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Treatment of Depression in Schizophrenia: A Systematic Review and Meta-Analysis

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Summary

Background

Depression in schizophrenia predicts poor outcomes, including suicide, yet the effectiveness of antidepressants for its treatment remains uncertain. The aim of this study was to synthesise the evidence of the effectiveness of antidepressants for the treatment of depression in schizophrenia.

Methods

Following Prisma guidelines, multiple databases were searched for trials investigating the effectiveness of antidepressant treatment for people with schizophrenia and depression. Inclusion criteria included participants aged over 18 years with schizophrenia or related psychosis with a depressive episode. Papers were quality assessed using the Cochrane risk bias tool. Data was extracted with meta-analyses performed for risk difference and standardised mean difference of all antidepressants, antidepressant class and individual antidepressant where sufficient studies allowed.

Results

26 moderate to low quality trials met inclusion criteria. In meta-analysis a significant risk difference was found in favour of antidepressant treatment, with a number needed to treat of 5 (95% CI 4-9). Studies using tools specifically designed to assess depression in schizophrenia showed a larger effect size. However, after sensitivity analysis standardised mean difference of all antidepressants did not show a statistically significant improvement in depression score at end-point, neither did any individual antidepressant class.

Conclusion

Antidepressants may be effective for the treatment of depression in schizophrenia, however the evidence is mixed and conclusions must be qualified by the small number of low or moderate quality studies. Further sufficiently powered, high quality studies are needed.

1. Introduction

Depression is now widely recognised as a common, discrete syndrome within schizophrenia, with prevalence of over 50% (1, 2). Depression in schizophrenia is associated with more frequent psychotic episodes (3), increased duration of illness (4), substance abuse (5), poor quality of life and suicide (6, 7). Depression in schizophrenia also has impact on systems outside of the individual and health care burden with greater use of the mental health services and criminal justice system (1). Despite the clear need for effective management of depression in schizophrenia, there is a lack of specific guidance. The British Association for Psychopharmacology guidelines on the treatment of schizophrenia conclude that “*the potential benefit of adjunctive antidepressants for comorbid depressive symptoms has not received the attention it might seem to warrant, given how often depression occurs*”(8). The National Institute for Health and Care Excellence (NICE) guidelines for the treatment schizophrenia and first-episode psychosis emphasise that it is important to “*routinely monitor for other coexisting conditions, including depression.... particularly in the early phases*”, but make no specific recommendation for the treatment of depression occurring in schizophrenia (9). Clinicians presently are left to personal experience in treatment decisions, and thus prescribing varies considerably (10).

A 2002 meta-analysis identified 11 appropriate trials in this field; these studies had multiple methodological flaws including small sample size, absent reporting of allocation concealment and few using an intention to treat analysis(4). The majority of included studies assessed effect of tricyclic antidepressants, which in the modern age would not be first line therapy for depression. This review concluded that there may be some benefit of co-prescribing antidepressants in schizophrenia, however a fairer conclusion would be evidence at the time was “unproven”.

Additional medication, and subsequent polypharmacy, is not without risk in severe mental illness, where patients already have high side effect burden and poor physical health (11). Concomitant use of antidepressants with antipsychotics potentially leads to cardiac effects, and require additional monitoring including for prolongation of QTc (12). However, Helfer and colleagues recently reported on the safety and efficacy of antidepressants added to antipsychotics in the treatment of schizophrenia. They conclude that this is a low risk combination that may produce

some beneficial effects (13). Their review had a broad focus, including all papers where antidepressants were co-prescribed, and did not specifically aim to investigate the effect of antidepressants for the treatment of comorbid depression in schizophrenia. Thus the benefit of additional antidepressant use for the treatment of depression in schizophrenia still needs a more robust evidence base.

In summary, the current lack of evidence exacerbates the challenge of providing optimal pharmacotherapy for individuals with schizophrenia who are depressed. This systematic review and meta-analysis aimed to synthesise evidence and estimate the aggregate effectiveness of antidepressants for the treatment of depression in people with schizophrenia. We also explore whether any particular antidepressant class or individual antidepressant had stronger evidence of effect.

2. Methods

Search strategy and selection criteria

This meta-analysis adhered to PRISMA guidelines and followed a predetermined published protocol. In this paper, we report results from our primary outcome as included in the published protocol(14): response to antidepressant treatment (responder/non responder) and improvement in depression score using a standardised rating scale.

