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Antidepressants for depressed elderly (Review)

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Mottram PG, Wilson K, Strobl JJ.
Antidepressants for depressed elderly.
Cochrane Database of Systematic Reviews 2006, Issue 1. Art. No.: CD003491.
DOI: 10.1002/14651858.CD003491.pub2.

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[Intervention Review]

Antidepressants for depressed elderly

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Editorial group: Cochrane Common Mental Disorders Group.
Publication status and date: Edited (no change to conclusions), published in Issue 1, 2009.

Citation: Mottram PG, Wilson K, Strobl JJ. Antidepressants for depressed elderly. *Cochrane Database of Systematic Reviews* 2006, Issue 1. Art. No.: CD003491. DOI: 10.1002/14651858.CD003491.pub2.

ABSTRACT

Background

Depression is a relatively common experience in older adults. The syndrome is associated with considerable distress, morbidity and service commitment. Approximately two thirds of patients presenting with severe forms will respond to antidepressant treatment and the last twenty years has witnessed a great increase in the number of these drugs. Older, frail people are particularly vulnerable to side effects.

Objectives

The aims of this review were to examine the efficacy of antidepressant classes, to compare the withdrawal rates associated with each class and describe the side effect profile of antidepressant drugs for treating depression in patients described as elderly, geriatric, senile or older adults, aged 55 or over.

Search methods

The Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register (CCDANCTR-Studies) was searched (2003-08-13). Reference lists of relevant papers and previous systematic reviews were hand searched for published reports and citations of unpublished studies.

Selection criteria

Only randomised controlled trials were included. Trials had to compare at least two active antidepressant drugs in the treatment of depression.

Data collection and analysis

Reviewers extracted data independently. In examining efficacy, the reviewers assumed that people who died or dropped out had no improvement. Withdrawal rates irrespective of cause and specifically due to side effects were compared between drug classes. Relative risk (RR) for dichotomous data and weighted mean difference for continuous data were calculated with 95% confidence intervals (CI). Qualitative side effect data were reported in terms of ratios of side effects and percentage of patients experiencing specific side effects.

Main results

A total of 32 trials provided data for inclusion in the review in terms of efficacy, withdrawal and side effect analysis. We were unable to find any differences in efficacy when comparing classes of antidepressants. Tricyclic antidepressants (TCAs) compared less favourably with selective serotonin reuptake inhibitors (SSRIs) in terms of numbers of patients withdrawn irrespective of reason (RR: 1.23, CI 1.05 to 1.43) and number withdrawn due to side effects (RR: 1.36, CI 1.09 to 1.70). Further analyses demonstrated that TCA related antidepressants had similar withdrawal rates to SSRIs irrespective of reason of withdrawal (RR: 1.49, CI 0.74 to 2.98) or withdrawal due to side effects (RR: 1.07, CI 0.43 to 2.70). The qualitative analysis of side effects showed a small increased profile of gastro-intestinal and neuropsychiatric side effects associated with classical TCAs.

Authors' conclusions

Our findings suggest that SSRIs and TCAs are of the same efficacy. However, we have found some evidence suggesting that TCA related antidepressants and classical TCAs have different side effect profiles and are associated with differing withdrawal rates when compared with SSRIs. The review suggests that classical TCAs are associated with a higher withdrawal rate due to side effect experience, although these results must be interpreted with caution due to the heterogeneity of the drugs and patient populations.

PLAIN LANGUAGE SUMMARY

Antidepressants for depressed older people

This review compared the efficacy, withdrawal rates and side effects of different antidepressant classes in the treatment of depression in older people. Thirty-two studies provided data for the review. Our main findings indicate that tricyclic antidepressants (classical and tricyclic related) and selective serotonin reuptake inhibitors (SSRIs) are equally efficacious. However, when comparing the two tricyclic groups with SSRIs we found that tricyclic related antidepressants were similar to SSRIs in terms of overall withdrawal rate, and classical tricyclic antidepressants were associated with a higher withdrawal rate due to side effects. These findings are reflected in the differing side effect profiles when comparing both tricyclic groups with SSRIs. The findings of the review must be interpreted with some caution in view of the relatively low patient numbers and lack of side effect data.

BACKGROUND

The presence of depression in the community ranges from 10-15%. This includes both major and minor depression (Katona 1994). The prevalence of major depression in people over the age of sixty is between two and five percent. It is considerably higher in older people with physical illness (Murphy 1982). Approximately 50-60% of patients are thought to improve clinically as a consequence of antidepressant treatment (Schneider 1995). These findings are supported by a systematic review of antidepressant versus placebo in the treatment of depression in this age group (Wilson 2005).

It is generally acknowledged that older, frail depressed patients are particularly prone to side effects of antidepressants (Katona 1994). The effects of multiple drug prescribing often encountered in this population may well compound these. Older patients are more prone to the cardio-vascular side effects of antidepressants (Woodhouse 1992). The anticholinergic side effects of many of these antidepressants are likely to promote cognitive dysfunction (Moskowitz 1986). Such side effects are likely to affect compliance, treatment outcome and the effectiveness of both short and long term treatment.

Antidepressants are drugs that are effective in the treatment of depression (usually moderate or severe). The last decade has witnessed the development of a wide range of antidepressants with differing pharmacological characteristics, with varying side effect profiles. Antidepressants may be grouped in accordance with the classification provided by the British National Formulary (BNF) (BMA 1999). Tricyclic antidepressants (TCAs) refer to those antidepressants that are characterised by a three-ring structure (classical TCAs), and to those antidepressants with one, two and four rings with broadly similar properties (TCA -related antidepressants). The selective serotonin reuptake inhibitors class (SSRIs) refers to a group of drugs that selectively inhibit the re-uptake of serotonin, a chemical of recognised importance in the biochemical causes of depression. Likewise, the mono-amine oxidase inhibitors (MAOIs) refer to a class of drugs designed to inhibit monoamine oxidase, which in turn results in accumulation of amine neurotransmitters. Lastly, the newer antidepressants that do not readily fall within these pharmacological classes may be grouped as 'atypical' antidepressants.

This review examines randomised controlled trials of antidepressants in people aged 55 and over, or classified as 'elderly'. In undertaking this review we completed the search for all trials of antidepressants in this age group, identified those trials that generated data regarding efficacy, rates of withdrawal and side effects. Antidepressants were grouped in accordance with the classifications provided by the BNF described above, maintaining consistency with a related Cochrane review examining the relative efficacy of antidepressants compared to placebo in this age group (Wilson 2005). We aimed to compare the comparative efficacy of differing drug classes and the withdrawal rates in trials of antidepressants, and to describe the side effects experienced by patients taking these drugs.

OBJECTIVES

To examine the comparative efficacy of different antidepressant classes in the treatment of depression in older people.

To test the hypothesis that different groups of antidepressants are similar in terms of withdrawal rates, irrespective of cause and due to drug related side effects.

To compare the profile of side effects experienced by older people taking different classes of antidepressants.

METHODS

Criteria for considering studies for this review

Types of studies

The review included all randomised controlled trials that compared two or more antidepressants in the treatment of depression in subjects over the age of 55 or described as elderly, senile, geriatric or older adults. Dosage finding trials were excluded.

Types of participants

Patients of both sexes were included in the review if diagnosed as suffering from depression by any criteria. This included patients suffering from major depression, dysthymia, unipolar depression and non-specified depression. The review included patients over the age of 55 or described as elderly, senile, geriatric or older adults. Patients suffering from concomitant physical illness were included in the review.

Trials including patients under the age of 55 (or those not described as elderly, senile, geriatric or older adult) were excluded unless data concerning those patients were randomised and analysed separately. Patients suffering from other mental disorders (including both bipolar affective disorder and dementia) were excluded from the review.

Types of interventions

The review included all drugs described by the author as antidepressant drug treatments. Trials that used psychotherapy or psychosocial interventions in combination with all antidepressant treatments were also included.

Antidepressants were grouped by class of drug as defined by British National Formulary (BMA 1999). When not classified by the BNF, drugs were allocated to the pharmacological class to which they were most similar. The principal classes of drugs identified were:

1. Tricyclic antidepressants (TCAs)

a) Classical tricyclics (classical TCAs): doxepin, amitriptyline, imipramine, clomipramine, dothiepin, nortriptyline, trimipramine, desipramine, nomifensine

b) Tricyclic related (TCA related): mianserin, trazodone, maprotiline, viloxazine

2. Selective serotonin reuptake inhibitors (SSRIs): paroxetine, fluoxetine, citalopram, fluvoxamine, sertraline

3. Monoamine oxidase inhibitors (MAOIs): phenelzine, moclobemide

4. Atypical antidepressants: buspirone, bupropion, milnacipan, venlafaxine, reboxetine (the heterogeneity of drugs included within the atypical antidepressant class limits the relevance of combining these drugs as one class of antidepressants, however the review authors wished to determine whether these newer antidepressants were less likely to be associated with efficacy and withdrawal when compared with more established TCAs.

Trials that randomised psychotherapy against an antidepressant were excluded, as were trials that randomised to more than one antidepressant simultaneously.

The comparisons planned to be conducted by this review (if trials were available) were:
1. TCAs versus SSRIs
2. TCAs versus MAOIs
3. TCAs versus atypicals
4. SSRIs vrsus MAOIs
5. SSRIs versus atypicals
6. MAOIs versus atypicals

Types of outcome measures

Primary outcome

The primary outcome was efficacy, measured firstly as recovery rates (recovery versus failure to recover) between drug classes. In undertaking the efficacy analysis it was assumed that patients who dropped out or died during the trial demonstrated no improvement. Efficacy was also measured as a continuous outcome, using rating scales such as the Hamilton Depression Rating Scale (Hamilton 1967).

Secondary outcome

The secondary outcome was withdrawal rates, which referred to the number of patients withdrawn from antidepressant class groups irrespective of the cause, and the total number of patients withdrawn from receiving antidepressant treatment as a consequence of experiencing side effects.

Tertiary outcome

Tertiary outcomes included comparisons of side effects experienced by patients receiving antidepressants. These data were expressed qualitatively in terms of the percentage of different side effects experienced by patients and the ratio of side effects experienced by patients receiving each class of antidepressant, enabling comparison between differing drug classes. Data were presented by organ system as determined by symptomatic expression. Patients who died or were withdrawn were included in the side effect analysis.

Search methods for identification of studies

See Collaborative Review Group search strategy
The two-stage search strategy devised by CCDAN was employed. The first stage involved the employment of the review group search strategy to identify all antidepressant trials. The second stage involved the employment of validated MESH terms to identify trials that include older people (Wilson 2005). Reference lists of relevant papers and previous systematic reviews were hand searched for published reports and citations of unpublished studies. The searches were conducted with the assistance of an information specialist.

Electronic bibliographic databases

The Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register (CCDANCTR-Studies) was searched (2003-08-13) using the search terms.
Diagnosis = Depressi* or Dysthymi*
and
Intervention = Antidepressive Agents or "Monoamine Oxidase Inhibitors" or "Selective Serotonin Reuptake Inhibitors" or "Tricyclic Drugs" or Acetylcarnitine or Alaproclate or Amersergide or Amiflamine or Amineptine or Amitriptyline or Amoxapine or Befloxatone or Benactyzine or Brofaromine or Bupropion or Butriptyline or Caroxazone or Chlorpoxiten or Cilosamine or Cimoxatone or Citalopram or Clomipramine or Clorgyline or Clorimipramine or Clovoxamine or Deanol or Demexiptiline or Deprenyl or Desipramine or Dibenzipin or Diclofensine or Dothiepin or Doxepin or Duloxetine or Etoperidone or Femoxetine or Fluotracen or Fluoxetine or Fluparoxan or Fluvoxamine or Idazoxan or Imipramine or Iprindole or Iproniazid or isocarboxazid or Litoxetine or Lofepramine or Maprotiline or Medifoxamine or Melitracen or Metapramine or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Nefazodone or Nialamide or Nomifensine or Nortriptyline or Noxiptiline or Opipramol or Oxaflozane or Oxaprotiline or Pargyline or Paroxetine or Phenelzine or Piribedil or Pirlindole or Pivagabine or Prosulpride or Protriptyline or Quinupramine or Reboxetine or Rolipram or Sertraline or Setiptiline or Teniloxine or Tetrindole or Thiazesim or Thozalinone or Tianeptine or Toloxatone or Tomoxetine or Tranylcypromine or Trazodone or Trimipramine or Venlafaxine or Viloxazine or Viqualine or Zimeldine
and
Age Group = Aged

Handsearches

Reference lists of relevant papers and previous systematic reviews were hand searched for published reports and citations of unpublished studies.

Data collection and analysis

Selection of studies

Two reviewers independently assessed the relevance of each abstract and classified them as:
1. eligible
2. unclear eligibility
3. not eligible
Those falling into either category 1 or 2 had the full article retrieved. These were then assessed by two reviewers, blind to the decision made by each other, against preset criteria and rated on a scoring sheet. In cases of disagreement a decision was reached by open discussion and consensus. Reasons for exclusion and/or inclusion were recorded.

Quality assessment

All trials included in the review were classified according to the quality assessment criteria set out in the Cochrane Reviewers' Handbook (Alderson 2004). Studies were rated as A (adequate allocation concealment), B (unclear) or C (inadequate allocation concealment). The 23-item quality assessment instrument developed by Montcrieff 2001 was also used to assess the methodological quality of studies. The Montcrieff 2001 scale rates trials 0, 1 or 2 on the reporting of /conducting of the trial, with the higher score showing a higher quality study. Items include information provided on randomisation, blindness of researchers and subjects, allocation concealment, description of sample, power analysis report etc. The total score of these items enables each trial to compared in terms of the quality of studies.

Data extraction

Data were extracted from each study, using a pre-designed form by two reviewers, differences were resolved following discussion and re-examination of the study. Studies were categorised into three groups: trials that generated efficacy data, trials that provided data

concerning side effects and trials that generated data regarding withdrawals.

