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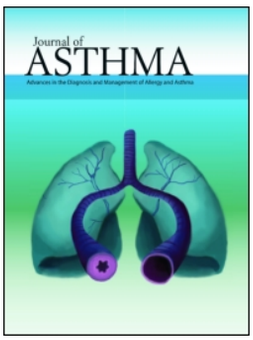
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Pharmacological interventions for the treatment of psychological distress in patients with asthma: a systematic review and meta-analysis

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ABSTRACT

OBJECTIVE: To evaluate the effectiveness and safety of pharmacological interventions for the treatment of psychological distress in people with asthma. **DATA SOURCES:** Electronic searches were performed in Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, PubMed/Medline, Embase, PsycInfo, Health Technology Assessment Database and Web of Science (inception to April 2019). **STUDY SELECTIONS:** Included studies were randomised controlled trials (RCT) or controlled clinical trials investigating the effect of pharmacological interventions for psychological distress in people with asthma. Records were screened and data extracted by two independent authors into standardised pilot-tested extraction templates. Data was analysed according to standard Cochrane methodology and entered into Review Manager Software version 5.3. **RESULTS:** From 5,689 studies, six RCTs (n = 215) met inclusion criteria and were included in the systematic review, of which four studies were

included in the meta-analysis. A meta-analysis of four studies (n = 158) indicated no evidence of an effect for selective serotonin reuptake inhibitors (Citalopram or Escitalopram) on reduction of psychological distress in adult patients with asthma. Similarly, antiepileptic medication (Levetiracetam) was no better than placebo in the treatment of psychological distress in people with asthma. Adverse events were poorly reported across all studies but were slightly increased among intervention participants compared to control participants. **CONCLUSIONS:** There was great heterogeneity between studies and overall poor methodological quality providing insufficient evidence to make recommendations for or against the use of pharmacotherapy in asthma patients with psychological distress. Further confirmatory trials are warranted to make recommendations for clinical practice.

KEY WORDS: asthma, psychological stress, depression, anxiety, systematic review and meta-analysis

SYSTEMATIC REVIEW REGISTRATION NUMBER: CRD42018118260

INTRODUCTION

Epidemiological studies identify that children and adults with asthma are more likely to experience psychological co-morbidity, particularly anxiety disorders (11-37%) and depressive disorders (11-18%), compared to the general population (1-8). Despite an association between psychological distress and future adverse prognosis among this cohort, the inadequate recognition and treatment of these symptoms is common in clinical practice (3, 9). Psychological problems in asthma patients is associated with poor health outcomes, including increased asthma symptom severity, impaired asthma control, over-use of rescue medications and reduced quality of life (10, 11). These factors result in increased patient, health service and societal costs (12, 13). As such, effective management strategies for psychological distress in asthma patients are required.

The multi-factorial nature of asthma and psychological symptoms has made the identification of underlying mechanisms difficult (3, 14). Literature suggests a bi-directionality between psychological distress and asthma, whereby asthma may precede the onset of psychological distress, but also the presence of psychological distress may contribute to and/or cause asthma (15, 16). Psychological distress may affect asthma severity in a number of ways, such as altering the symptom perceptions of an individual with asthma or by influencing patient health behaviours (11). Furthermore, common medications used to treat asthma symptoms are associated with increased heart rate and peripheral tremor, which may contribute to or exacerbate anxiety states (14). Therefore, management strategies focussing solely on the physiological factors of asthma without addressing the psychological factors are likely to result in sub-optimal treatment outcomes (17).

Several pharmacotherapies are available to manage psychological distress in the general population. Selective serotonin re-uptake inhibitors (SSRI) are considered first-line therapy for the management of anxiety and depression due to proven efficacy and a relatively favourable adverse effect profile (18, 19). Current evidence to support pharmacological interventions for psychological distress in people with asthma is conflicting. Limited data suggests that antidepressant medications may improve psychological distress in patients with asthma (20, 21). Antidepressants may provide therapeutic effects other than the regulation of monoamines by altering the inflammatory mechanisms involved in asthma, such as by influencing the hypothalamic-pituitary-adrenal axis and suppressing key pro-inflammatory mediators and reactive oxygen species (ROS) (21-23). Depression in itself is strongly associated with non-adherence to treatment for many health conditions, therefore, antidepressants may also help improve asthma-related outcomes by promoting more effective self-management (11). However, clinicians currently are unlikely to prescribe these medications to asthma patients, particularly adolescents and children, unless absolutely necessary, given concerns regarding side-effects (24). It remains uncertain whether the treatment of psychological distress using pharmacological interventions results in improved asthma outcomes.

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There are currently no systematic reviews or meta-analyses that evaluate the efficacy and safety of pharmacological treatments for psychological distress, specifically in people with asthma. Moreover, international asthma management guidelines provide no clear direction, citing inconsistent evidence (25, 26). This systematic review and meta-analysis aims to address this gap and investigate the efficacy and safety of pharmacological interventions for the management of psychological distress in people with asthma. Findings from this review may be useful to inform recommendations for the clinical practice, policy and future research directions in asthma management.