Inclusion Criteria were as follows:

Participants: Human subjects aged 18 years or older with schizophrenia or related psychosis (e.g. schizoaffective disorder and psychotic disorder not otherwise specified) with a depressive episode as assessed using a standardised rating scale or clinical interview.

Intervention: Antidepressant (any class) versus usual care or placebo.

Types of Outcome: 1) Response to antidepressant therapy using dichotomous outcomes (responder/ non responder). 2) Continuous outcomes, as measured by change on standardised depression rating scales.

Types of Studies: All randomised controlled trials or quasi-experimental studies.

Exclusion criteria were as follows:

Observational or qualitative studies; studies including participants with a primary diagnosis of organic brain disorder or bipolar disorder, on the basis that depression experienced in these disorders would have a very different aetiology and would be managed differently to the focus of this review. Therapeutic agents with only theoretical antidepressant property not approved for the treatment of depression, review articles and studies not published in English were also excluded.

MEDLINE, EMBASE, Psycinfo, CINAHL and the Cochrane Library were searched from inception to the final update in March 2017. Combination of keywords and index terms were used to describe the population, condition and intervention and included: [«Schizophreni*» OR «Schizoaffective»] OR [«Psychosis» OR «Psychoses»] AND [«Depress*» OR «Depressive disorder»] AND [«Antidepressant*» OR «Antidepressive*» OR «Tricyclic*» OR «Serotonin reuptake inhibitor» OR «Monoamine oxidase inhibitors»] (see published protocol). Information regarding ongoing trials was obtained by searching the International Clinical Trials Registry and ClinicalTrials.gov. Key authors were contacted to identify whether any further trials could be identified and seek additional data from studies as required.

Data Analysis

Data was extracted using the Cochrane data collection form to capture: design, inclusion/exclusion criteria, population, details of intervention and control conditions, attrition rates, outcomes and times of measurement, concurrent medications and results. Publications pertaining to the same research group and examining the same antidepressant were checked for data overlap. Two reviewers (AG and RU) independently assessed the methodological quality of each study using the Cochrane risk of bias tool without blinding to authorship or source.

The primary outcomes were 1) Response to antidepressant therapy and 2) Improvement in follow-up depression score. Means and standard deviation of follow-up scores were extracted from reports or by conversion of the standard error. The final assessment of outcomes was used when studies reported multiple follow-up times. To summarise effect of trials, risk difference (RD) was calculated for binary outcomes and standardised mean difference (SMD) for continuous outcomes. A fixed-effects analysis was undertaken in the absence of heterogeneity ($I^2 < 50\%$).

Sub group meta-analyses were also carried out according to a) length of follow up b) antidepressant class and c) individual antidepressant where possible. Individual subgroup analysis were conducted, rather than meta-regression, as these were specific pre identified questions with less than ten identified studies in each group, in keeping with Cochrane guidance (15). As our retrieval of published papers allowed, we also included a sub-analysis on studies using the Calgary Depression Scale for Schizophrenia (CDSS), which is established as having greater specificity for rating depression in schizophrenia (16).

One of the trials evaluated two antidepressants, to avoid counting the same individuals twice, the sample size in the placebo group was halved in both comparisons. Statistical analyses used Revman 5.3.

3. Results

A total of 1416 non-duplicated articles were identified. Following application of inclusion criteria, 26 trials were included in the review (see Figure 1 and supplementary table 1). Of the 26 trials, 4 were identified through citation list inspection of included sources. The main reasons for exclusion of full text articles were publications reviewing existing literature (n39), populations with no depression at baseline, those not investigating schizophrenia or related disorder (n14), and observational trials lacking a control (n20).

Characteristics of Included Studies

Participants of 19 studies included individuals with a core diagnosis of schizophrenia, 1 with a schizoaffective disorder, 6 with mixed schizophrenia and schizoaffective disorder. Most trials used ICD-10(17), DSM II-IV(18) or RDC(19) definitions of schizophrenia. However, 2 studies stated only that a diagnosis of schizophrenia had been made (20, 21) and 2 trials used positive Feighner or Schneiderian symptoms (22, 23).

Outcome measures: 15 studies evaluated depression as their primary outcome. 8 focused on treatment of negative symptoms or cognitive functioning but included depressed subjects and reported depression specific outcome measures.