Statistical Analysis

Pooling of data
Efficacy analysis: For dichotomous data, relative risk (RR) together with 95% confidence intervals were used to provide a pooled estimate for studies, using a random effects model. Continuous data were pooled by calculating the weighted mean difference where studies used the same instruments and standardised mean differences where different scales were used to measure the same outcome.

Withdrawal rates: Overall withdrawal rates (withdrawal irrespective of cause) were examined using relative risk (RR) and 95% confidence intervals to provide a pooled estimate, which was calculated using a random effects model. A second analysis was undertaken examining withdrawal due to side effects, using the same techniques.

Side effects: Side effect data for each drug class were presented by organ system in the form of side effect: patient ratio to enable comparison between classes. Data regarding side effect profile were extracted from all available studies and reported qualitatively. Individual side effect symptom and signs were listed. Where terms describing individual side effects were similar, they were combined. All side effect categories were grouped by organ system. Systems included: Neuropsychiatric, Gastrointestinal, Respiratory, Sensory, Genitourinary, Dermatological and Cardiovascular.

Assessment of heterogeneity
We anticipated that other variables associated with ageing (such as physical ill health) were likely to influence the efficacy, withdrawal rates and expression of side effects as a consequence of antidepressant medication. Where possible the influence of patient characteristics, for example, inpatients, outpatients and community samples, subtypes of depression, physical illness, people under the age of 75 versus patients over the age of 75 were studied. As numbers of patients withdrawn due to side effects has been shown to be dependent on the frequency of assessments (Williams 2000), this issue was examined in the context of the trials included in the review. In addition, a formal test for statistical heterogeneity, the natural approximate chi-squared test, was conducted.

Subgroup analyses
Antidepressant drugs were categorised by group as determined by the British National Formulary. This has the potential of generating the following groups of antidepressants; trycyclic antidepressants, trycyclic related antidepressants, monoamine oxidase inhibitors (and reversible monoamine oxidase inhibitors, selective serotonin re-uptake inhibitors and 'other' or atypical antidepressants. In this review, we compared all tricyclic antidepressants (classical and related) with SSRIs and then explored the subcategories as defined by the British National Formulary as follows:
1. classical TCAs versus SSRIs
2. related TCAs versus SSRIs
3. classical TCAs versus MAOIs
4. related TCAs versus MAOIS
5. classical TCAs versus atypicals
6. related TCAs versus atypicals

Our intention is to compare the efficacy, withdrawal rates and side effect profiles of these groups.

Other planned subgroup analyses:
Setting (inpatient/outpatient/community)
Subtypes of depression
Comorbid physical illness
Age (under 75 vs 75 and over)

Sensitivity analysis
As a test of robustness of our results, sensitivity analysis was conducted by two reviewers to assess the effects of excluding lower methodological quality studies, using the quality assessment instrument developed by Montcrieff 2001.

Publication bias
A funnel plot was used to assess publication bias.

RESULTS

Description of studies

A total of 163 studies were identified by the search strategy. Of these, 32 had usable data, and were included in the review as given below. The 119 studies excluded from the review are presented in the table of Characteristics of excluded studies, with reasons for exclusion. The remaining 12 studies are awaiting assessment. Included trials were classified into those that provided data regarding efficacy, withdrawal rates and side effects.

Included studies

Seventeen studies contributed data towards the efficacy analysis (Bocksberger 1993; De Ronchi 1998; Dorman 1991; De Ronchi 1998; Georgotas 1986; Geretsegger 1995; Halikas 1995; Hoyberg 1996; Hutchinson 1991; Kyle 1998; Mahapatra 1997; Mulsant 1998; Nair 1995; Navarro 2001; Pelicier 1993; Smeraldi 1998; Tignol 1998).

Twenty-six studies provided sufficient data to enable analysis of withdrawal rates (Bocksberger 1993; Brion 1996; De Ronchi 1998; Dorman 1991; Dunningham 1994; Falk 1989; Feighner 1985; Georgotas 1986; Geretsegger 1995; Guillibert 1989; Halikas 1995; Hoyberg 1996; Hutchinson 1991; Katona 1999; Kyle 1998; La Pia 1992; Mahapatra 1997; Mulsant 1998; Nair 1995; Navarro 2001; Pelicier 1993; Phanjoo 1991; Rahman 1991; Schweizer 1998; Smeraldi 1998; Tignol 1998)

Twenty studies provided data of sufficient quality to be included in the side effect analysis (Ather 1985; Dorman 1991; Eklund 1986; Falk 1989; Feighner 1985; Geretsegger 1995; Guillibert 1989; Gwirtsman 1983; Hoyberg 1996; Hutchinson 1991; Katona 1999; Kyle 1998; La Pia 1992; Nugent 1979; Pelicier 1993; Phanjoo 1991; Rahman 1991; Siegfried 1986; Scardigali 1982; Smeraldi 1998). Where terms describing individual side effects were similar, they were combined. This occurred in four circumstances: The terms 'anxiety', 'agitation', 'restlessness', 'excitability' and 'nervousness' were combined as 'anxiety'. 'Vertigo' and 'dizziness' were combined as 'dizziness'. 'Fatigue', 'drowsiness' and 'somnolence' were combined as 'drowsiness'. 'Nausea' and 'vomiting' were combined as 'nausea and vomiting'.

Dose of Drugs

A number of trials employed a fixed dose drug regime, often increasing the dose over a number of weeks, reaching the prescribed dose within 2-4 weeks. More trials employed varying

dosages of antidepressants. The dose was usually titrated by the clinician according to response and side effect tolerability. Dose range varied considerably, both within studies and between studies. The doses of antidepressants used in trials included within the efficacy analysis are tabled Table 1.

Trial design

All trials were of parallel group design. Patients were randomly assigned to receive one of the trial drugs (or placebo) in appropriately designed trials. Data regarding placebo were excluded in examining efficacy and side effect profile. Three trials included more than two active drugs (Siegfried 1986; Smeraldi 1998). In those trials in which there were more than two active drugs compared, one drug was excluded from the meta-analyses regarding efficacy.

Age Range

Trials comparing patients as elderly, geriatric, senile or older adult used different minimum ages for this group. Some studies did not indicate age ranges (Tignol 1998), however all those that did included patients aged 55 or over. A minority of studies had limits on the upper age range (80 or 90 years old).

Diagnoses and severity of depression

Twenty-two studies employed DSM-111, DSM-111R or DSM-IV diagnostic criteria for major depressive disorder and some included dysthymic disorder. Dorman 1991 included DSM-III unipolar depression. Two trials used DSM-III mixed depressive states (Katona 1999; La Pia 1992). Two studies (Mulsant 1998; Navarro 2001) used DSM-IV criteria. Pelicier 1993 used Feighner's criteria (Feighner 1972). Nugent 1979; Scardigali 1982 and Tignol 1998 either failed to report or did not use validated diagnostic criteria. Entry diagnostic criteria were usually supported by the concomitant use of severity rating as defined by the Hamilton Depression Rating Scale (HDRS) (Hamilton 1967) or the Montgomery and Asberg Depression Rating Scale (MADRS) (Montgomery 1979). The 21, 24 and 17 item versions of the HDRS were used in 31 studies. Cut-off severity scores included >15, >16, >17, >19. The MADRS was used in a similar fashion in six studies, employing cut-offs of >23 and >29.

Outcome measures

Efficacy

Change in the HDRS was used as a primary outcome measures in the majority of studies (usually a reduction of 50% or to drop below a prespecified score). This was augmented by the Clinical Global Impression (CGI) in 21 studies. Change in MADRS score was employed as a primary outcome measure in six trials (Pelicier 1993; Phanjoo 1991; Kyle 1998; Smeraldi 1998; Bocksberger 1993; Brion 1996) and used in conjunction with the HDRS by De Ronchi 1998; Geretsegger 1995; Halikas 1995; Hoyberg 1996; Smeraldi 1998; Feighner 1985; Mahapatra 1997; Mulsant 1998; Navarro 2001; Tignol 1998. The Geriatric Depression Scale was used as a secondary outcome measure in two trials (La Pia 1992; Nair 1995). Other rating scales included: The Leeds Sleep Evaluation Questionnaire (no reference available), which was used by Dorman 1991. The Treatment Emergent Side Effect Scale (no reference available) was used by Falk 1989. The Raskin Scale (Feighner 1985) and the Zung Depression Scale (Zung 1965) were used by Georgotas 1986; Gwirtsman 1983; Halikas 1995; Pelicier 1993. The Wakefield Self Assessment Scale was used by Nugent 1979 as a secondary outcome measure. Eklund 1986 used a visual analogue scale and Guillibert 1989 used the Newcastle Scale as secondary outcome measures. Other than the listed scales and instruments, Siegfried 1986 examined the occurrence of specific drug related side effects, including change in cardiac status. No studies included outcomes of quality of life measures. Patients who discontinued, dropped out or died were assumed to have experienced no improvement in terms of depression severity.

Withdrawal rates

In examining the withdrawal rates associated with each class of antidepressants, we examined both data pertaining to the 'overall withdrawal rates' (irrespective of cause) and withdrawal due to side effects (as described by the trialist). In presenting the 'overall withdrawal rates' we provided the context in which withdrawal rates due to side effects could be considered, to provide consistency with a related Cochrane review (Wilson 2005). In interpreting these results it is evident that 'overall withdrawal' was not a surrogate for side effect experience.

Side effects

Due to the small size of the dataset, variety in description of side effects, variability in reporting and problems in grouping side effects by organ system, the data were presented in a qualitative format through percentages and ratios, so as to facilitate comparison between antidepressant classes, specifically avoiding formal analysis.

Study size

Studies were both single and multi-site, with the largest number of sites being nine (Mahapatra 1997); comparing venlafaxine with dothiepin. The following studies had 50 or more patients receiving each drug: Ather 1985; Brion 1996; Feighner 1985; Hoyberg 1996; Katona 1999; Kyle 1998; Mulsant 1998 Schweizer 1998; Smeraldi 1998; Tignol 1998. All the other studies had less than 50 patients in either or both arms of the study.

Duration of trials

Five trials had the shortest duration of four weeks. Two trials had a duration of five weeks and 12 trials lasted six weeks. Three trials lasted seven weeks and four trials lasted eight weeks. Of the remainder (for which the duration was available) De Ronchi 1998, a trial of fluoxetine compared with amitriptyline lasted 10 weeks. Three trials lasted 12 weeks; Dunningham 1994, a trial of moclobemide compared with imipramine, Mulsant 1998 a trial of nortriptyline compared with paroxetine and Navarro 2001, a trial of citalopram compared with nortriptyline. Brion 1996, a trial comparing tienepine with mianserin lasted 24 weeks.

Recruitment source and patient exclusions

The following trials recruited patients from inpatient services: Bocksberger 1993; Eklund 1986; Geretsegger 1995; (older persons medical inpatient unit), Siegfried 1986 (older person acute medical inpatient unit and nursing home residents) and Nugent 1979 (females from an inpatient unit). The following recruited from both inpatient and out patient populations: Ather 1985; Hoyberg 1996; Katona 1999; La Pia 1992; Mahapatra 1997; Mulsant 1998; Navarro 2001; Phanjoo 1991; Tignol 1998. The studies that recruited from outpatient and community samples include: De Ronchi 1998; Dunningham 1994; Falk 1989; Feighner 1985; Georgotas 1986; Halikas 1995; Hutchinson 1991; Kyle 1998; Nair 1995; Pelicier 1993; Schweizer 1998; Smeraldi 1998. The remaining six studies failed to report population recruitment sources.

Risk of bias in included studies

All trials included in the review were classified as 'B', using the quality assessment criteria from the Cochrane Reviewers' Handbook (Alderson 2004). In most trials the quality of reporting was poor. Trials reported randomisation without any information on allocation concealment. A majority of trials reported dropouts and post randomisation exclusions. The majority of trials did not use the intent-to-treat approach. A significant number of trials failed to provide useable data due to lack of efficacy analysis or the omission of standard deviations. A number of studies also omitted basic information about the study population (gender, setting etc).

The 23-item quality assessment instrument developed by Montcrieff 2001 was also used to assess the methodological quality of studies. Studies varied in score between 16 and 33 with a mean score of 23.04 (SD 6.18). There were no significant differences in quality between the types of studies or the age of the study.

Effects of interventions

Meta analyses were firstly conducted to compare efficacy and withdrawal rates between classes of antidepressants. We compared all TCAs (classical and related) with SSRIs. In subsequent subgroup analyses, we compared classical TCAs with SSRIs and TCA related antidepressants with SSRIs. Where data enabled comparisons of efficacy and withdrawal rates between TCAs, atypical antidepressants and MAOIs, further subgroup analyses were conducted. In the second part of the analysis we examined side effects by organ system and class of antidepressant, with findings presented descriptively. Side effect events were presented in ratio format of events experienced by 10 patients to enable comparison of side effects associated with each organ system between drug classes. We also conducted a qualitative analysis of individual side effects in terms of percentage of patients experiencing each side effect.

Efficacy

All TCAs versus SSRIs

Nine studies (De Ronchi 1998; Dorman 1991; Feighner 1985; Geretsegger 1995; Hutchinson 1991; Kyle 1998; Mulsant 1998; Navarro 2001; Pelicier 1993) included paroxetine, fluoxetine, and citalopram (SSRIs) and mianserin, doxepin, trazodone, amitriptyline, nortriptyline and clomipramine (TCAs). These trials generated 528 TCA recipients and 552 SSRI recipients. There was no difference in efficacy at the 5% level of significance between the drug classes (RR: 1.07, CI 0. 94 to 1.22). Only one trial generated continuous data (Falk 1989) and no significant differences were found in terms of change in depression severity between the two groups.