METHODS

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria (27). The pre-specified protocol was registered prospectively on PROSPERO (Registration ID: CRD42018118260).

Search strategies

Electronic searching of the Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL), PubMed/MEDLINE, Embase, PsycInfo, Health Technology Assessment Database and Web of Science (Science and Social Science Citation Index) was conducted from database inception until April 2019. The search strategy was developed in consultation with an academic librarian and included 'asthma' and keywords/index terms 'psychological distress', 'anxiety', 'depression' and 'pharmacotherapy'. An example search strategy for MEDLINE is provided in Supplementary Table S1. Grey literature was searched through the World Health Organisation International Clinical Trials Registry Platform online and reference lists of included studies. To minimise publication bias, key authors and researchers in the field were contacted to identify further published and unpublished studies. No additional restrictions were applied for language, publication date or year. Two independent review authors (LT, KS) screened titles and abstracts, followed by full text articles to identify studies for inclusion. Disagreements were resolved through discussion and consensus with consultation of a third author (ZK) if necessary.

Eligibility criteria

Randomised controlled trials (RCT) and controlled clinical trials (CCT) were eligible for inclusion where participants (all ages) had a primary diagnosis of asthma and psychological distress by self-report or diagnosed using a validated instrument. Contrary to previous studies that failed to distinguish between psychological diagnosis (i.e. depressive disorders) and psychological symptoms (i.e. non-specific depressive symptoms), psychological distress was defined as a self-rated condition measured by psychological symptoms, such as non-specific symptoms of anxiety, stress and/or depression. Interventions included the use of any pharmacological intervention for the treatment of psychological distress in people with asthma within any healthcare setting. Co-interventions were also considered, providing the intervention effect could be isolated. Acceptable comparators were placebo, usual practice or no intervention control.

Outcomes

The primary outcome measure was the reduction in psychological distress symptoms measured by psychometrically-validated self-report measures. Secondary outcomes included asthma control, exercise tolerance, dyspnoea, corticosteroid use, quality of life, hospital utilisation, lung function and adverse events.

Data extraction and quality assessment

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Data for included studies was extracted into a standardised pilot-tested template by two independent review authors (LT, KS), with results compared to reach consensus (Supplementary Appendix S1). This included study and participant characteristics, review outcomes and methodological quality. Disagreements were resolved through discussion and consensus as well as consultation with a third party (KVC). Where data were missing, study authors were contacted to retrieve further information. Risk of bias for included studies was assessed by two independent review authors (LT, KS) in accordance with the Cochrane Handbook of Systematic Reviews guidelines (28). These assessments were undertaken using a domain-based evaluation with each domain classified as a low, high or unclear risk of bias. Reliability of the body of evidence was assessed using the GRADE (Grading of Recommendations Assessment, Develop and Evaluation) system to rate quality of evidence for each outcome (29). This utilised explicit criteria against study design, risk of bias, imprecision, inconsistency, indirectness and magnitude of effect. Data was summarised and presented in a table constructed with GRADEpro version 3.6.

Statistical analysis

The meta-analysis was performed using RevMan (Review Manager, version 5.3, 2014, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Where appropriate, continuous or dichotomous data were pooled using standard statistical techniques with a random effect model (as heterogeneity between studies was expected). Continuous data was reported as a weighted mean difference or standardised mean difference with a 95% confidence interval, while dichotomous variables were presented as relative risk with 95% confidence interval. The Chi^2 and I^2 statistics were used to quantify inconsistency across studies. Data for efficacy was analysed using RevMan software. Where statistics essential for analysis were missing and could not be calculated from other data, attempts were made to contact study authors. Loss of participants that occurred prior to randomisation was assumed to have no effect on eventual study outcomes. Pre-defined sub-group analyses and sensitivity analyses would have been performed if there had been 10 or more studies.

RESULTS

A total of 5,689 studies were identified from the initial search resulting in 32 potentially relevant records requiring full text review (Figure 1). Six studies (n = 215) met all inclusion criteria. All six studies were included in the systematic review (30-34)(Heaney, unpublished, 2018) and four were included in the meta-analysis (30-32)(Heaney, unpublished, 2018). One study was an unpublished trial with the data provided by study authors (Heaney, unpublished, 2018). Four studies evaluated a SSRI compared to placebo (n = 158) (30-32)(Heaney, unpublished, 2018), a single study evaluated the use of an anti-epileptic medication compared to placebo (n = 24) (34), and another study investigated the use of an atypical antidepressant in conjunction with conventional therapy compared with conventional inhaled asthma therapy alone (n = 33) (33). All patients had a primary diagnosis of asthma, where two studies evaluated patients with moderate to severe asthma and the remaining studies did not specify asthma severity (32)(Heaney, unpublished, 2018). Baseline major depressive disorder was diagnosed in asthma patients in three studies by the Diagnostic and Statistical Manual of Mental Disorders (4^{th} edition) and/or clinical diagnosis by a psychiatrist (30-32). The average baseline depressive symptoms across five studies ranged from 11.6 ± 6.4 to 32.04 ± 4.2 using the Hamilton Depression Rating Scale (HDRS) (30-32, 34), and in one study (Heaney, unpublished, 2018), average baseline symptoms of anxiety was 13.05 ± 3.1 measured using The Hospital Anxiety and Depression Scale (HADS-anxiety). In another study, the mean stress symptoms using the Perceived Stress Scale (PSS) across both treatment groups was 22.6 ± 10.9 (33).