Depression inclusion criteria varied; 8 studies incorporated a Hamilton Depression

Rating Scale (HAM-D) cut off which ranged from greater than 8 to 18, 5 studies stated participants must have met DSM or RDC diagnoses for a major depressive episode, 3 studies used the Becks Depression Inventory (BDI), 2 used Raskin Depression Scale and 1 study used a Calgary Score for Depression in Schizophrenia (CDSS) with cut off of 5. 1 study stated only that 'clinically significant subsyndromal depressive symptoms' were present (24).

Response: The definition of response from depression varied between studies. We defined our outcome of 'response' directly according to those of the original authors; 2 studies used a 50% or greater reduction in standardised depression measure scores (25, 26) and 6 reported response on a Clinical Global Impression or equivalent scale (22, 23, 27-30).

All studies also reported an evaluation of change in depression score, HAM-D, BDI, and CDSS.

Phase of Illness: 6 studies did not report the phase of psychotic illness. 18 described their participants as having chronic illness and 2 studies included populations with early psychosis (31, 32), however both of these trials contained populations of both first episode and recurrently ill participants.

Duration of follow up: 12 studies were 6 weeks in length and 15 were 8 or more weeks.

Antidepressant: The most frequent antidepressant class examined was selective serotonin reuptake inhibitors (SSRIs) followed by tricyclic antidepressants (TCAs). Placebo was the comparator in all except 2 trials (31, 33) where antipsychotics alone were the control.

See supplementary table 1 for full details.

Quality Assessment

Less than half of studies had a sample size of over 50 participants and only 4 trials indicated an a priori sample size calculation (24, 25, 34, 35). All studies specified eligibility criteria and conducted randomisation. 8 trials gave detail on randomisation procedures and 4 described the method of allocation concealment (34-37). The

primary outcome was explicitly stated prior to research commencing in 13 studies. 3 trials were open-label (31, 33, 37) and 4 trials explicitly detailed blinding of assessors (25, 33, 35, 38). Analysis was carried out on an intention to treat basis in 11 studies. To summarise, 19 out of the 26 included articles would not meet current standards for reporting randomised controlled trials (See supplementary figure 1 for full details).

Quantitative Synthesis

i. Response to antidepressant: Categorical Outcome

Binary data (responder/non responder) at end point follow up was reported by 8 included studies. In meta-analysis of these studies homogeneity was found ($\chi^2 = 7.09$ df=7 p=0.42, n=515). Meta-analysis demonstrated a significant benefit of antidepressants with a small summary risk difference -0.19 (95% CI -0.27 to -0.11), (I^2 1%), and corresponding number needed to treat (NNT) of 5 (95% CI 4 to 9) (see Figure 2).

Subgroup analysis indicated no significant difference between studies that combined schizophrenia and schizoaffective disorder in their population compared to populations with a core diagnosis of schizophrenia (see supplementary figure 2).

ii. Improvement in in follow-up depression score

a. All Antidepressants

Random effects meta-analysis of 17 studies reporting end point depression score showed a significant improvement in favour of treatment; SMD -0.24 (95% CI -0.48 to 0.01). However, within a sensitivity analysis, with removal of one very small study with large effect size (Kasckow 2001) this became non-significant: SMD -0.20 (95% CI -0.40 to 0.02). See supplementary figure 3.

b. Length of Follow up

Subgroup analysis comparing trials with long term (>8 weeks) and short term (<6 weeks) intervention showed this length of treatment did not affect the outcome. See supplementary figure 4.

c. Antidepressant Class

Meta-analysis of 8 studies investigating the efficacy of SSRI on the improvement of depression score using the HAM-D did not reveal a significant difference; SMD -0.11 (95% CI -0.48 to 0.27). See supplementary figure 5. The format and lack of continuous data given by studies investigating TCAs prevented meta-analysis of this class. Analysis of all other antidepressants (e.g. SNRI, receptor blockers) which reported outcome by change in depression score showed no significant improvement; SMD -0.16 (95% CI -0.63 to 0.32). See supplementary figure 6.

d. Individual Antidepressants

Citalopram was the only individual antidepressant with a sufficient number of trials to combine in meta-analysis. All 4 studies (n=324) measured endpoint depressive symptoms using the HAM-D. However there was significant heterogeneity ($\chi^2 = 15.23$ df=3, p=0.002). Thus, although some studies demonstrate a significant difference, a random-effects model showed no significant effect (see Figure 3).

e. Trials Reporting Depression using the Calgary Depression scale for Schizophrenia (CDSS)

Trials reporting results using the CDSS as a continuous outcome (n= 331) demonstrated antidepressant therapy was statistically superior to placebo, with moderate effect; SMD -0.47 (95% CI -0.92 to -0.02). See Figure 4.