All TCAs versus MAOIs

We were able to compare the efficacy of all TCAs with MAOIs. However, this meta-analysis of two studies (Georgotas 1986; Nair 1995) only generated data on 121 patients receiving phenelzine and moclobemide (MAOIs) and nortriptyline (TCA) (RR: 1.16, CI 0.74 to 1.83). The lack of data makes any generalisation concerning the comparative efficacy of these groups of drugs unreliable. No data were generated with regard to continuous outcome variables.

All TCAs versus atypicals

Four trials contributed to All TCAs versus atypical comparison (Halikas 1995; Hoyberg 1996; Mahapatra 1997; Smeraldi 1998). No differences were found between all the TCA (number of patients = 223) and atypical (number of patients = 161) when considering efficacy in terms of failure to recover (RR 0.84 CI 0.51 to 1.38). One trial (Hoyberg 1996) generated a small number of patients (n=91) to enable comparison in terms of continuous data; failing to show differences between the two groups of drugs.

SSRIs versus MAOIs

Only one trial was found in this group (Bocksberger 1993) with 20 recipients in each arm, there was no significant difference between the groups (RR: 0.81 CI 0.55 to 1.20).

MAOIs versus atypicals

No trials were found for this comparison

Classical TCAs versus SSRIs

Seven studies (Feighner 1985; Geretsegger 1995; Hutchinson 1991; Kyle 1998; Mulsant 1998; Navarro 2001; Pelicier 1993) generated 388 patients receiving classical TCAs and 402 patients receiving SSRIs. No significant differences were found in terms of recovery (RR: 1.07, CI 0.93 to 1.24). Likewise, in the one study generating continuous data (De Ronchi 1998), no significant differences were found.

Related TCAs versus SSRIs

The only study from which data could be extracted (Dorman 1991) generated less than 50 patients in each experimental arm (RR: 1.59, CI 1.07 to 2.35). Falk 1989 generated 25 patients in a trial comparing fluoxetine with trazodone and failed to demonstrate differences in terms of change in depression severity.

Heterogeneity

A random effects model was used as statistical heterogeneity was found in the analysis. Heterogeneity was found in All TCAs versus atypicals (Chi squared 6.19, df=2, p=0.05) efficacy and withdrawal rate (Chisquared 18.18, df=7, p=0.01).

Publication bias

A funnel plot failed to demonstrate clear evidence of publication bias due to insufficient data.

Withdrawal rates

All TCAs versus SSRIs

Fourteen studies (De Ronchi 1998; Dorman 1991; Falk 1989; Feighner 1985; Geretsegger 1995; Guillibert 1989; Hutchinson 1991; Kyle 1998; La Pia 1992; Mulsant 1998; Navarro 2001; Pelicier 1993; Phanjoo 1991; Rahman 1991) generated 651 TCA recipients and 677 SSRI recipients. The trials included mianserin, trazodone, doxepin, amitriptyline, imipramine, clomipramine, nortriptyline and dothiepin (TCAs) compared with paroxetine, fluoxetine, citalopram and fluvoxamine (SSRIs). Meta analysis demonstrated that patients receiving SSRIs were less likely to be withdrawn in general (RR: 1.23, CI 1.05 to 1.43), and more specifically, due to side effects (RR: 1.36, CI 1.09 to 1.70).

All TCAs versus MAOIs

In comparing withdrawal rates (irrespective of cause) of all TCAs recipients with MAOI recipients three studies were identified (Dunningham 1994, Georgotas 1986, Nair 1995). They compared moclobemide and phenelzine (MAOIs; n=88) with nortriptyline and imipramine (TCAs: n= 93). No differences in withdrawal rates were noted (RR: 0.91, CI 0.64 to 1.29). The Dunningham 1994 trail did not generate data of sufficient quality to be included in the comparison of withdrawal due to side effects. This analysis (Georgotas 1986,

Nair 1995) compared moclobemide and phenelzine (MAOIs: an=58) and nortriptyline (TCA an=63). TCA recipients were more likely to be withdrawn due to side effects (RR: 2.27, CI 0.44 to 11.81).

All TCAs versus atypical antidepressants
The systematic search of the literature failed to generate more than one trial examining identical drugs that did not fall into the drug classes as defined by the British National Formulary. The heterogeneity of drugs included within the atypical antidepressant class limits the relevance of combining these drugs as one class of antidepressants. However the review authors wished to determine whether these newer antidepressants were less likely to be associated with withdrawal due to side effects when compared with more established TCAs.

Eight studies (Brion 1996, Halikas 1995, Hoyberg 1996, Katona 1999, Mahapatra 1997, Schweizer 1998, Smeraldi 1998, Tignol 1998) included six different antidepressant drugs of differing pharmacological groups including tianeptine, mirtazepine, reboxetine, venlafaxine, buspirone, and milnaciprin (typicals: 748 patients). They were compared with mianserin, trazodone, amitriptyline, dothiepin, imipramine, and clomipramine (TCAs: 709 patients). Analysis of withdrawal rates showed no significant differences between these groups (RR: 0.96, CI: 0.75 to 1.24). Similar findings were noted when we examined withdrawal due to side effects (RR: 1.36, CI 0.96 to 1.94).

Further subgroup analysis of classical and related TCA antidepressants demonstrated that subjects receiving the 'atypical' antidepressants tianeptine and mirtazepine were more likely to be withdrawn from trials (irrespective of cause) when compared to patients receiving trazodone and mianserin (related TCAs) (RR: 1.41, CI 1.16 to 1.71). However these findings were not reflected in different withdrawal rates induced by drug side effects (RR: 1.38, CI 0.74 to 2.59). No differences were found between classical TCAs and the 'atypical' group in terms of withdrawal.

SSRIs versus MAOIs
Only on trial generated data to be incorporated in efficacy analysis (Bocksberger 1993), using both continuous and dichotomous data. The forty patients included within the trial failed to show significant differences between the groups of drugs.

SSRIs versus atypicals
No trials were found for this comparison

Classical TCAs versus SSRIs
Further analysis was conducted in order to examine sub-classes of TCAs in relationship to SSRIs. We examined amitriptyline, clomipramine, doxepin and dothiepin (classical TCAs) with paroxetine, fluoxetine and citalopram (SSRIs). In the analysis concerning withdrawal rates irrespective of cause we included ten studies (De Ronchi 1998; Feighner 1985; Geretsegger 1995; Guillibert 1989; Hutchinson 1991; Kyle 1998; Mulsant 1998; Navarro 2001; Pelicier 1993; Rahman 1991). These generated 565 classical TCA recipients and 589 SSRI recipients. The findings show an increased total withdrawal rate for recipients of classical TCAs compared to SSRI recipients (RR: 1.24, CI 1.05 to 1.46). In comparing withdrawal rates due to side effects; eight studies generated 505 recipients of classical TCAs and 528 recipients of SSRIs. The findings were similar (RR: 1.40, CI 1.11 to 1.77).

Classical TCAs versus atypicals
We were unable to demonstrate differences between groups in terms of withdrawal rates (RR: 0.84 CI 0.70 to 1.01). Six trials provided data for this analysis (Hoyberg 1996; Katona 1999; Schweizer 1998; Smeraldi 1998; Tignol 1998) providing 560 recipients of classical TCAs compared to 500 recipients of atypicals. Withdrawal due to side effects also failed to show a difference RR: 1.27 CI 0.73 to 2.22).

Related TCAs versus SSRIs
In the next subgroup analysis we compared antidepressants related to TCAs with SSRIs. Four studies (Dorman 1991; Falk 1989; La Pia 1992; Phanjoo 1991) generated data relating to mianserin and trazodone (TCA related) and paroxetine, fluvoxamine and fluoxetine (SSRIs). Eighty-six patients received TCA related drugs and 88 received SSRIs. Meta analysis demonstrated that there was no significant differences in either total withdrawal rates (RR: 1.49, CI 0.74 to 2.98) or withdrawal due to side effects (RR: 1.07, CI 0.43 to 2.70).

Assessment frequency, number and withdrawal rates
Williams 2000 has demonstrated that withdrawal rates of patients from trials are dependent on the duration of the interval between assessments. We examined this issue in the context of the current study. As predicted by Williams 2000, we found an inverse relationship between duration of interval between assessments and patient withdrawal (irrespective of reason of withdrawal), (Pearson Correlation, 2 tailed -0.71). However, no correlations were found between interval duration and withdrawal due to side effects.

Publication bias
A funnel plot failed to demonstrate clear evidence of publication bias.

Side effects by drug group
As patients are likely to suffer from more than one side effect simultaneously, side effect events were reported qualitatively in the form of the ratio of number of side effect events experienced by ten patients. The trials generated enough data to describe the patient: side effect ratios between patients receiving classical TCAs and SSRIs as one comparison, and classical TCAs and related TCAs as a second comparison. The ratios are provided in Additional Table 2. Individual side effects are expressed by organ system as a percentage of patients potentially exposed by organ system.

Classical TCAs versus SSRIs
Seven trials (Feighner 1985; Geretsegger 1995; Guillibert 1989; Hutchinson 1991; Kyle 1998; Pelicier 1993; Rahman 1991) were examined. Four of these generated data that could be included in the analysis (Hutchinson 1991, Kyle 1998, Pelicier 1993, Rahman 1991). Classical TCAs included amitriptyline, clomipramine, doxepin, and dothiepin. The four studies generated a total population of 294 patients receiving classical TCAs and 307 patients receiving paroxetine, fluvoxamine and citalopram (SSRIs).

Cardiovascular side effects
Hypotension was the only cardiovascular side effect recorded: with one event experienced by patients taking classical TCAs and four events by patients taking SSRIs.

Gastrointestinal side effects
The experience of 'dry mouth' significantly contributed to the difference between ratios in the two drug classes (28% of classical

TCA recipients compared to 7% of SSRI recipients). However nausea and vomiting was more common in SSRI recipients (17% of SSRI recipients compared to 7.5% of classical TCA recipients). Constipation was a common side effect, experienced by 7.4% of classical TCA recipients and 4.5% of SSRI recipients. Diarrhoea was experienced by 3% (classical TCA recipients) and 1.3% (SSRI recipients). Anorexia was the least frequent side effect, experienced by 2.7% (classical TCA group) and 1.6% (SSRI group). No other side effects were reported by more than 1% of either group.

Neuropsychiatric side effects
15.3% of classical TCA recipients and 6.5% of SSRI recipients experienced drowsiness and somnolence. Dizziness was experienced by 12.2% and 7.8% by classical TCA and SSRI recipients respectively. Lethargy was the next most commonly experienced side effect, with 4.4% of TCA recipients and less than 1% of SSRI recipients experiencing the side effect. Four percent of patients receiving classical TCAs and 2.6% of SSRIs recipients experienced sleep disturbance. Three percent of classical TCA recipients and 1.6% of SSRI recipients experienced tremor and less than 1% of each drug group experienced anxiety. No other neuropsychiatric side effects were recorded.

Dermatological side effects
Sweating was the only side effect reported in either drug group with 1.7% of classical TCA recipients and less than 1% or SSRI recipients experiencing it.

Classical TCAs versus TCA related antidepressants
Seven studies generated data of sufficient quality to be included in the analysis (Ather 1985, Eklund 1986, Gwirtsman 1983; Nugent 1979; Scardigali 1982; Siegfried 1986; Smeraldi 1998). These trials included trazodone, maprotiline, mianserin, viloxazine (TCA related drugs), generating 206 patients; and compared them with amitriptyline, doxepin and clomipramine (classical TCAs), generating 231 patients.

Cardiovascular side effects
Hypotension was the commonest side effect experienced by both groups (classical TCA recipients 3.9%, TCA related recipients 3.4%). Hypertension was experienced by just over 1% of each group (classical TCA 1.3%, TCA related 1.45%). ECG abnormality (classical TCA 4.3%, TCA related 0.97%) and palpitations (classical TCA; 1.3%, TCA related 0.5%) were experienced by greater percentages of classical TCA recipients compared with TCA related recipients. 5.8% of TCA related recipients and 0% classical TCA recipients experienced bradycardia. Tachycardia was experienced by 6.9% of classical TCA recipients compared with 0% of TCA related recipients.

Gastrointestinal side effects
'Dry mouth ' was the commonest experienced side effect (classical TCA 16.9%, TCA related 26.2%). This was followed by constipation experienced by 11.2% of classical TCA recipients and 10.6% of TCA related recipients. A significant minority of patients receiving classical TCAs experienced nausea and vomiting compared to those receiving TCA related drugs (classical TCA 9.5%, TCA related 4.3%). Weight gain was experienced by 1.3% classical TCA recipients compared to 2.4% of TCA related recipients. Increased salivation was experienced by 1.3% classical TCA recipients and 1.5% TCA related recipients. Less than 1% of each group experienced diarrhoea.

Neuropsychiatric side effects
Drowsiness was the commonest side effect experienced by 15.6% of classical TCA recipients and 18.9% of TCA related recipients. This was closely followed by sleep disturbance experienced by 15.6% classical TCA recipients and 14% of TCA related recipients. Over 10% of the sample experienced dizziness (12.6% of classical TCA recipients and 11.6% of TCA related recipients). Anxiety was experienced by approximately 1: 10 of the study population (8.2% of classical TCA recipients and 10.2% of TCA related recipients). Tremor was experienced by 3.5% of classical TCA sample and 7.8% of TCA related sample. Blurred vision was experienced by 3.5% classical TCA recipients and 5.3% of TCA related recipients. 4.3% of classical TCA recipients and 5.3% of TCA related recipients experienced rigidity and stiffness. 4.8% classical TCA recipients and 2.4% of TCA related recipients experienced headache. Syncope was experienced by just over 1% of each group (classical TCA 1.3%, TCA related 1.4%) and a similar percentage experienced 'confusion' (classical TCA 0.9%, TCA related 1.5%). Paraesthesia was experienced by 0.4% of patients receiving classical TCAs.

Dermatological side effects
Seven patients (3%) receiving classical TCAs and 5 (2.4%) receiving TCA related drugs experienced skin rashes.

