	ED to inpatient								
Unit									
Acute mental health unit	General medical unit	0.083	0.064	-0.005	0.172				
Acute medical unit									
Medical subspecialty units									
Geriatric unit									
Length of stay		0.004	**<0.0001**	0.002	0.005	0.004	**<0.0001**	0.003	0.005
Mean number of medications		0.028	**<0.0001**	0.015	0.040	0.025	**<0.0001**	0.013	0.038
R-square		0.213				0.209			
Adjusted R-square		0.207				0.205			
n		710				711			

Supplementary Table 5. Stepwise backward selection multiple regression models for the changes in sedative load

		Model 1				Model 2				Model 3			
Predictor variables	Reference category	coefficient	p-value	95% confident interval		coefficient	p-value	95% confident interval		coefficient	p-value	95% confident interval	
				lower bound	higher bound			lower bound	higher bound			lower bound	higher bound
Constant		1.008	**<0.0001**	0.551	1.464	1.013	**<0.0001**	0.558	1.468	0.971	**<0.0001**	0.544	1.398
Pre-admission sedative load		-0.463	**<0.0001**	-0.527	-0.400	-0.463	**<0.0001**	-0.526	-0.400	-0.462	**<0.0001**	-0.525	-0.399
Gender													
Male	Female	0.224	**0.011**	0.052	0.396	0.221	**0.011**	0.050	0.393	0.222	**0.011**	0.051	0.394
Age		-0.010	**<0.0001**	-0.015	-0.004	-0.010	**<0.0001**	-0.015	-0.005	-0.010	**<0.0001**	-0.015	-0.005
Discharge location													
Residential Care Facility	Home	-0.030	0.796	-0.261	0.201								
Visit type													
Inpatient	ED to inpatient	-0.134	0.245	-0.359	0.092	-0.134	0.241	-0.360	0.091	-0.134	0.244	-0.359	0.091
Unit													
Acute mental health unit	General medical unit	0.137	0.324	-0.136	0.411	0.137	0.324	-0.136	0.410	0.174	0.146	-0.061	0.409
Acute medical unit		-0.086	0.637	-0.443	0.271	-0.094	0.603	-0.449	0.261				
Medical subspecialties units		-0.199	0.280	-0.560	0.162	-0.194	0.288	-0.553	0.165	-0.157	0.351	-0.488	0.173
Geriatric unit		0.421	**0.026**	0.050	0.792	0.429	**0.022**	0.063	0.794	0.464	**0.008**	0.124	0.804
Length of stay		0.007	**<0.0001**	0.003	0.010	0.007	**<0.0001**	0.003	0.010	0.007	**<0.0001**	0.003	0.010
Mean number of medications		0.100	**<0.0001**	0.070	0.130	0.100	**<0.0001**	0.070	0.129	0.099	**<0.0001**	0.070	0.129
R-square		0.279				0.278				0.278			
Adjusted R-square		0.267				0.268				0.269			
n		708				709				709			

Supplementary Table 5. Continued

		Model 4				Model 5			
Predictor variables	Reference category	coefficient	p-value	95% confident interval		coefficient	p-value	95% confident interval	
				lower bound	higher bound			lower bound	higher bound
Constant		0.901	**<0.0001**	0.500	1.301	0.805	**<0.0001**	0.435	1.174
Pre-admission sedative load		-0.460	**<0.0001**	-0.523	-0.397	-0.460	**<0.0001**	-0.522	-0.397
Gender		0.224	**0.010**	0.053	0.395	0.227	**0.009**	0.056	0.399
Male	Female								
Age		-0.010	**<0.0001**	-0.015	-0.004	-0.010	**<0.0001**	-0.015	-0.005
Discharge location									
Residential Care Facility	Home								
Visit type									
Inpatient	ED to inpatient	-0.139	0.224	-0.364	0.085				
Unit									
Acute mental health unit	General medical unit	0.225	**0.034**	0.017	0.434	0.236	**0.026**	0.028	0.444
Acute medical unit									
Medical subspecialties units									
Geriatric unit		0.503	**0.003**	0.173	0.833	0.498	**0.003**	0.168	0.829
Length of stay		0.007	**<0.0001**	0.003	0.010	0.007	**<0.0001**	0.003	0.010
Mean number of medications		0.100	**<0.0001**	0.070	0.129	0.098	**<0.0001**	0.068	0.127
R-square		0.277				0.275			
Adjusted R-square		0.269				0.268			
n		709				709			