Publication Bias

Funnel plot did not reveal any indication of publication bias. Supplementary figure 7.

4. Discussion

This systematic review and meta-analysis of studies produced some evidence in favour of antidepressant treatment for depression in schizophrenia. Response, as defined by authors as a 50% reduction in depression score or clinically 'not depressed', was significantly more likely when this depression was treated with an antidepressant. In studies that reporting endpoint using a measure specifically designed to assess depression in schizophrenia (the CDSS) there was a larger effect size of improvement. This suggests that efficacy for the treatment of depression may be larger than appears using broader assessment tools. Significant improvement was found in depression scores for all antidepressants, however this

result did not survive sensitivity analysis. Building on previous evidence, Whitehead in 2002 reported just one trial investigating an selective serotonin reuptake inhibitor (4), whereas in this present review the class formed the majority of studies. While non-significant summary risk differences were found for selective serotonin reuptake inhibitors as a class, an important contribution may be possible with citalopram; however, with significant heterogeneity and random effects modelling this result was also not statistically significant.

Over and above evidence from Helfer and colleagues (13), who reviewed the impact of antidepressants prescribed for many reasons in schizophrenia, we were able to demonstrate the potential effectiveness of antidepressants when targeting the treatment of depression. However, the evidence is not strong or conclusive; although a major influence for this is size and quality of trials available, other factors may be contributing to the weaker signal of efficacy detected. We have previously investigated the aetiology and phenomenology of depression in schizophrenia; and reported on significant pathways including the increased role of shame, anhedonia and hopelessness (39, 40). It is possible that depression in schizophrenia is qualitatively different to unipolar depression, and more specific tailored treatments are needed. Also, individual SSRI's have differing additional properties, with some suggestion of an anti-inflammatory effect of citalopram which may be pertinent in depression seen in the context of schizophrenia (41). Further studies should explore these effects in the context of schizophrenia (12).

However, recent reports do emphasise the safety of antidepressants in schizophrenia, including the use in combination with antipsychotics (13). Thus, clinical recommendations may wish to consider antidepressant medication for patients with depression and schizophrenia, although conclusions should be tempered by the moderate to low quality of studies available. Our findings do give an increase in the strength of evidence from previous literature that demonstrated mixed or weak effectiveness of antidepressants for depression in schizophrenia (4). Our analysis of trials reporting response to antidepressant therapy demonstrates a number needed to treat (NNT) of five, which is equivalent to the NNT of antidepressant medications used for the treatment of depression (in the absence of schizophrenia), documented to be between seven and nine (42).

Depression adds to the extensive burden of schizophrenia and its management is crucial to recovery (1). Improvement in depression status may lead to better long-

term functional outcomes such as medication adherence, service utilisation, substance misuse, suicide attempts, and quality of life (1, 43). In April 2015 the first NHS access and waiting time standards in mental health services came into effect, and considerable investment is to focus on the treatment of first episode psychosis (44). Depression is common in first episode psychosis and it is both timely and essential that the evidence base around which treatments are effective and the extent of their effectiveness is robust. Our current findings further extend prior research by demonstrating a moderate effect size in favour of antidepressants over placebo, with effect sizes comparable to that found in meta-analysis of Cognitive Behavioural Therapy for psychosis (CBTp) (45). NICE continues to recommend that CBTp should be offered to all patients with schizophrenia and psychosis (46). It is therefore reasonable to assume our novel findings should similarly influence clinical guidelines.