DISCUSSION

In undertaking this meta-analysis we have conducted a systematic search of the literature and identified randomised controlled trials comparing antidepressants in the treatment of depression on older people. We have grouped together in accordance with the British National Formulary groupings so as to enable comparison between commonly used antidepressants in terms of efficacy, withdrawal and side effect profile.

The diversity of trial design and drug pharmacology present particular difficulties in the design of the review and interpretation of the findings. These issues are of considerable importance when considering the grouping of antidepressants, the efficacy, withdrawal rate and side effect analysis. The grouping of 'atypical' antidepressants is particularly vulnerable to criticism in that none of the antidepressants are of similar pharmacological design and all are noted for their differing pharmacological actions. We have drawn attention to this within the results and methodological sections of the review. Despite the obvious problems associated with this aspect of the meta-analysis the reviewers thought that it would be of clinical merit to examine these drugs as a group and compare them (in terms of side effects) to the more well established TCAs with view to examining them as a group of 'newer' antidepressants likely to be used in the treatment of older people. The trials were carried out on patients drawn from inpatient populations, out patient clinics, community volunteers and residents of nursing and care homes. The relatively small number of studies (when examined by antidepressant group) restricted the nature and validity of conducting subgroup analysis on these differing populations, including the potential effect of differing different types of depression and the experience of physical illness. Likewise, the small number of studies and the size of patient populations involved prohibit comparison between some of the drug groups.

In examining comparative efficacy data our findings have been limited through small sample sizes and poverty of data. Previous studies have demonstrated all these drug classes are superior to

placebo (Wilson 2005). However we were able to compare efficacy between TCAs and SSRIs finding no difference in efficacy based on 'recovery', however the total withdrawal rate was significant less favouring SSRIs . Similar results are obtained when comparing classical TCAs with SSRIs and atypical drugs. However, in the latter case (mirtazepine compared with trazodone and venlafaxine compared with clomipramine) only two trials were included, providing a combined population of 223 patients, limiting the implications of the findings.

Very few of the trials employed standardised instruments in the reporting of side effects, and many of the side effects experienced by patients prescribed these drugs may readily be confused with symptoms and signs of depression in this age group. Notably, only one study defined side effects as a change in the patients' experience since commencing the antidepressants. The lack of standardised instruments in qualifying and quantifying side effect experiences promotes significant problems in undertaking a meta-analysis. It is evident that trialists place differing emphasis on capturing side effect data when designing trials, which is likely to explain some of the differences in their findings. As a consequence, the reviewers have included an analysis of withdrawal rates. We extracted data from trials that described the cause of withdrawal, identifying numbers of patients identified by the trialists as being withdrawn specifically due to antidepressant side effects. These data included patients that had died but had also been identified as suffering from side effects during the trials. We excluded patients who died that were described as being free of side effect during whilst taking the antidepressants. Analysis pertaining to comparative withdrawal rates due to side effects does not provide detail concerning quantity or severity of the side effects experience of individual patients. This analysis is presented in the context of an analysis of 'overall withdrawal' (irrespective of cause).

In examining the qualitative experience of antidepressant recipients, the review authors were presented with an array of poorly defined terms with little information concerning severity or frequency of side effects. In the analysis we used terms as used by the trialists. When terms were combined or altered, these have been described in the methodology section of the review. We have grouped side effects into broad categories to enable a more comprehensive, qualitative description of the experiences of patients receiving antidepressants. The categories are loosely based on organ system. The authors accept that categories are poorly defined and offer little inherent legitimacy. Consequently we have been careful not to conduct formal analysis in comparing side effect prevalence rates, and have merely expressed our findings as ratios of the number of side effect events experienced by ten patients. We have provided percentages of patients experiencing individual side effects when possible.

The review has generated some interesting findings. It is evident that when the tricyclic antidepressants are considered as one group and compared with SSRIs (over 1000 patients included within the analysis) they have a higher rate of withdrawal due to side effects. The TCA group included mianserin and trazodone as TCA related drugs; and amitriptyline, imipramine, clomipramine, dothiepin and doxepin as classical TCAs. In comparing classical TCAs (amitriptyline, clomipramine, doxepin, and dothiepin) with SSRIs (paroxetine, citalopram, fluoxetine and fluvoxamine), both classes are of similar efficacy. However, classical TCA recipients are more likely to be withdrawn due to side effects. These findings are reflected in the differing side effect profiles generated by each drug class. Classical TCA recipients experienced more gastrointestinal (a ratio of 4.6 side effect experiences for each 10 TCA recipients compared to 2.9 experienced by 10 SSRI recipients) and neuropsychiatric side effects (4.1 side effects experienced by 10 classical TCA recipients compared to 2.3 side effects experienced by 10 SSRI recipients). The most notable differences in side effect experiences include 28% of classical TCA recipients experiencing dry mouth compared to 7% of SSRI recipients. However nausea and vomiting was experienced by a greater percentage of SSRI recipients.

The findings differ when comparing TCA related drugs with SSRIs. Some caution should be taken in interpreting these findings. The four studies only generated 174 patients, receiving mianserin and trazodone (related TCAs) or paroxetine, fluvoxamine and fluoxetine (SSRIs). There was no difference in withdrawal rates. The trials failed to generate enough data of sufficient quality to enable an analysis of comparative efficacy or a break down of the side effect profile in relationship to these studies.

We were able to examine the side effect profiles experienced by patients involved in trials comparing classical TCAs and TCA related antidepressants. Four hundred and thirty seven patients participated in these trials and were recipients of four different TCA related antidepressants and four classical tricyclics. There was relatively little difference in terms of side effect: patient ratio. There were slight differences in terms of the experiences of individual side effects with slightly greater percentage of classical TCA recipients experiencing ECG abnormalities and bradycardia. The drug classes have a similar profile in terms of neuropsychiatric side effects. Drowsiness, sleep disturbance, dizziness and anxiety were most frequently experienced side effects with tremor, blurred vision, stiffness, headache syncope and confusion occasionally experienced. Both groups experienced similar profiles of gastrointestinal side effects. Dry mouth and constipation were the commonest side effects, followed by nausea and vomiting and weight gain.

Comparing withdrawal rates of TCAs with newer, 'atypical' antidepressants is of limited value as a consequence of the heterogeneity of drugs within the 'atypical' group. When these newer antidepressants are collectively considered, our findings suggest that they are similar to classical TCAs in terms of withdrawal rates. However, as already mentioned, caution must be taken in drawing conclusions with clinical implications as more comparative trials are required before their relative tolerability can be judged. The meta analysis of withdrawal rates of MAOIs in comparison with TCAs was hampered by the few trials available. Not only were the patient numbers small but relatively few drugs were included. Hence the findings and potential clinical implications should be considered with due caution.

AUTHORS' CONCLUSIONS

Implications for practice

The clinical implications of our findings are tentative in view of the difficulties in generalising results from trials into the general population. With this caveat the findings suggest that SSRIs and TCAs are of equal efficacy. Older patients receiving TCA related antidepressants have a similar withdrawal rate compared to SSRIs, both in terms of overall withdrawal rate irrespective of cause, and

withdrawal specifically due to side effect experience (as defined by the trialists). In contrast, when All TCAs and classical TCAs trials are analysed significantly higher withdrawal rates than those receiving SSRIs. Complementing this, there is evidence of differing side effect profiles, especially when comparing gastrointestinal side effects between SSRIs and classical TCAs. However it must be noted that when the two subgroups of TCAs (classical and related TCAs) are compared in terms of side effect ratios we could establish no real differences. A cautious interpretation of these findings is that TCA related antidepressants might offer a relatively low side effect profile compared to the classical TCAs and may be associated with better tolerability. The withdrawal rate of TCA related antidepressants appears similar to that of SSRIs, and provided they are of similar efficacy, they may offer the clinician and patient an acceptable alternative in those situations in which SSRIs are not acceptable.

Implications for research

This review has been not been able to conduct all comparisons planned due to lack of or small numbers of trials or low numbers of patient participants. The diversity of pharmacological profile of drugs that have been grouped together and difficulty in categorising side effect experiences has caused difficulty in interpretation. The later issue is of particular importance in the context of older people in which both somatic symptoms of depression and concomitant physical illness are likely to mask the side effect profile of drugs. These issues demand focus in future research in this field. It is evident that older people are vulnerable to side effects, yet relatively few studies have examined this issue in this age group. Secondly, it is evident that standardised techniques should be adopted in identifying and quantifying side effect experiences. These techniques should be designed to cater for the identification of those effects that are most likely caused by the prescription of drugs, comparing the experience of the patient before drug prescription with that of the patient after the drug has been prescribed. The sensitivity and specificity of such techniques should be subjected to carefully designed studies in differing patient populations both with and without concomitant physical illness.

ACKNOWLEDGEMENTS

Cheshire & Wirral Partnership NHS Trust

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ather 1985

Methods	Double blind RCT Concealment of allocation - unclear Analysis - n/a Active treatment - 6 weeks
Participants	Inclusion criteria 13+ HMD Age over 59 Country: UK Setting: hospital in or outpatients
Interventions	Trazodone Versus Amitriptyline versus Diazepam
Outcomes	Side effects 'Marked improvement assessed by physician' Drop out
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Ather 1985 *(Continued)*

Allocation concealment?	Unclear risk	B - Unclear

Bocksberger 1993

Methods	Double blind RCT. Concealment of allocation - unclear. Analysis: Endpoint Active treatment: 4 weeks
Participants	Inclusion criteria: DSM IIIR, Major Depression and 20+ MADRS Age: over 65 Country: Switzerland Setting: inpatient
Interventions	Fluvoxamine versus moclobemide
Outcomes	Side effects MADRS Drop out
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Brion 1996

Methods	Double blind RCT. Concealment of allocation - unclear. Analysis: Intent to treat Active treatment: 6 months
Participants	Inclusion criteria: DSM IIIR, Major Depression and 24+ MADRS Age: over 70 Country: France Setting: General Medicine
Interventions	Tianeptine versus mianserin
Outcomes	Side effects Drop out HMD MADRS
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

De Ronchi 1998

Methods	Double blind RCT. Concealment of allocation - unclear. Active treatment 10 weeks
Participants	Inclusion criteria: DSMIIIR major depressive disorder, HMD 16+. Age 60+ Country Italy Setting: Outpatients
Interventions	Fluoxetine versus amitriptyline
Outcomes	HMD Drop out
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Dorman 1991

Methods	Double blind RCT. Concealment of allocation - unclear. Analysis: Endpoint Active treatment: 6 weeks
Participants	Inclusion criteria: DSM IIIR, Unipolar Depression and 17+ HMD Age: over 65 Country: UK Setting: Outpatient
Interventions	Paroxetine versus mianserin
Outcomes	Side effects HMD Drop out
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Dunningham 1994

Methods	Double blind RCT. Concealment of allocation - unclear. Analysis: Not Applicable Active treatment: 6 weeks
Participants	Inclusion criteria: DSM IIIR, Major Depression and 18+ HMD

Dunningham 1994 *(Continued)*

	Age: over 60 Country: Brazil Setting: Outpatient
Interventions	Moclobemide versus imipramine
Outcomes	Side effects Drop out
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Eklund 1986

Methods	Double blind RCT Concealment of allocation - unclear Endpoint analysis Active treatment 4 weeks
Participants	Inclusion criteria: 17+ HMDR primary illness Age: 60-80 Country:Sweden /Netherlands Setting: unclear
Interventions	Mianserin versus Imipramine
Outcomes	Side effects Drop out HMD(21 item)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Falk 1989

Methods	Double blind RCT. Concealment of allocation - unclear. Analysis: Endpoint Active treatment: 6 weeks

Falk 1989 *(Continued)*

Participants	Inclusion criteria: DSM III, Major Depressive unipolar episode of at lease 4 weeks, and 20+ HMD (21 item) Age: over 62 Country: USA Setting: Outpatient
Interventions	Fluoxetine versus trazodone
Outcomes	Side effects HMD (21 item) Drop out
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Feighner 1985

Methods	Double blind RCT. Concealment of allocation - unclear. Analysis: Not applicable Active treatment: 6 weeks
Participants	Inclusion criteria: DSM IIIR, Major Depression of at least 1 month, 20+ HMD Age: over 61 Country: USA Setting: Outpatient
Interventions	Fluoxetine versus doxepin
Outcomes	Side effects Drop out
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Georgotas 1986

Methods	Double blind RCT. Concealment of allocation - unclear. Analysis: Endpoint Active treatment: 7 weeks
Participants	Inclusion criteria: RDC Major Depression and 16+ HMD Age: over 55 Country: USA

Georgotas 1986 *(Continued)*

	Setting: Outpatient
Interventions	Nortriptyline versus phenelzine
Outcomes	Side effects Drop out
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Geretsegger 1995

Methods	Double blind RCT. Concealment of allocation - unclear. Analysis: Endpoint Active treatment: 6 weeks
Participants	Inclusion criteria: DSM IIIR, Major Depression and 18+ HMD, inpatient for 3 weeks +, Age: over 65 Country: Germany & Austria Setting: Inpatient
Interventions	Paroxetine versus amitriptyline
Outcomes	Side effects HMD Drop out
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Guillibert 1989

Methods	Double blind RCT. Concealment of allocation - unclear. Analysis: Not applicable Active treatment: 6 weeks
Participants	Inclusion criteria: DSM IIIR, Major Depressive Disorder and 20+ HMD (21 item) (Washout responders declined if 20% reduction) Age: over 65 Country: France Setting: Outpatient
Interventions	Paroxetine versus clomipramine
Outcomes	Side effects

Guillibert 1989 *(Continued)*

	Drop out
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Gwirtsman 1983

Methods	Double blind RCT Concealment of allocation - unclear Analysis - n/a Active treatment 6 weeks
Participants	Inclusion criteria: DSM-III, Major Depression HDR 17+ Age: 55+ Country: USA Setting: unclear
Interventions	Maprotiline versus Doxepin
Outcomes	Side effects Drop out
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Halikas 1995