All included studies were double-blind RCTs. The mean age of participants was 36 to 45 years (range: 18-75 years), with a higher ratio of female to male participants (1.4:1) across all studies. The

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studies were generally short term, with an average treatment length of 9.5 weeks (range: 1-12 weeks). Characteristics of the included studies are presented in Table 1.

Risk of bias and quality assessment

Risk of bias assessments for the six included studies are summarised in Figure 2 and presented for individual studies in Figure 3. Overall, risk of bias for included studies across the seven domains was deemed 'unclear'. Whilst all the studies were RCTs, four studies did not provide detailed information about their randomisation method (30, 33, 34)(Heaney, unpublished, 2018). Allocation concealment was not clearly described in five of the studies (30, 31, 33, 34)(Heaney, unpublished, 2018). One study was at high risk of bias for allocation concealment, using an unblinded statistician to determine participant allocation (32). In five studies, placebo controls were identical in appearance to the intervention drug and, therefore, blinding of participants was deemed as adequate (30-32, 34)(Heaney, unpublished, 2018). All six studies were reported as double-blind trials, however exactly who was blinded (e.g. study investigators, data collectors, statisticians, etc.) was unable to be determined in five studies and thus, this was judged as unclear (30, 31, 33, 34)(Heaney, unpublished, 2018). Incomplete outcome data were addressed adequately in one study (31), unclear in two studies (32, 34), and inadequate in three studies (30, 33)(Heaney, unpublished, 2018). Attrition rates ranged from 0.04% to 52%. Two studies had attrition of more than 40%, and did not conduct intention-to-treat analysis (31, 32). Overall, missing data was poorly handled among the studies. Only one study provided an adequate description of comparison between dropouts versus completers (32). Five of six studies provided insufficient data to determine if there was selective reporting of outcomes (30-32). All studies were conducted on small sized-samples (n = 13-77). Despite small sample sizes, none of the studies reported power and sample size calculations. GRADE assessment further identified that due to an overall unclear risk of bias and imprecision, the quality of evidence presented in this review must be regarded as low (Supplementary Table S3).

Primary outcomes

Psychological distress

Psychological distress was reported as a primary outcome in six studies (n = 215). These studies were divided by drug type for the purpose of analysis.

Of the six included studies, five reported on change in psychological distress related to antidepressant drug therapy. Three studies used Escitalopram (SSRI), two used Citalopram (SSRI) and one used Tianeptine (atypical antidepressant). In one study, it was not possible to obtain data on depressive symptom score change and this study was therefore excluded from the analysis (33). Four studies (n =158) examined the use of SSRI (Citalopram or Escitalopram) on depressive symptoms using the HDRS and their outcome data were pooled in a meta-analysis (Figure 4) (30-32)(Heaney, unpublished, 2018). Statistical significance was not demonstrated for depressive symptoms compared with placebo after 12 weeks (Z = 1.43, P = 0.15, SMD = -0.33, 95% CI: -0.78 to 0.12). There was moderate heterogeneity between studies (I^2 = 42%), likely secondary to different drug dosages, follow-up time, sample size and characteristics of populations, such as baseline psychological stress.

One study examined the effect of Levetiracetam (antiepileptic medication) compared to placebo on depressive symptoms using the HDRS in 24 patients with asthma, demonstrating no effect after 8 weeks (34).

Secondary outcomes

Asthma control

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Four studies reported on asthma control using one of two reporting tools; three studies used the Asthma Control Score (ACS) and one study used the Asthma Control Questionnaire (ACQ) (30-32)(Heaney, unpublished, 2018). No significant difference between pharmacotherapy and asthma control was noted on meta-analysis (Z = 0.61, *P* = 0.54, SMD = -0.10, 95% CI = -0.43 to 0.23) (Figure 5).

Corticosteroid use

Four studies assessed differences between groups on corticosteroid use in comparison to placebo (30-32)(Heaney, unpublished, 2018), however, there was insufficient data provided to conduct a meta-analysis. None of the four studies reported a significant change in corticosteroid use between groups at final follow-up.