Supplementary Table 6. Stepwise backward selection multiple regression models for the changes in Sed-DBI score for patients admitted to acute mental health units

		Model 1				Model 2				Model 3			
Predictor variables	Reference category	coefficient	p-value	95% confident interval		coefficient	p-value	95% confident interval		coefficient	p-value	95% confident interval	
				lower bound	higher bound			lower bound	higher bound			lower bound	higher bound
Constant		0.529	**<0.0001**	0.348	0.711	0.530	**<0.0001**	0.361	0.698	0.529	**<0.0001**	0.360	0.697
Pre-admission Sed-DBI score		-0.433	**<0.0001**	-0.512	-0.353	-0.433	**<0.0001**	-0.512	-0.353	-0.432	**<0.0001**	-0.512	-0.353
Gender													
Male	Female	0.160	**0.002**	0.061	0.259	0.160	**0.002**	0.061	0.259	0.160	**0.002**	0.061	0.258
Age		-0.003	**0.041**	-0.007	0.000	-0.003	**0.040**	-0.007	0.000	-0.003	**0.040**	-0.007	0.000
Discharge location													
Residential Care Facility	Home	0.013	0.842	-0.118	0.145	0.013	0.841	-0.118	0.145				
Visit type													
Inpatient	ED to inpatient	0.000	0.995	-0.111	0.112								
Length of stay		0.002	**0.046**	0.000	0.005	0.002	**0.046**	0.000	0.005	0.002	**0.046**	0.000	0.005
Mean number of medications		0.038	**<0.0001**	0.018	0.057	0.038	**<0.0001**	0.018	0.057	0.038	**<0.0001**	0.018	0.057
R-square		0.246				0.246				0.246			
Adjusted R-square		0.233				0.235				0.237			
n		406				406				406			

Supplementary Table 7. Stepwise backward selection multiple regression models for the changes in sedative load for patients admitted to acute mental health units

		Model 1				Model 2				Model 3			
Predictor variables	Reference category	coefficient	p-value	95% confident interval		coefficient	p-value	95% confident interval		coefficient	p-value	95% confident interval	
				lower bound	higher bound			lower bound	higher bound			lower bound	higher bound
Constant		1.058	**<0.0001**	0.655	1.461	1.060	**<0.0001**	0.659	1.461	1.027	**<0.0001**	0.654	1.399
Pre-admission sedative load		-0.580	**<0.0001**	-0.674	-0.486	-0.580	**<0.0001**	-0.674	-0.487	-0.580	**<0.0001**	-0.674	-0.487
Gender													
Male	Female	0.367	**0.001**	0.145	0.590	0.368	**0.001**	0.146	0.590	0.370	**0.001**	0.148	0.592
Age		-0.005	0.149	-0.013	0.002	-0.006	0.137	-0.013	0.002	-0.006	0.126	-0.013	0.002
Discharge location													
Residential Care Facility	Home	-0.015	0.922	-0.317	0.286								
Visit type													
Inpatient	ED to inpatient	-0.056	0.664	-0.310	0.198	-0.057	0.657	-0.310	0.196				
Length of stay		0.003	0.215	-0.002	0.009	0.003	0.212	-0.002	0.009	0.003	0.213	-0.002	0.009
Mean number of medications		0.123	**<0.0001**	0.078	0.167	0.123	**<0.0001**	0.079	0.167	0.122	**<0.0001**	0.078	0.166
R-square		0.293				0.293				0.293			
Adjusted R-square		0.281				0.283				0.284			
n		406				406				406			

Supplementary Table 7. Continued

		Model 4				Model 5			
Predictor variables	Reference category	coefficient	p-value	95% confident interval		coefficient	p-value	95% confident interval	
				lower bound	higher bound			lower bound	higher bound
Constant		1.024	**<0.0001**	0.651	1.397	0.855	**<0.0001**	0.597	1.114
Pre-admission sedative load		-0.582	**<0.0001**	-0.675	-0.488	-0.576	**<0.0001**	-0.669	-0.483
Gender									
Male	Female	0.374	**0.001**	0.152	0.595	0.386	**0.001**	0.165	0.607
Age		-0.004	0.218	-0.011	0.003				
Discharge location									
Residential Care Facility	Home								
Visit type									
Inpatient	ED to inpatient								
Length of stay									
Mean number of medications		0.124	**<0.0001**	0.080	0.168	0.112	**<0.0001**	0.073	0.152
R-square		0.290				0.287			
Adjusted R-square		0.283				0.282			
n		406				406			