Methods	Double blind RCT. Concealment of allocation - unclear. Analysis: Endpoint Active treatment: 6 weeks
Participants	Inclusion criteria: DSM III, Major Depressive Episode and 17+ HMD (17 item) Age: Over 55 Country: USA Setting: Private psychiatric practice
Interventions	Mirtazapine versus trazodone placebo controlled
Outcomes	Side effects Drop out

Halikas 1995 *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Hoyberg 1996

Methods	Double blind RCT. Concealment of allocation - unclear. Analysis: Endpoint Active treatment: 6 weeks
Participants	Inclusion criteria: DSM IIIR, Major Depression and 18+ HMD (21 item) Age: over 55
Interventions	Mirtazapine versus Trazedone versus placebo
Outcomes	Side effects Drop out HMD MADRS
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Hutchinson 1991

Methods	Double blind RCT. Concealment of allocation - unclear. Analysis: Endpoint Active treatment: 6 weeks
Participants	Inclusion criteria: DSM IIIR, Major Depression and 18+ HMD (21 item) Age: over 65 Country: UK Setting: Primary Care
Interventions	Paroxetine versus amitriptyline
Outcomes	Side effects Drop out
Notes	

Risk of bias

Hutchinson 1991 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Katona 1999

Methods	Double blind RCT. Concealment of allocation - unclear. Analysis: Endpoint Active treatment: 8 weeks
Participants	Inclusion criteria: DSM IIIR, Major Depressive disorder or Dysthymia and 17+ HMD, Mini Mental State 21+ Age: Over 65 Country: Australia, Belgium, Brazil, France, Germany, Ireland & UK Setting: Inpatient + Outpatient
Interventions	Reboxetine versus imipramine
Outcomes	Side effects Drop out
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Kyle 1998

Methods	Double blind RCT. Concealment of allocation - unclear. Analysis: Endpoint Active treatment: 8 weeks
Participants	Inclusion criteria: DSM IIIR, Major Depressive disorder and 22+ MADRS Age: Over 65 Country: UK Setting: General Practice
Interventions	Clitalopram and amitriptyline
Outcomes	Side effects Drop out
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

La Pia 1992

Methods	Double blind RCT. Concealment of allocation - unclear. Analysis: Endpoint Active treatment: 6 weeks
Participants	Inclusion criteria: DSM IIIR, Major Depressive disorder and 18+ HMD (21 item) Age: 60-80 Country: Italy Setting: Inpatient + Outpatient
Interventions	Fluoxetine versus mianserin
Outcomes	Side effects Drop out HMD, GDS
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Mahapatra 1997

Methods	Double blind RCT. Concealment of allocation - unclear. Analysis: Intent to treat Active treatment: 6 weeks
Participants	Inclusion criteria: DSM IIIR, Major Depression, symptoms for 1 month + and 18+ HMD (21 item) minimum of 23 on Mini Mental State Examination Age: 64 - 87 Country: UK + Netherlands Setting: Inpatients, Outpatients day treatment centre patients
Interventions	Venlafaxine versus dothiepin
Outcomes	Side effects Drop out
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Mulsant 1998

Methods	Double blind RCT. Concealment of allocation - unclear.

Mulsant 1998 *(Continued)*

	Analysis: Intent to treat Active treatment: 12 weeks
Participants	Inclusion criteria: Major Depressive episode, and 15+ HMD (17 item) minimum of 15 plus on Mini Mental State Examination Age: 60+ Country: USA Setting: Inpatients + outpatients
Interventions	Nortiptyline versus Paroxetine
Outcomes	Drop out Side effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Nair 1995

Methods	Double blind RCT. Concealment of allocation - unclear. Analysis: Endpoint Active treatment: 7 weeks
Participants	Inclusion criteria: DSM IIIR, Major Depressive disorder and 17+ HMD (17 item) Age: Over 60 Country: Canada, Denmar & UK Setting: Unknown
Interventions	Moclobemide versus nortriptyline versus placebo
Outcomes	Side effects Drop out
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Navarro 2001

Methods	Single blind (doctor blind to treatment) RCT. Concealment of allocation - D Analysis: Modified Intent to treat Active treatment: 12 weeks
Participants	Inclusion criteria: Unipolar Major Depression DSM IV, HMD >20 minimum of 25 on Mini Mental State Examination

Navarro 2001 *(Continued)*

	Age: 60+ Country: Spain Setting: Inpatients, Outpatients
Interventions	Citalopram versus Nortriptyline
Outcomes	Drop out
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Nugent 1979

Methods	Double blind RCT Concealment of allocation: unclear Analysis: n/a Active treatment: 4 weeks
Participants	Inclusion criteria: depressive illness Age: 60+ Females Country: UK Setting Inpatients
Interventions	Viloxazine versus amitriptyline
Outcomes	Side effects Drop out Hamilton
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Pelicier 1993

Methods	Double blind RCT. Concealment of allocation - unclear. Analysis: Not applicable Active treatment: 5 weeks
Participants	Inclusion criteria: Reactive depression using Feighner criteria Age: over 60 Country: France Setting: Outpatient
Interventions	Paroxeting versus clomipramine

Pelicier 1993 *(Continued)*

Outcomes	Side effects Drop out
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Phanjoo 1991

Methods	Double blind RCT. Concealment of allocation - unclear. Analysis: Endpoint Active treatment: 6 weeks
Participants	Inclusion criteria: DSM IIIR, Major Depression and 30+ MADRS Age: over 65 Country: UK Setting: Inpatient + outpatients
Interventions	Fluvoxamine versus mianserin
Outcomes	Side effects Drop out
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Rahman 1991

Methods	Double blind RCT. Concealment of allocation - unclear. Analysis: Endpoint Active treatment: 6 weeks
Participants	Inclusion criteria: DSM IIIR, Major Depression and 30+ MADRS Age: over 65 Country: UK Setting: Inpatient
Interventions	Fluvoxamine versus dothiepin
Outcomes	Side effects Drop out
Notes	

Rahman 1991 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Scardigali 1982

Methods	Double blind RCT Concealment of allocation unclear Analysis n/a Active treatment: 4 weeks
Participants	Inclusion criteria: endogenous, reactive, involutional depression Age: 'elderly' Country: Italy Setting: unclear
Interventions	Mianserin versus trazodone versus nomifensine
Outcomes	Side effects Beck Self Rating Scale CGI
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Schweizer 1998

Methods	Double blind RCT. Concealment of allocation - unclear. Analysis: Endpoint Active treatment: 8 weeks
Participants	Inclusion criteria: DSM IIIR, Major Depressive disorder for minimum of 3 months, 18+ HMD Age: Over 65 Country: USA Setting: Primary care
Interventions	Buspirone versus imipramine
Outcomes	Side effects Drop out
Notes	

Risk of bias

Schweizer 1998 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Siegfried 1986

Methods	Double blind RCT Concealment of allocation - unclear Analysis: n/a Active treatment: 4 weeks
Participants	Inclusion criteria: DSM-III major depression single or recurrent, HDR 17+ Age: 65 + Country: Germany Setting: Combined inpatient old aged people's home and geriatric cline
Interventions	Maprotiline versus mianserin versis nomifensine
Outcomes	Side effects Drop out HDRS
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Smeraldi 1998

Methods	Double blind RCT. Concealment of allocation - unclear. Analysis: Endpoint Active treatment: 6 weeks
Participants	Inclusion criteria: DSM IIIR, Major Depressive disorder for at least 1 month and 22+ MADRS Age:Over 65 Country: Italy Setting: Geriatric Inpatients + Outpatients
Interventions	Venlafaxine versus clomipramine versus trazodone
Outcomes	Side effects Drop out
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Smeraldi 1998 *(Continued)*

Allocation concealment?	Unclear risk	B - Unclear

Tignol 1998

Methods	Double blind RCT. Concealment of allocation - unclear. Analysis: Endpoint Active treatment: 8 weeks
Participants	Inclusion criteria: DSM IIIR, Major Depressive disorder and 16+ HMD (17 item) Age: Over 65 Country: France Setting: Inpatient + Outpatient
Interventions	Milnacipran versus imipramine
Outcomes	Side effects Drop out
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ahlfors 1988	Mixed adult / aged population
Altamura 1989a	No extractable data
Altamura 1989b	No extractable data
Amore 2001	Mixed adult / aged population
Aslan 1986	No extractable data
Behnke 1992	Includes bipolar patients
Bjerre 1981	Dose-finding study
Bornstein 1979	Mixed adult / aged population
Botros 1989	Mixed adult / aged population
Branconnier 1983	No extractable data
Branconnier 1987	Mixed adult / aged population

Study	Reason for exclusion
Brodie 1975	Combination therapy
Burch 1983	Crossover study
Burke 1967	Mixed adult / aged population
Butters 2000	Not all patients depressed
Casacchia 1994	No extractable data
Cassano 1998	Includes bipolar patients
Cohn 1984	No extractable comparable data
Cohn 1990	Nomifensine + 1
Cohn 1991	No extractable comparable data
Dachary 1985	Mixed adult / aged population
De Leon 1977	Not elderly
De Vanna 1990	No extractable data
Delaunay 1978	Mixed adult / aged population
Dell'Agnello 2001	Open-label study
Dunner 1992	Re-analysis
Evans 1981	Mixed adult / aged population
Fabian 1999	Not all patients depressed
Fabre 1983	Only one active drug
Fairbairn 1989	No extractable data
Fairweather 1993	No extractable data
Feighner 1990	No extractable data
Finkel 1995	Sub-analysis of trial
Flicker 1998	No extractable comparable data
Forrest 1964	Mixed adult / aged population
Freed 1996	Mixed adult / aged population
Gattaz 1996	No extractable data
Gentili 1984	Includes bipolar patients
Gerner 1980	No extractable data

Study	Reason for exclusion
Goldstein 1982	Nomifensine + 1
Gonella 1990	Mixed adult / aged population
Green 1999	Not RCT
Haider 1968	Mixed adult / aged population
Harding 1973	Mixed adult / aged population
Hebenstreit 1988	Mixed adult / aged population
Hell 1994	Mixed adult / aged population
Hostmaelingen 1989	No extractable data
Jarvik 1982	Not RCT
Jessel 1981	No extractable data
Kane 1983	No extractable comparable data
Karlsson 2000	Mixed diagnosis
Katona 1999b	No extractable comparable data
Katona 1998	No extractable comparable data
Kerr 1984a	Mixed adult / aged population
Khan 1981	No extractable comparable data
Kivella 1987	Only one active drug
Koncevoj 1989	Includes patients with dementia
Koran 1995	Only one active drug
Laghrissie-Thode '95	No extractable data
Lapierre 1991	Includes bipolar patients
Lauritzen 1994	CCT Not RCT
Lauritzen 1996a	Mixed adult / aged population
Lauritzen 1996b	Mixed diagnosis
Lipsedge 1971	Mixed adult / aged population
Malsch 1996	Includes bipolar patients
Mamo 2000	No extractable comparable data
Marais 1974	Mixed adult / aged population

Study	Reason for exclusion
McEntee 1996	No extractable comparable data
Meignan-Debray 1990	Only one active drug
Meredith 1994	Nomifensine + 1
Middleton 1975	Not RCT
Moizeszowicz 1977	Dementia patients included
Moller 1993	Includes bipolar patients
Moller 2000	Mixed adult / aged population
Monteleone 1994	No extractable data
Montgomery 1981	No extractable data
Montgomery 1983	Not elderly
Murphy 1975b	Mixed adult / aged population
Murphy 2000	No extractable data
Nair 1993	No extractable data
Newhouse 1988	Not RCT
Newhouse 1996	No extractable data
Nielsen 1993	Mixed adult / aged population
Pancheri 1994	Includes bipolar patients
Poldinger 1982b	Mixed adult / aged population
Pollock 1998	No extractable comparable data
Rickels 1994c	Mixed adult / aged population
Robertson 1994	Mixed adult / aged population
Robinson 2000	Mixed adult / aged population
Roose 1987	Mixed adult / aged population
Roose 1994	Re-analysis
Roose 1998	Mixed adult / aged population
Rothblum 1982	Combination therapy
Sacchetti 1997	Mixed adult / aged population
Scarzella 1985	Not elderly

Study	Reason for exclusion
Schatzberg 2000	No extractable data
Schifano 1990	No extractable comparable data
Schiwy 1989a	Dose-finding study
Schiwy 1989b	Dose-finding study
Schneider 1998a	
Schneider 1998b	
Schone 1994	No extractable comparable data
Stanley 1998	No extractable data
Stewart 1968	Mixed adult / aged population
Stoppe 1998	No extractable data
Strik 1998	Mixed adult / aged population
Taragano 1997	Mixed diagnosis
Thayssen 1981	No comparative data
Tourigny-Rivard 1996	No extractable data
Volz 1995	Not elderly
Volz 1997a	Mixed adult / aged population
Von Bauer 1969	Mixed diagnosis
Waite 1986	No extractable data
Wakelin 1986	Re-analysis
Weber 2000	No extractable comparable data
Weihls 2000	No extractable comparable data
Weissman 1992	Combination therapy
Wilkins 1989	No extractable data
Zapletalek 1990	Mixed adult / aged population

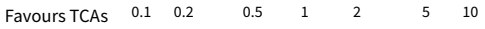
DATA AND ANALYSES

Comparison 1. All TCAs versus SSRIs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Failed to recover	9	1080	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.94, 1.22]
2 Depression severity (HAM-D Scale)	2	90	Mean Difference (IV, Random, 95% CI)	2.41 [-3.68, 8.50]
3 Withdrawal due to side-effects	12	1207	Risk Ratio (M-H, Random, 95% CI)	1.36 [1.09, 1.70]
4 Total withdrawal rates	14	1328	Risk Ratio (M-H, Random, 95% CI)	1.23 [1.05, 1.43]

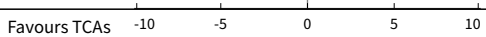
Analysis 1.1. Comparison 1 All TCAs versus SSRIs, Outcome 1 Failed to recover.