Quality of life

Two studies measured quality of life using the Asthma Quality of Life Questionnaire (AQLQ) (30)(Heaney, unpublished, 2018). A meta-analysis showed no significant between-group differences at post-assessment (overall Z effect = 1.74, *P* = 0.08, MD 0.49, 95% CI: -0.06 to 1.05, *P* = 0.08; *n* = 95) (Supplementary Figure S1).

Hospital utilisation

One study measured hospital utilisation by number of hospital admissions (31). Three serious adverse events were reported requiring hospitalisation. In the control group, one participant was admitted for asthma exacerbation induced by a viral respiratory infection, however, still completed the study. In the treatment group, two hospitalisations resulted from asthma exacerbations where one patient was discontinued from the study, and the other participant was able to complete the study. These hospitalisations were deemed as non-study related by the author.

Lung function

Lung function was reported in two of the included studies, with one using Forced Expiratory Volume in One Second (FEV1) and Forced Vital Capacity (FVC) (33), while another study used Peak Expiratory Flow Rate (PEFR) (Heaney, unpublished, 2018). Due to differences in reporting outcomes across individual studies, meta-analysis was not possible. One study comparing the effect of Tianeptine with conventional therapy showed a significant difference in favor of the intervention group at final follow-up (overall Z effect = 2.16, *P* = 0.03) (33). Another study evaluated lung function with no statistically significant difference or clinical significance between groups for change in FEV1 (Treatment: 80.8% ± 11.5 vs placebo: 63.4% ± 17.5, *P* = 0.07) or FVC (Treatment: 2.7L ± 0.8, vs placebo: 3.0L ± 0.4, *P* = 0.9) at 12 weeks (Heaney, unpublished, 2018).

Adverse events

Adverse events were reported in five studies (Table S4) (30-32, 34)(Heaney, unpublished, 2018). Three studies reported adverse events related to antidepressant therapy which included insomnia, sedation, headache, dry mouth, sexual dysfunction, gastrointestinal symptoms, nausea, decreased appetite, dizziness, respiratory infection and asthma exacerbation (30, 31, 34). One study, comparing Escitalopram (SSRI) with placebo, reported three adverse events where two participants in the intervention group experienced severe asthma attacks and one participant in the control group had a viral respiratory infection (31). Another study using Escitalopram reported a non-significant difference in adverse events between groups using the PRD-III Somatic Symptom scale (31). The same study provided participant-reported data for adverse events, with the most common symptoms

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being insomnia (treatment = 50%, control = 52%), sedation (treatment = 33%, control = 56%) and headache (treatment = 50%, control = 16%). The increased placebo-response was attributed by the authors to the study environment and non-specific treatment effect. One study using Citalopram (SSRI) reported no change in adverse events in either group at final follow-up (Heaney, unpublished, 2018). In a single study where participants received Escitalopram (SSRI) or placebo, the overall adverse effect profile was similar in both treatment arms ($P = 0.98$) (32). The authors reported on adverse events as a general outcome and failed to specify the type of adverse events in each treatment arm. One study reported on adverse events related to an anti-epileptic medication, Levetiracetam, which included diarrhoea, psychomotor retardation, fatigue, headache and agitation in the treatment group ($n = 2$), and anxiety in the placebo group ($n = 1$) (34). Overall, a slightly higher number of adverse events occurred in subjects who received pharmacotherapy. Due to heterogeneity in reporting outcomes across studies, meta-analysis was not possible. In the context of these findings, the included trials may have lacked sufficient statistical power to detect differences in adverse events due to the considerably small number of participants.

Other secondary outcomes

No studies assessed outcomes related to exercise tolerance or dyspnoea.

Subgroup and sensitivity analyses

Due to the small number of trials and lack of appropriate data in this review, subgroup and sensitivity analyses were not conducted.

DISCUSSION

This systematic review and meta-analysis is the first to review the effects of pharmacological interventions for psychological distress in asthma patients. Only six RCTs including 215 participants met the inclusion criteria. The main results identify a paucity of evidence for the role of pharmacotherapy in managing psychological distress in asthma patients. These results highlight that there is a pressing need for further research to demonstrate the efficacy and safety of pharmacotherapy for psychological distress in individuals with asthma.

Between-group results for the studies using an antidepressant treatment arm were mixed. The only statistically significant finding was from a study, whereby Tianeptine in conjunction with conventional therapy, was superior to conventional therapy alone in respect to psychological distress outcome in the short term (8 weeks) (33). This finding was similar to a previous observational study demonstrating an improvement of clinical symptoms in patients with asthma prescribed Tianeptine (35). In contrast to SSRIs which work by inhibiting serotonin uptake, Tianeptine improves mood function by enhancing the level of serotonin re-uptake and thus decreasing plasma levels of serotonin, which are elevated in symptomatic asthma patients (36). These findings are encouraging and suggest the need for further research to confirm drug efficacy with more established medications. Only one of the secondary outcome measures, lung function, showed a statistically significant effect in one study (33). Although the six trials were RCTs, the methodological quality was generally poor. The majority of trials did not report sufficient information about randomisation, blinding or allocation concealment, limiting interpretation of results. Furthermore, most of the studies included in this review were conducted under the same research group (30-32, 34). This may carry a risk of systematic bias and should be kept in mind when interpreting results. Therefore, these findings from our review may reflect the paucity of evidence and sub-optimal methodological quality, rather than a true indicator of intervention efficacy.