A lack of rigorous reporting of adverse outcomes in included trials in this review prevented calculation of number needed to harm and caution must be taken when recommending pharmacological interventions and the avoidance of unnecessary polypharmacy. In particular, the Medicines and Health Products Regulatory Authority issued guidance against the use of citalopram with medication that can also prolong QTc interval and lead to potential arrhythmias (47). However evidence has demonstrated this combination can be used without excess mortality and, in practice, antidepressants and antipsychotics are commonly prescribed together without incident (48). Likewise, psychosocial interventions are also not without their own potential adverse effects (49) yet often escape the close scrutiny that drug interventions are subject to, with detrimental effects unreported (50, 51). Thus on the whole, our results suggest antidepressant medication should be considered, whilst also accepting that further high quality robust studies are needed to give definitive guidance.

Limitations

The primary focus of seven studies was not the treatment of depression and this contributed to the heterogeneity of results. Some trials lacked clear depressive inclusion criteria and participants were recruited in different phases of illness, with the majority of trials evaluating antidepressants in chronic illness. Only two studies investigated antidepressants in early psychosis and both mixed these participants

with recurrently ill patients; this was disappointing given the significant evidence that depression is most prevalent in early years of illness and when risk of suicide is highest (52, 53). Studies did not report on any concurrent psychological or family based treatments, and it is possible if present these added further confounding factors. It should also be noted that even evidence for a significant response to treatment is not equivalent to evidence of recovery, would require studies to measure many factors in addition to change on a depression scale or objective clinical response. Finally, trials were disparate in outcome reporting. Most frequently depressive symptoms were evaluated using the HAM-D which is not designed to distinguish depressive from negative and extrapyramidal symptoms.

Conclusion and Clinical Recommendation

This systematic review and meta-analysis demonstrates qualified evidence that antidepressants may be effective in treating depression in people with schizophrenia. Future research should consider the methodological limitations of current published findings and above recommendations to ensure rigorous and conclusive results. Large-scale randomised controlled trials should prioritise the appropriate measurement of depressive symptoms in schizophrenia, include reporting of adverse outcomes and use an adequate method of randomisation, allocation concealment and have specific depression inclusion criteria. However, clinical guidelines should focus on the best evidence available to give treatment advice for this pressing area of clinical need. Current evidence suggests that it is possible that antidepressant medication is effective for the treatment of depression in schizophrenia, and clinicians would be justified in discussing an individual therapeutic trial with their patients.