Study or subgroup	All TCAs n/N	SSRIs n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
De Ronchi 1998	15/33	16/32		6%	0.91[0.55,1.51]
Dorman 1991	23/28	15/29		9.48%	1.59[1.07,2.35]
Feighner 1985	41/79	40/78		14.27%	1.01[0.75,1.37]
Geretsegger 1995	29/47	22/44		10.35%	1.23[0.85,1.79]
Hutchinson 1991	13/32	26/58		6.06%	0.91[0.55,1.5]
Kyle 1998	87/186	83/179		22.2%	1.01[0.81,1.26]
Mulsant 1998	19/54	20/62		5.97%	1.09[0.65,1.82]
Navarro 2001	20/27	25/29		17.22%	0.86[0.66,1.12]
Pelicier 1993	26/42	18/41		8.44%	1.41[0.93,2.15]
Total (95% CI)	**528**	**552**		**100%**	**1.07[0.94,1.22]**
Total events: 273 (All TCAs), 265 (SSRIs)					
Heterogeneity: Tau²=0.01; Chi²=9.94, df=8(P=0.27); I²=19.55%					
Test for overall effect: Z=0.98(P=0.33)					



Analysis 1.2. Comparison 1 All TCAs versus SSRIs, Outcome 2 Depression severity (HAM-D Scale).

Study or subgroup	All TCAs N	Mean(SD)	SSRIs N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
De Ronchi 1998	33	13.9 (9.4)	32	14.2 (8.3)		57.15%	-0.28[-4.59,4.03]
Falk 1989	12	16.1 (8.5)	13	10.1 (7.6)		42.85%	6[-0.34,12.34]
Total ***	**45**		**45**			**100%**	**2.41[-3.68,8.5]**
Heterogeneity: Tau²=12.07; Chi²=2.58, df=1(P=0.11); I²=61.19%							
Test for overall effect: Z=0.78(P=0.44)							

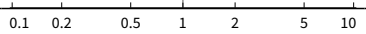


Analysis 1.3. Comparison 1 All TCAs versus SSRIs, Outcome 3 Withdrawal due to side-effects.

Study or subgroup	All TCAs n/N	SSRIs n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Hutchinson 1991	6/32	8/58		5.28%	1.36[0.52,3.57]
Falk 1989	4/13	2/14		2.13%	2.15[0.47,9.85]
Geretsegger 1995	6/47	5/44		3.98%	1.12[0.37,3.42]
Kyle 1998	48/186	31/179		30.47%	1.49[1,2.23]
La Pia 1992	3/20	0/20		0.59%	7[0.38,127.32]
Pelicier 1993	9/42	10/41		7.88%	0.88[0.4,1.94]
Dorman 1991	2/28	3/29		1.68%	0.69[0.12,3.83]
Feighner 1985	34/79	25/78		29.22%	1.34[0.89,2.02]
Guillibert 1989	5/39	3/40		2.66%	1.71[0.44,6.67]
Rahman 1991	2/26	2/26		1.39%	1[0.15,6.57]
Phanjoo 1991	4/25	7/25		4.1%	0.57[0.19,1.71]
Mulsant 1998	18/54	10/62		10.62%	2.07[1.05,4.09]
Total (95% CI)	**591**	**616**		**100%**	**1.36[1.09,1.7]**
Total events: 141 (All TCAs), 106 (SSRIs)					
Heterogeneity: Tau^2=0; Chi^2=7.73, df=11(P=0.74); I^2=0%					
Test for overall effect: Z=2.72(P=0.01)					

Analysis 1.4. Comparison 1 All TCAs versus SSRIs, Outcome 4 Total withdrawal rates.

Study or subgroup	All TCAs n/N	SSRIs n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Falk 1989	10/13	4/14		3.06%	2.69[1.12,6.49]
De Ronchi 1998	11/33	9/32		4.39%	1.19[0.57,2.47]
Dorman 1991	3/28	5/29		1.33%	0.62[0.16,2.36]
Feighner 1985	48/79	37/78		27.57%	1.28[0.96,1.72]
Geretsegger 1995	12/47	10/44		4.43%	1.12[0.54,2.33]
Guillibert 1989	12/39	9/40		4.29%	1.37[0.65,2.88]
Hutchinson 1991	11/32	12/58		4.91%	1.66[0.83,3.33]
Kyle 1998	56/186	44/179		20.83%	1.22[0.87,1.72]
La Pia 1992	4/20	1/20		0.54%	4[0.49,32.72]
Mulsant 1998	27/54	25/62		14.56%	1.24[0.83,1.86]
Navarro 2001	3/27	5/29		1.34%	0.64[0.17,2.44]
Pelicier 1993	10/42	12/41		4.57%	0.81[0.4,1.67]
Phanjoo 1991	10/25	9/25		4.71%	1.11[0.55,2.26]
Rahman 1991	7/26	9/26		3.49%	0.78[0.34,1.77]
Total (95% CI)	**651**	**677**		**100%**	**1.23[1.05,1.43]**
Total events: 224 (All TCAs), 191 (SSRIs)					
Heterogeneity: Tau^2=0; Chi^2=9.65, df=13(P=0.72); I^2=0%					
Test for overall effect: Z=2.61(P=0.01)					

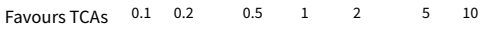


Comparison 2. All TCAs versus MAOIs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Failed to recover	2	121	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.74, 1.83]
2 Depression severity (HAM-D Scale)	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 Withdrawal due to side effects	2	121	Risk Ratio (M-H, Random, 95% CI)	2.27 [0.44, 11.81]
4 Total withdrawal rates	3	181	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.64, 1.29]

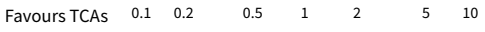
Analysis 2.1. Comparison 2 All TCAs versus MAOIs, Outcome 1 Failed to recover.

Study or subgroup	All TCAs n/N	MAOIs n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Georgotas 1986	13/25	11/22		65.19%	1.04[0.59,1.83]
Nair 1995	12/38	8/36		34.81%	1.42[0.66,3.07]
Total (95% CI)	**63**	**58**		**100%**	**1.16[0.74,1.83]**
Total events: 25 (All TCAs), 19 (MAOIs)					
Heterogeneity: Tau^2=0; Chi^2=0.43, df=1(P=0.51); I^2=0%					
Test for overall effect: Z=0.64(P=0.52)					



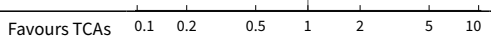
Analysis 2.3. Comparison 2 All TCAs versus MAOIs, Outcome 3 Withdrawal due to side effects.

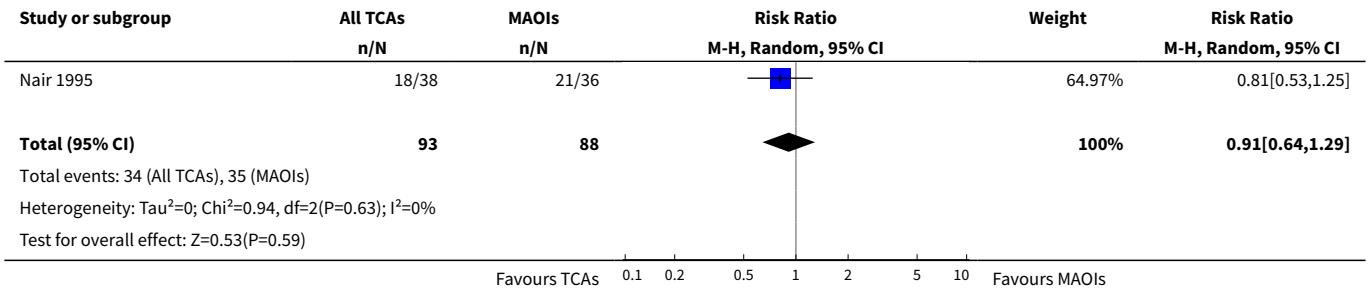
Study or subgroup	All TCAs n/N	MAOIs n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Georgotas 1986	2/25	2/22		43.58%	0.88[0.14,5.73]
Nair 1995	10/38	2/36		56.42%	4.74[1.11,20.16]
Total (95% CI)	**63**	**58**		**100%**	**2.27[0.44,11.81]**
Total events: 12 (All TCAs), 4 (MAOIs)					
Heterogeneity: Tau^2=0.71; Chi^2=1.97, df=1(P=0.16); I^2=49.13%					
Test for overall effect: Z=0.98(P=0.33)					



Analysis 2.4. Comparison 2 All TCAs versus MAOIs, Outcome 4 Total withdrawal rates.

Study or subgroup	All TCAs n/N	MAOIs n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Dunningham 1994	12/30	10/30		27.33%	1.2[0.61,2.34]
Georgotas 1986	4/25	4/22		7.69%	0.88[0.25,3.11]

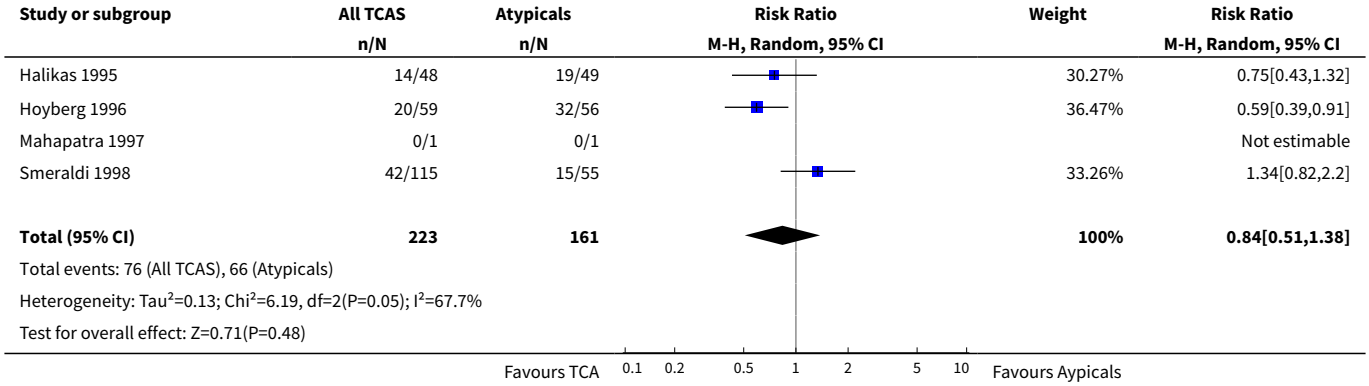




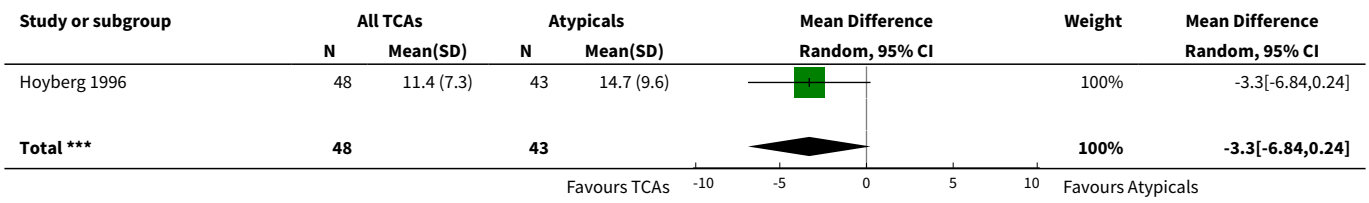
Comparison 3. All TCAs versus Atypicals

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Failed to recover	4	384	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.51, 1.38]
2 Depression severity (HAM-D Scale)	1	91	Mean Difference (IV, Random, 95% CI)	-3.30 [-6.84, 0.24]
3 Withdrawal due to side effects	8	1456	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.96, 1.94]
4 Total withdrawal rates	8	1457	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.75, 1.24]

Analysis 3.1. Comparison 3 All TCAs versus Atypicals, Outcome 1 Failed to recover.



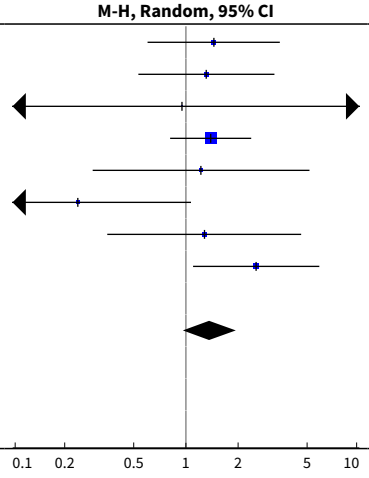
Analysis 3.2. Comparison 3 All TCAs versus Atypicals, Outcome 2 Depression severity (HAM-D Scale).



Study or subgroup	All TCAs N	All TCAs Mean(SD)	Atypicals N	Atypicals Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%							
Test for overall effect: Z=1.83(P=0.07)							

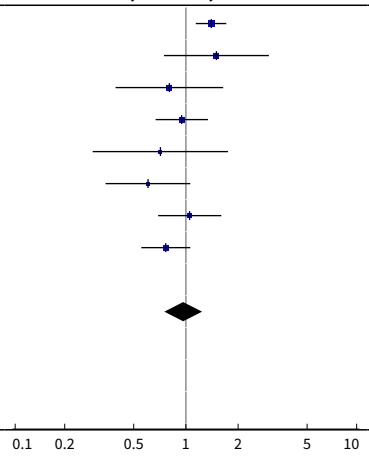
Analysis 3.3. Comparison 3 All TCAs versus Atypicals, Outcome 3 Withdrawal due to side effects.