Several other systematic reviews have reported on the effectiveness of pharmacological treatment in people with psychological disorders and physical illnesses, such as diabetes and stroke (37, 38).

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Notably, the authors report that few trials have been conducted on the treatment of psychological distress in people with asthma. Results from our review and others (39, 40), agree with the lack of information about effective treatment strategies for psychological distress in asthma patients.

Antidepressants may demonstrate clinically relevant anti-inflammatory properties that reduce neuroinflammation involved in psychological disorders but also for inflammatory diseases, such as asthma (41, 42). Animal studies have demonstrated that antidepressants decrease the production of inflammatory mediators, such as TNF-a, and suppress the ROS pathway involved in the inflammatory pathogenesis of asthma (42, 43). This raises a potential benefit for the anti-inflammatory role of antidepressants in asthma, although further studies are needed to establish the influence of these drugs in human participants. However, there are concerns that SSRIs may result in bronchoconstriction and pulmonary vasoconstriction, potentially limiting the clinical usefulness in patients with asthma (44). The inadequate reporting of adverse events in some studies in our review is particularly concerning and may result in the provision of misinformation for clinicians, researchers and policymakers.

Adequately-powered and appropriately-designed studies are required. These should include: clinically-appropriate intervention durations across multiple categories of pharmacotherapy that are tailored where appropriate to both paediatric and adult populations, reporting data on outcomes as specified in the protocol of this review and assessing at long-term follow-up (12 months). Research is also needed to clarify the physiological mechanisms and causal relationships between psychological distress and asthma pathogenesis. This is required to evaluate if improved disease management, which reduces asthma exacerbations, may be sufficient to significantly alleviate psychological distress. The early diagnosis of psychiatric disorders and access to effective treatment strategies are needed for people with asthma, as psychiatric co-morbidity is often under-diagnosed resulting in poor disease management (40).

There are several limitations to this review. Firstly, the quality of studies was sub-optimal due to incomplete/missing data, inadequate reporting of methodology and small sample sizes. In addition, high attrition rates were inadequately accounted for by individual study authors. However, methodological techniques used to synthesise evidence for this review, including the use of a prospectively registered protocol based on Cochrane methodology, does attempt to quantify and mitigate these concerns (28). Secondly, all included trials had a short follow-up period ranging from 1 week to 12 weeks, were limited to a few classes of pharmacotherapy and had substantial heterogeneity. Thirdly, participants across included studies were predominantly female. Although asthma prevalence is higher in women than men, evidence that men and women appear to react differently to psychological distress further limits external validity of this review (45, 46). Finally, in view of how many children with asthma report psychosocial comorbidity including severe symptoms of anxiety, there were no paediatric studies in our review (47, 48). These factors affect the generalisability of findings across varying ages.

CONCLUSION

Due to a paucity of evidence and sub-optimal methodological quality identified across the six included studies, definitive conclusions could not be drawn from this review. Available data does not show any evidence of effect to support pharmacological interventions for the treatment of psychological distress among people with asthma. This review has identified a compelling need for appropriately-powered, robust and methodologically-rigorous trials to underpin recommendations for clinical practice and that pharmacotherapy may not provide the additional level of efficacy many believe.

Acknowledgements

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Authors' Contributions

LT screened, extracted and analysed the data and drafted the manuscript. KS assisted with screening and extraction. KVC assisted with protocol development, interpretation of data and manuscript drafting. KS, ZK, HS, AT, NS and AE assisted with revision of the manuscript. All authors read and approved the final manuscript.

Declarations of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Table 1 Characteristics of included studies

Study	Study design	Population (I/C)	Participant characteristics	Intervention description	Control description	Follow-up	Outcome measures	Main findings
Brown (2005), USA (30)	Double blind, placebo-controlled RCT	43 (18/25)	Aged 18-65 years old with asthma and MDD *Mean age (SD):* 41.7 (10.5) *Gender*: 9 male, 34 female	Citalopram (20-60mg/d)	Placebo	12 weeks	$HRSD_{17}$*, $IDS\text{-}SR_{30}$, ACQ, corticosteroid use,	No significant difference between citalopram