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Figure 1: PRISMA Flow Chart

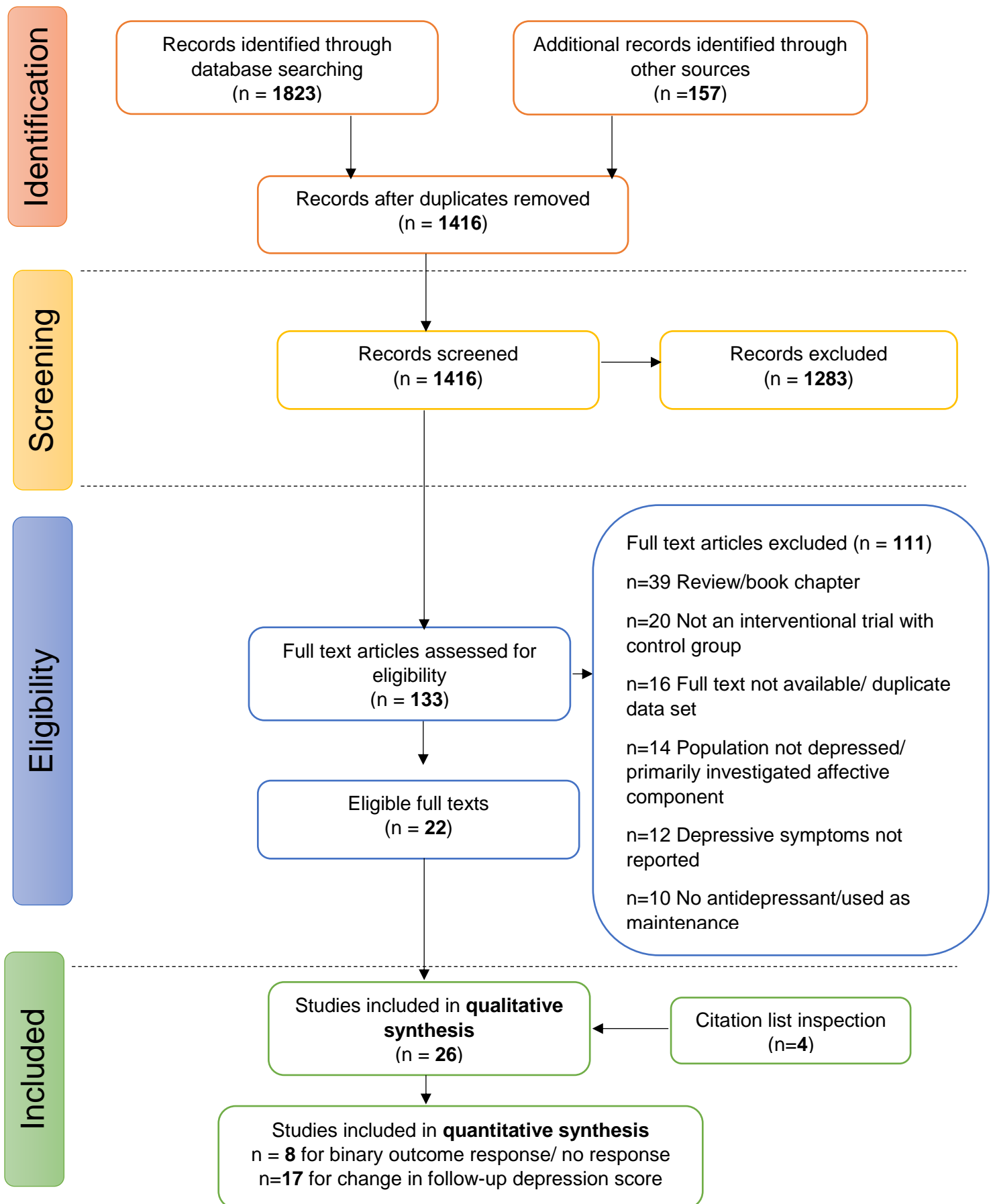


Figure 2: Forest plot of response to antidepressant

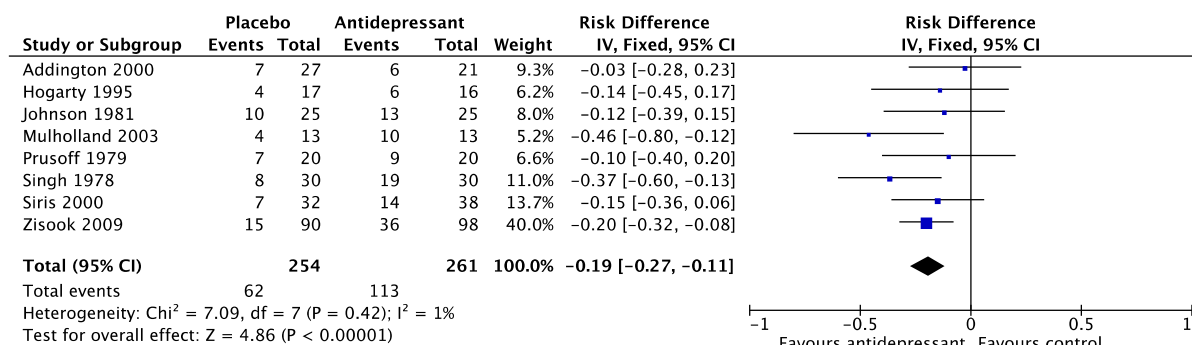


Figure 3: Forest plots of mean differences for citalopram in HAM-D score at follow up using a random effects model.

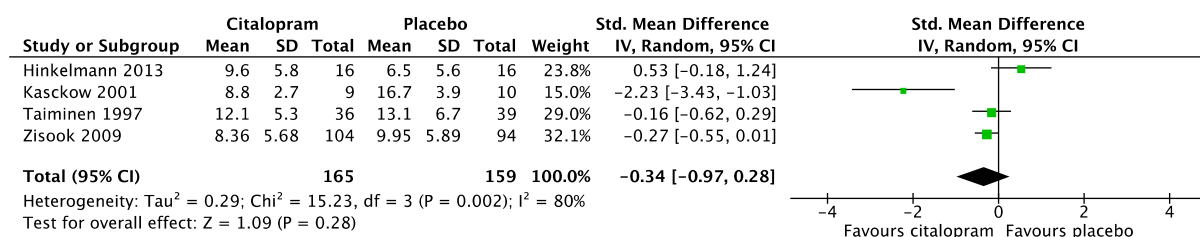


Figure 4: Forest plot of mean differences in CDSS score at follow up using a random effects model.