Study or subgroup	All TCAs n/N	Atypicals n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Brion 1996	8/100	11/199		14.83%	1.45[0.6,3.48]
Halikas 1995	9/48	7/49		14.06%	1.31[0.53,3.24]
Hoyberg 1996	1/59	1/56		1.62%	0.95[0.06,14.81]
Katona 1999	27/171	20/176		35.09%	1.39[0.81,2.38]
Mahapatra 1997	4/48	3/44		5.79%	1.22[0.29,5.16]
Schweizer 1998	2/60	8/57		5.3%	0.24[0.05,1.07]
Smeraldi 1998	8/115	3/55		7.19%	1.28[0.35,4.62]
Tignol 1998	17/107	7/112		16.12%	2.54[1.1,5.88]
Total (95% CI)	**708**	**748**		**100%**	**1.36[0.96,1.94]**
Total events: 76 (All TCAs), 60 (Atypicals)					
Heterogeneity: Tau²=0.02; Chi²=7.44, df=7(P=0.38); I²=5.92%					
Test for overall effect: Z=1.73(P=0.08)					



Analysis 3.4. Comparison 3 All TCAs versus Atypicals, Outcome 4 Total withdrawal rates.

Study or subgroup	All TCAs n/N	Atypicals n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Brion 1996	66/100	94/199		20.24%	1.4[1.14,1.71]
Halikas 1995	15/49	10/49		8.3%	1.5[0.75,3.01]
Hoyberg 1996	11/59	13/56		8.01%	0.8[0.39,1.64]
Katona 1999	45/171	49/176		16.14%	0.95[0.67,1.34]
Mahapatra 1997	7/48	9/44		5.79%	0.71[0.29,1.75]
Schweizer 1998	14/60	22/57		10.66%	0.6[0.34,1.06]
Smeraldi 1998	44/115	20/55		14.07%	1.05[0.69,1.6]
Tignol 1998	38/107	52/112		16.78%	0.76[0.55,1.06]
Total (95% CI)	**709**	**748**		**100%**	**0.96[0.75,1.24]**
Total events: 240 (All TCAs), 269 (Atypicals)					
Heterogeneity: Tau²=0.07; Chi²=18.18, df=7(P=0.01); I²=61.51%					
Test for overall effect: Z=0.29(P=0.78)					

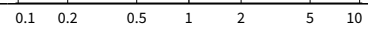


Comparison 4. SSRIs versus MAOIs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Failed to recover	1	40	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.55, 1.20]
3 Withdrawal due to side effects	1	40	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Total withdrawal rates	1	40	Risk Ratio (M-H, Random, 95% CI)	2.0 [0.20, 20.33]

Analysis 4.1. Comparison 4 SSRIs versus MAOIs, Outcome 1 Failed to recover.

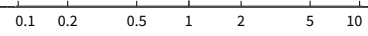
Study or subgroup	SSRIs n/N	MAOIs n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Bocksberger 1993	13/20	16/20		100%	0.81[0.55,1.2]
Total (95% CI)	**20**	**20**		**100%**	**0.81[0.55,1.2]**
Total events: 13 (SSRIs), 16 (MAOIs)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.05(P=0.3)					



Favours SSRIs — Favours MAOIs

Analysis 4.3. Comparison 4 SSRIs versus MAOIs, Outcome 3 Withdrawal due to side effects.

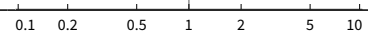
Study or subgroup	SSRIS n/N	MAOIs n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Bocksberger 1993	0/20	0/20			Not estimable
Total (95% CI)	**20**	**20**			**Not estimable**
Total events: 0 (SSRIS), 0 (MAOIs)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



Favours SSRIs — Favours MAOIs

Analysis 4.4. Comparison 4 SSRIs versus MAOIs, Outcome 4 Total withdrawal rates.

Study or subgroup	SSRIs n/N	MAOIs n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Bocksberger 1993	2/20	1/20		100%	2[0.2,20.33]
Total (95% CI)	**20**	**20**		**100%**	**2[0.2,20.33]**
Total events: 2 (SSRIs), 1 (MAOIs)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.59(P=0.56)					



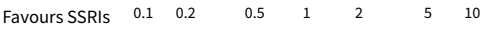
Favours SSRIs — Favours MAOIs

Comparison 5. Classical TCAs versus SSRIs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Failed to recover	7	790	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.93, 1.24]
2 Depression severity (HAM-D Scale)	1	45	Mean Difference (IV, Random, 95% CI)	0.28 [-4.92, 5.48]
3 Withdrawal due to side effects	8	1033	Risk Ratio (M-H, Random, 95% CI)	1.40 [1.11, 1.77]
4 Total withdrawal rates	10	1154	Risk Ratio (M-H, Random, 95% CI)	1.24 [1.05, 1.46]

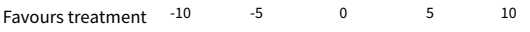
Analysis 5.1. Comparison 5 Classical TCAs versus SSRIs, Outcome 1 Failed to recover.

Study or subgroup	Classical TCAs n/N	SSRIs n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Feighner 1985	41/79	40/78		22.49%	1.01[0.75,1.37]
Geretsegger 1995	29/47	22/44		14.97%	1.23[0.85,1.79]
Hutchinson 1991	13/32	26/58		8.04%	0.91[0.55,1.5]
Kyle 1998	87/186	83/179		42.76%	1.01[0.81,1.26]
Mulsant 1998	0/1	0/1			Not estimable
Navarro 2001	0/1	0/1			Not estimable
Pelicier 1993	26/42	18/41		11.74%	1.41[0.93,2.15]
Total (95% CI)	**388**	**402**		**100%**	**1.07[0.93,1.24]**
Total events: 196 (Classical TCAs), 189 (SSRIs)					
Heterogeneity: Tau^2=0; Chi^2=3.05, df=4(P=0.55); I^2=0%					
Test for overall effect: Z=0.96(P=0.34)					

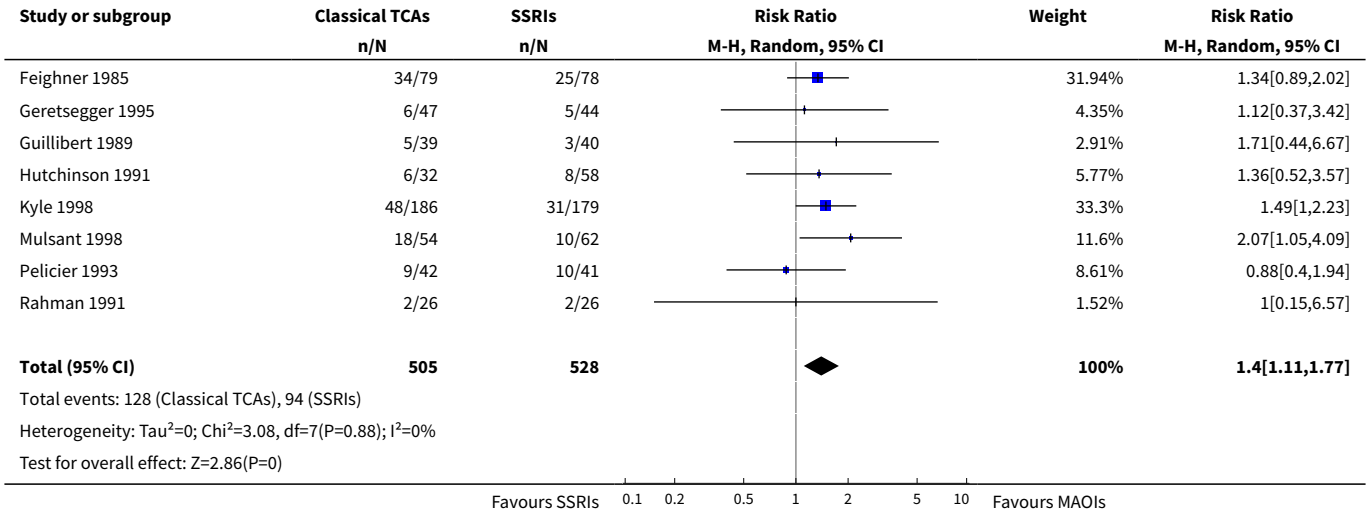


Analysis 5.2. Comparison 5 Classical TCAs versus SSRIs, Outcome 2 Depression severity (HAM-D Scale).

Study or subgroup	Classical TCAs N	Classical TCAs Mean(SD)	SSRIs N	SSRIs Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
De Ronchi 1998	23	14.2 (8.3)	22	13.9 (9.4)		100%	0.28[-4.92,5.48]
Total ***	**23**		**22**			**100%**	**0.28[-4.92,5.48]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.11(P=0.92)							

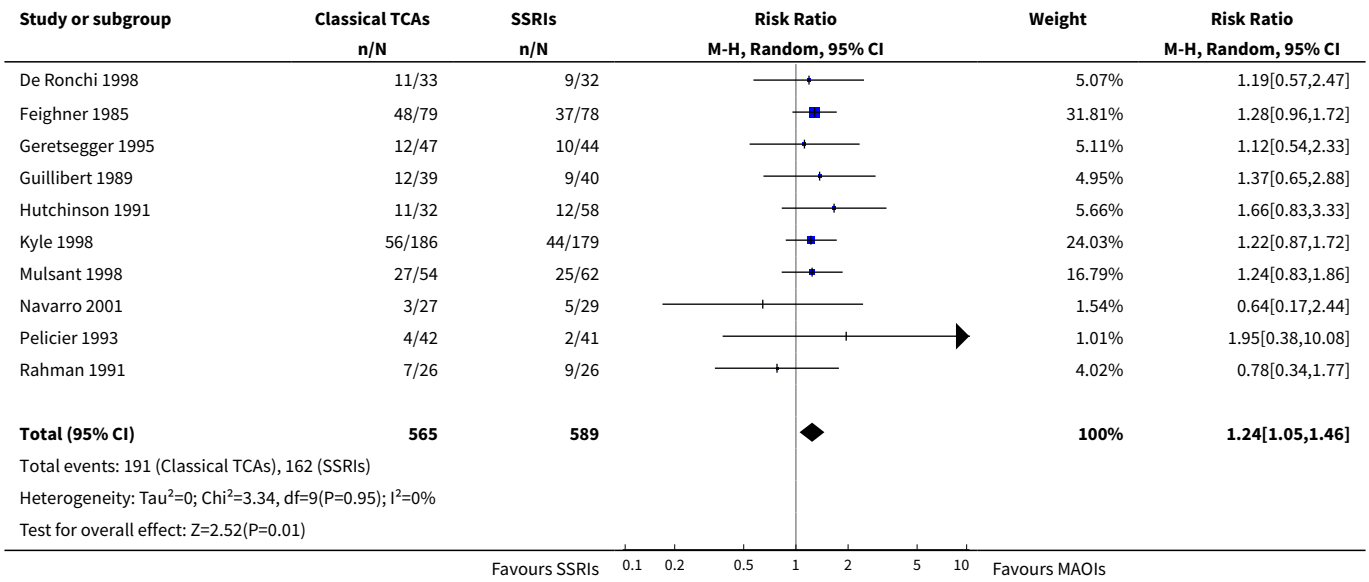


Analysis 5.3. Comparison 5 Classical TCAs versus SSRIs, Outcome 3 Withdrawal due to side effects.



Study or subgroup	Classical TCAs n/N	SSRIs n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Feighner 1985	34/79	25/78		31.94%	1.34[0.89,2.02]
Geretsegger 1995	6/47	5/44		4.35%	1.12[0.37,3.42]
Guillibert 1989	5/39	3/40		2.91%	1.71[0.44,6.67]
Hutchinson 1991	6/32	8/58		5.77%	1.36[0.52,3.57]
Kyle 1998	48/186	31/179		33.3%	1.49[1,2.23]
Mulsant 1998	18/54	10/62		11.6%	2.07[1.05,4.09]
Pelicier 1993	9/42	10/41		8.61%	0.88[0.4,1.94]
Rahman 1991	2/26	2/26		1.52%	1[0.15,6.57]
Total (95% CI)	**505**	**528**		**100%**	**1.4[1.11,1.77]**
Total events: 128 (Classical TCAs), 94 (SSRIs)					
Heterogeneity: Tau^2=0; Chi^2=3.08, df=7(P=0.88); I^2=0%					
Test for overall effect: Z=2.86(P=0)					

Analysis 5.4. Comparison 5 Classical TCAs versus SSRIs, Outcome 4 Total withdrawal rates.