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							adverse events	and placebo group was found for any of the outcome measures.
Brown (2007), USA (34)	Double blind, placebo-controlled RCT	24 (12/12)	Aged 20-62 years old with asthma *Mean age (SD)*: 46.5 (11.1) *Gender*: 7 male, 17 female	Levetiracetam (1500mg/d)	Placebo	1 week	HRSD$_{17}$, adverse events	No significant between-group changes from baseline to exit were found in HRSD scores.
Brown (2012), USA (31)	Double blind, placebo-controlled RCT	25 (13/12)	Aged 18-75 years old with asthma and MDD *Mean age (SD):* 45.6 (11.6) *Gender:* 12 male, 13 female	Escitalopram (10-20mg/d)	Placebo	12 weeks	HAM-D*, IDS-SR, ACQ, oral corticosteroid use	No significant improvement in depressive

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							, adverse events	outcomes was observed between groups.
Alsamarai (2014), Saudi Arabia (33)	Double blind RCT	33 (15/18)	Aged 18-70 years with asthma *Mean age (SD)*: 36.1 (13.7) *Gender*: 17 male, 16 female	Tianeptine (12.5mg three times daily) + conventional treatment	Conventional treatment (Symbicort and Salbutamol; dose unknown)	8 weeks	PSS$_{14}$, PEFR	A significant improvement was found in PSS$_{14}$ from baseline to follow-up between groups. A statistically significant improvement was also

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								noted in PEFR between intervention and control groups at final follow-up.
Brown (2018), USA (32)	Double blind, placebo-controlled RCT	77 (38/39)	Aged 18-70 years old with asthma and MDD *Mean age (SD):* 45.6 (11.5) *Gender*: 39 male, 38 female	Escitalopram (10-20mg/d)	Placebo	12 weeks	$HRSD_{17}$*, IDS-SQ, ACQ, corticosteroid use, adverse events	No significant difference was found in depressive outcomes scores between intervention and control at 12 weeks. In the hig

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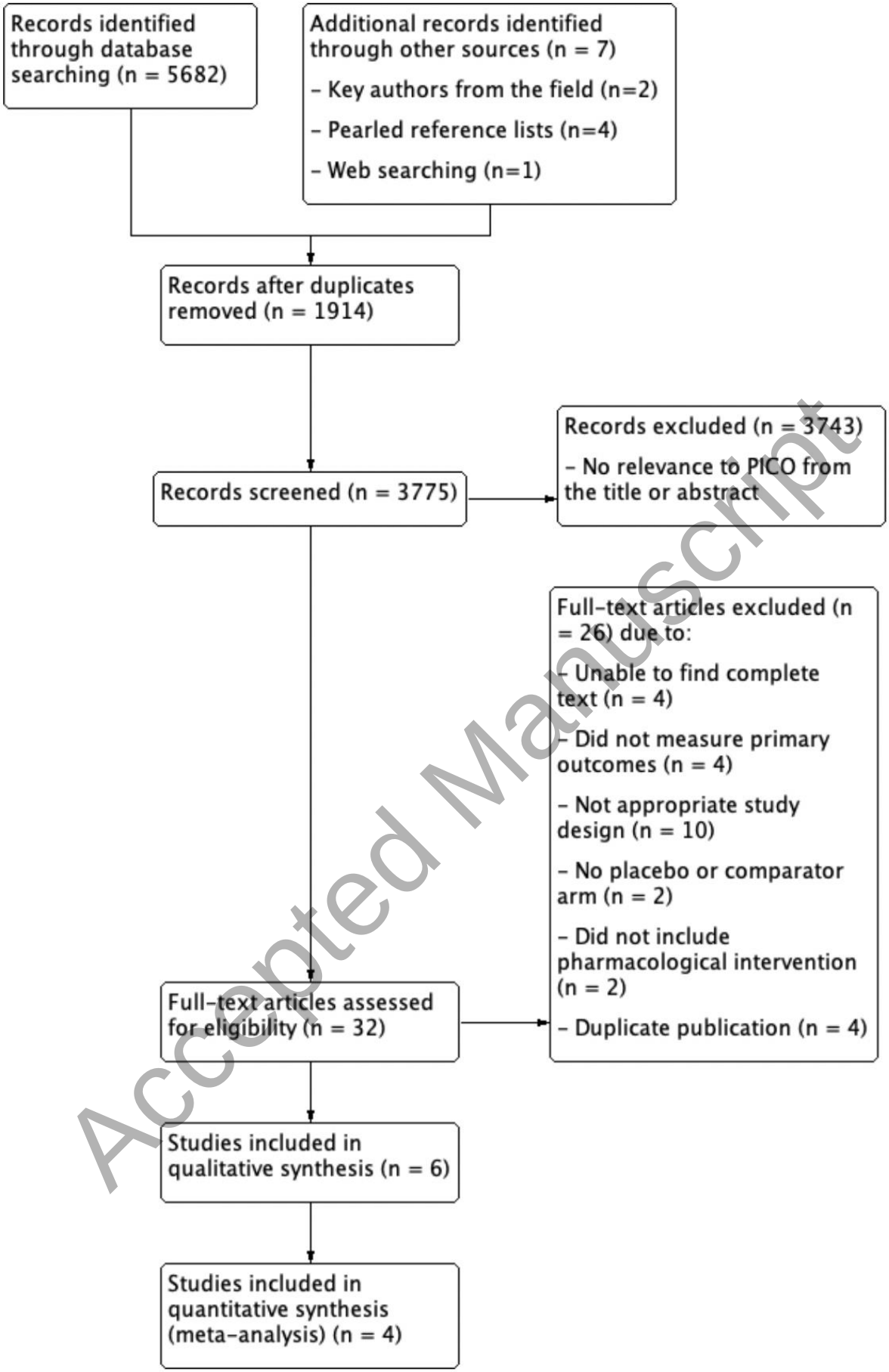
								her severity group, an overall significant difference was found for ACQ and corticosteroid use.
Heaney (unpublished, 2018), UK	Double blind, placebo-controlled RCT	13 (8/5)	Aged 18-65 years old with refractory asthma and depressive symptoms (HADS ≥11 and HDRS ≥ 17) *Mean age (SD):* 45.10 (8.1) years *Gender*: 3 male, 10 female	Citalopram (20-40 mg/d)	Placebo	12 weeks	ACS, HDRS, AQLQ, HADS-anxiety, lung function, corticosteroid use, adverse events	No significant difference was found between treatment and control group for any outcome measure. Statisti

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								call y sig nifi can t im pro ve me nt wit hin the trea tme nt gro up wa s not ed in HA DS - anx iety , HA DS - dep res sio n and HD RS sco res

Key: *HRSD is also known as the HAM-D and HDRS; ACS = Asthma Control Score; ACQ = Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; HADS = Hospital Anxiety and Depression Scale; HAM-D = Hamilton Rating Scale for Depression; $HRSD_{17}$ = Hamilton Rating Scale for Depression; HDRS = Hamilton Depression Rating Scale; IDS-SR = Inventory of Depressive Symptomatology Self Report; MDD = Major Depressive Disorder; PEFR = Peak Expiratory Flow Rate; PSS_{14} = Perceived Stress Scale; RCT, randomised controlled trial; YMRS = Young mania rating scale

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Figure 1 PRISMA flowchart depicting the study selection procedure

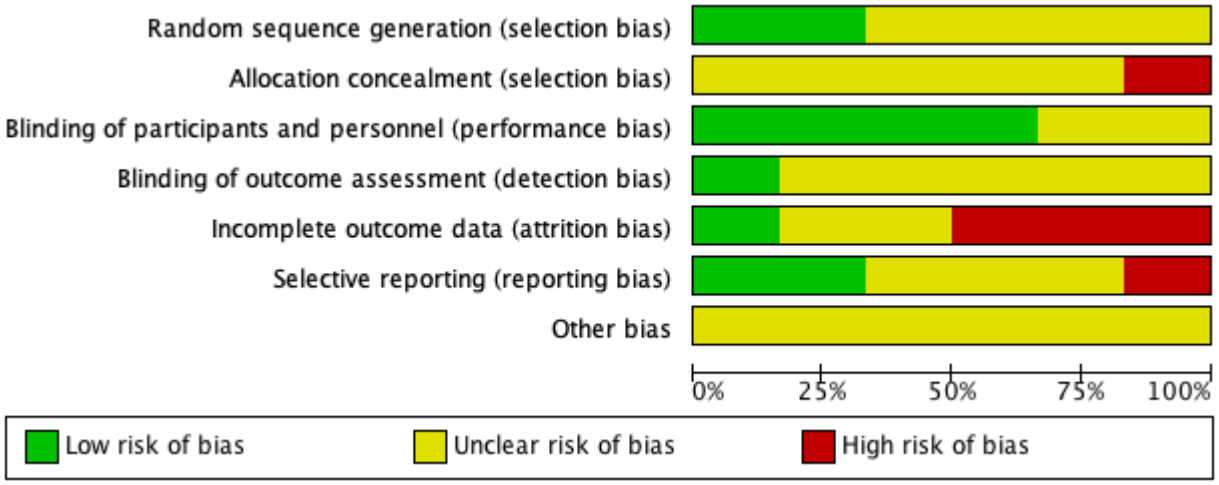


Figure 2 Methodological quality summary: review authors' judgements about each methodological quality item presented as percentage across all studies

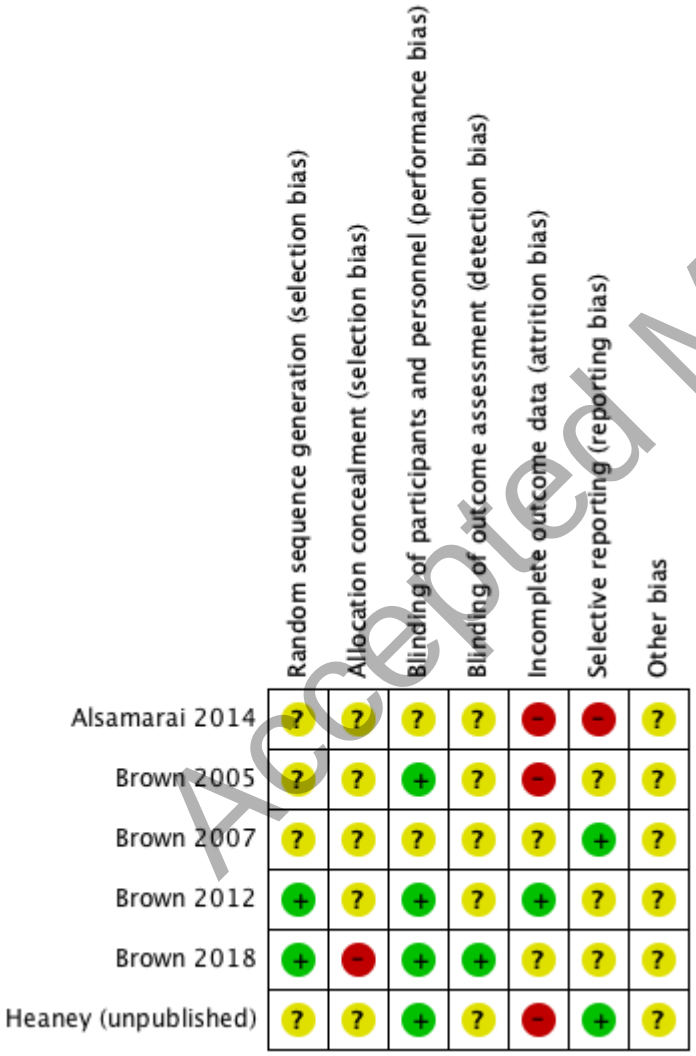


Figure 3 Methodological quality summary: review authors' judgements about each methodological quality item for each included study. Green circles with "+" sign indicate low risk, red circles with "–" sign indicate high risk, and yellow circles indicate unclear risk.

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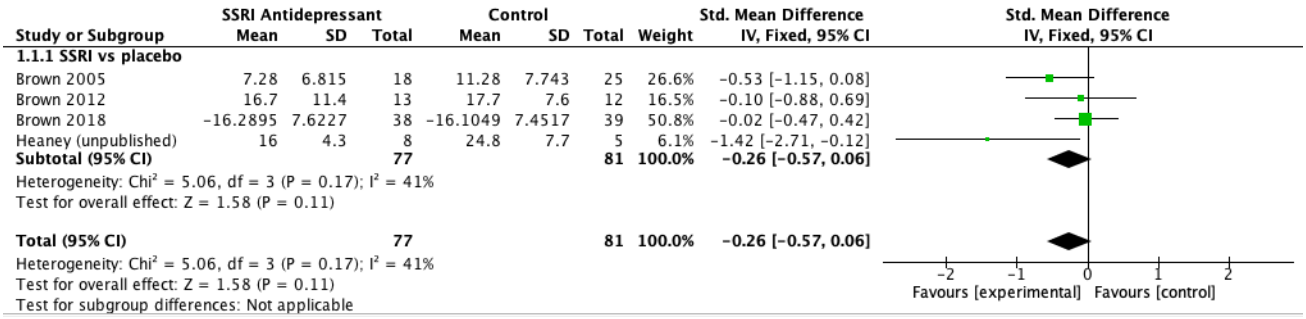


Figure 4 Forest plot of randomised controlled trials of selective serotonin reuptake inhibitors (SSRIs) vs placebo: Depression symptom rating scale score

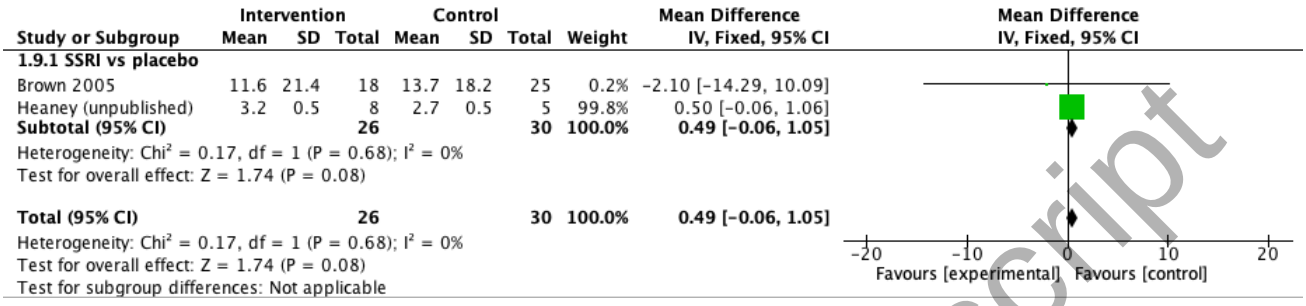


Figure 5 Forest plot of randomised controlled trials of selective serotonin reuptake inhibitors (SSRIs) vs placebo: Asthma control

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