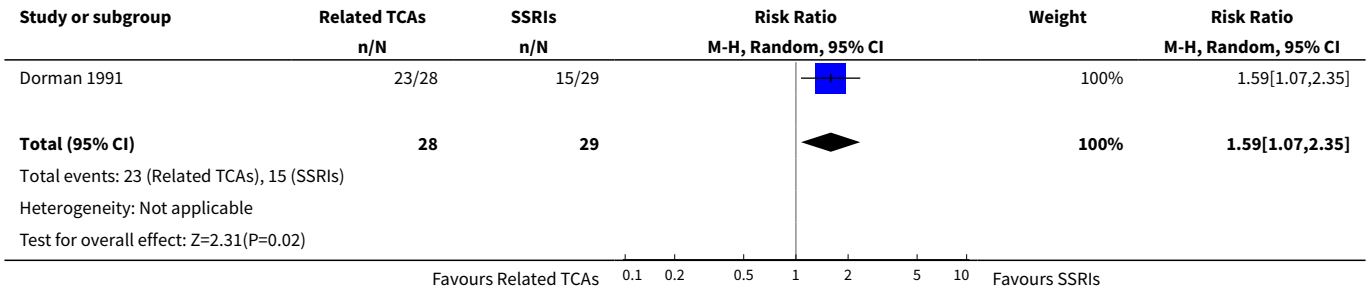
Study or subgroup	Classical TCAs n/N	SSRIs n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
De Ronchi 1998	11/33	9/32		5.07%	1.19[0.57,2.47]
Feighner 1985	48/79	37/78		31.81%	1.28[0.96,1.72]
Geretsegger 1995	12/47	10/44		5.11%	1.12[0.54,2.33]
Guillibert 1989	12/39	9/40		4.95%	1.37[0.65,2.88]
Hutchinson 1991	11/32	12/58		5.66%	1.66[0.83,3.33]
Kyle 1998	56/186	44/179		24.03%	1.22[0.87,1.72]
Mulsant 1998	27/54	25/62		16.79%	1.24[0.83,1.86]
Navarro 2001	3/27	5/29		1.54%	0.64[0.17,2.44]
Pelicier 1993	4/42	2/41		1.01%	1.95[0.38,10.08]
Rahman 1991	7/26	9/26		4.02%	0.78[0.34,1.77]
Total (95% CI)	**565**	**589**		**100%**	**1.24[1.05,1.46]**
Total events: 191 (Classical TCAs), 162 (SSRIs)					
Heterogeneity: Tau^2=0; Chi^2=3.34, df=9(P=0.95); I^2=0%					
Test for overall effect: Z=2.52(P=0.01)					

Comparison 6. Related TCAs versus SSRIs

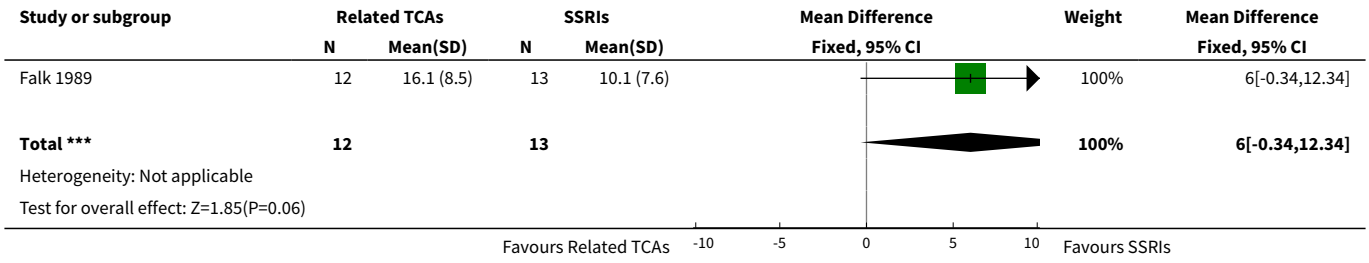
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Failed to recover	1	57	Risk Ratio (M-H, Random, 95% CI)	1.59 [1.07, 2.35]
2 Depression severity (HAM-D Scale)	1	25	Mean Difference (IV, Fixed, 95% CI)	6.00 [-0.34, 12.34]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Withdrawal due to side effects	4	174	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.43, 2.70]
4 Total withdrawal rates	4	174	Risk Ratio (M-H, Random, 95% CI)	1.49 [0.74, 2.98]

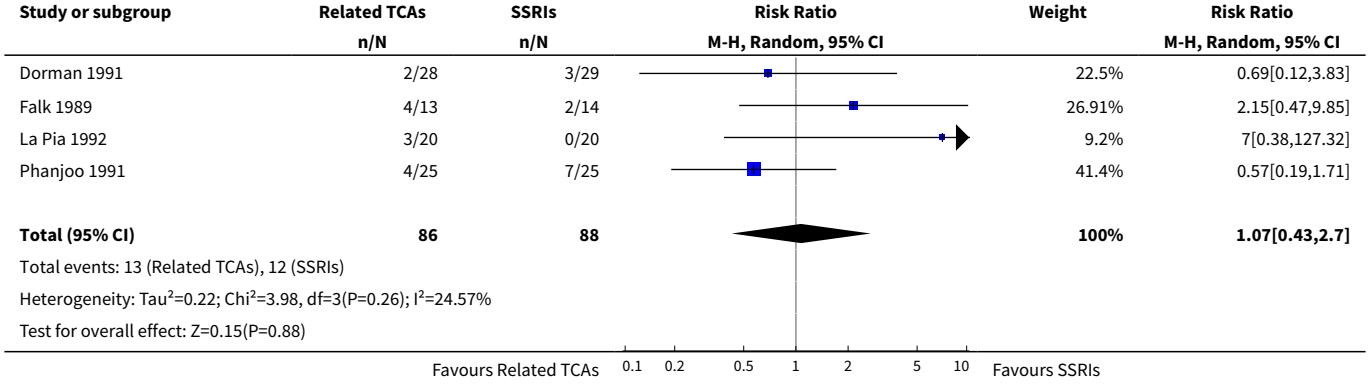
Analysis 6.1. Comparison 6 Related TCAs versus SSRIs, Outcome 1 Failed to recover.



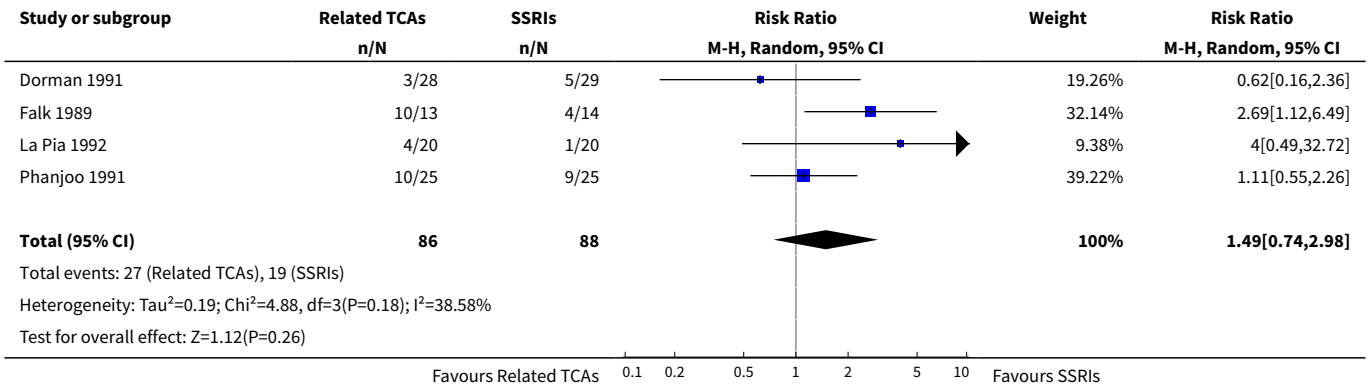
Analysis 6.2. Comparison 6 Related TCAs versus SSRIs, Outcome 2 Depression severity (HAM-D Scale).



Analysis 6.3. Comparison 6 Related TCAs versus SSRIs, Outcome 3 Withdrawal due to side effects.



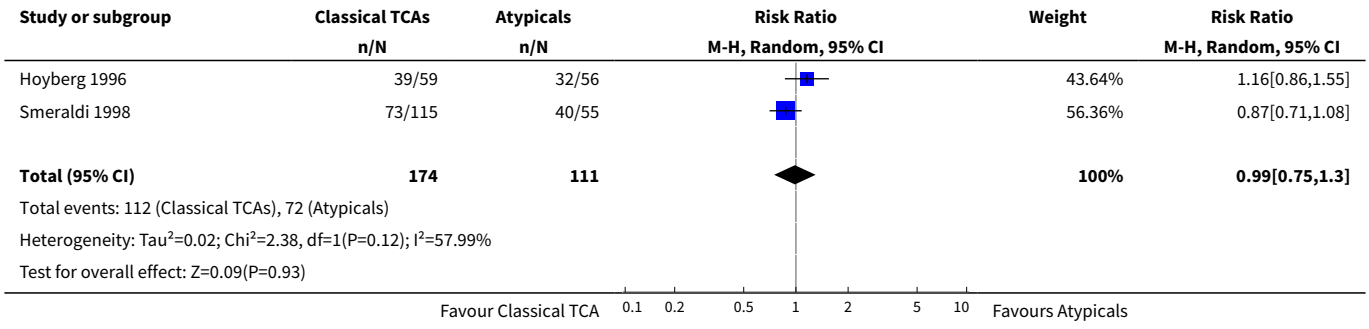
Analysis 6.4. Comparison 6 Related TCAs versus SSRIs, Outcome 4 Total withdrawal rates.



Comparison 7. Classical TCAs versus Atypicals

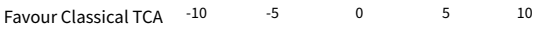
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Failed to recover	2	285	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.75, 1.30]
2 Depression severity (HAM-D Scale)	1	91	Mean Difference (IV, Fixed, 95% CI)	-3.30 [-6.84, 0.24]
3 Withdrawal due to side effects	6	1060	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.73, 2.22]
4 Total withdrawal rates	6	1060	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.70, 1.01]

Analysis 7.1. Comparison 7 Classical TCAs versus Atypicals, Outcome 1 Failed to recover.



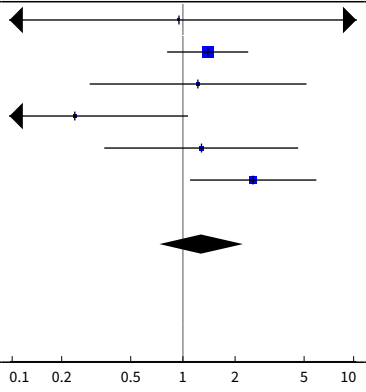
Analysis 7.2. Comparison 7 Classical TCAs versus Atypicals, Outcome 2 Depression severity (HAM-D Scale).

Study or subgroup	Classical TCAs N	Classical TCAs Mean(SD)	Atypicals N	Atypicals Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Hoyberg 1996	48	11.4 (7.3)	43	14.7 (9.6)		100%	-3.3[-6.84,0.24]
Total ***	**48**		**43**			**100%**	**-3.3[-6.84,0.24]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%							
Test for overall effect: Z=1.83(P=0.07)							



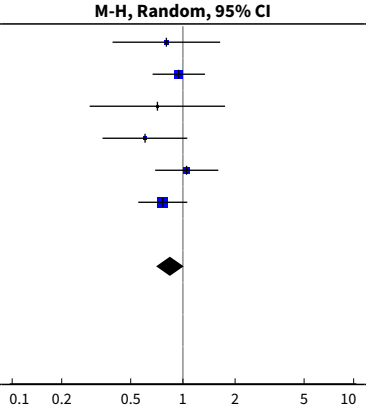
Analysis 7.3. Comparison 7 Classical TCAs versus Atypicals, Outcome 3 Withdrawal due to side effects.

Study or subgroup	Classical TCAs n/N	Atypicals n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Hoyberg 1996	1/59	1/56		3.78%	0.95[0.06,14.81]
Katona 1999	27/171	20/176		35.81%	1.39[0.81,2.38]
Mahapatra 1997	4/48	3/44		11.63%	1.22[0.29,5.16]
Schweizer 1998	2/60	8/57		10.83%	0.24[0.05,1.07]
Smeraldi 1998	8/115	3/55		13.81%	1.28[0.35,4.62]
Tignol 1998	17/107	7/112		24.14%	2.54[1.1,5.88]
Total (95% CI)	**560**	**500**		**100%**	**1.27[0.73,2.22]**
Total events: 59 (Classical TCAs), 42 (Atypicals)					
Heterogeneity: Tau²=0.15; Chi²=7.43, df=5(P=0.19); I²=32.67%					
Test for overall effect: Z=0.86(P=0.39)					



Analysis 7.4. Comparison 7 Classical TCAs versus Atypicals, Outcome 4 Total withdrawal rates.

Study or subgroup	Classical TCAs n/N	Atypicals n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Hoyberg 1996	11/59	13/56		6.54%	0.8[0.39,1.64]
Katona 1999	45/171	49/176		27.96%	0.95[0.67,1.34]
Mahapatra 1997	7/48	9/44		4.13%	0.71[0.29,1.75]
Schweizer 1998	14/60	22/57		10.52%	0.6[0.34,1.06]
Smeraldi 1998	44/115	20/55		18.97%	1.05[0.69,1.6]
Tignol 1998	38/107	52/112		31.89%	0.76[0.55,1.06]
Total (95% CI)	**560**	**500**		**100%**	**0.84[0.7,1.01]**
Total events: 159 (Classical TCAs), 165 (Atypicals)					
Heterogeneity: Tau²=0; Chi²=3.33, df=5(P=0.65); I²=0%					
Test for overall effect: Z=1.85(P=0.06)					

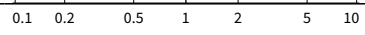


Comparison 8. Related TCAs versus Atypicals

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Failed to recover	1	97	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.35, 1.18]
2 Withdrawal due to side effects	2	396	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.74, 2.59]
3 Total withdrawal rates	2	397	Risk Ratio (M-H, Random, 95% CI)	1.41 [1.16, 1.71]

Analysis 8.1. Comparison 8 Related TCAs versus Atypicals, Outcome 1 Failed to recover.

Study or subgroup	Related TCAs n/N	Atypicals n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Halikas 1995	12/48	19/49		100%	0.64[0.35,1.18]
Total (95% CI)	**48**	**49**		**100%**	**0.64[0.35,1.18]**
Total events: 12 (Related TCAs), 19 (Atypicals)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.43(P=0.15)					

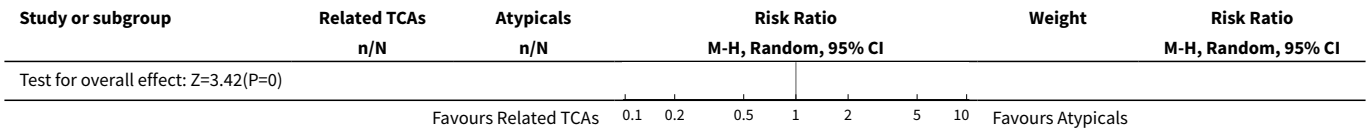


Analysis 8.2. Comparison 8 Related TCAs versus Atypicals, Outcome 2 Withdrawal due to side effects.

Study or subgroup	Related TCAs n/N	Atypicals n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Brion 1996	8/100	11/199		51.43%	1.45[0.6,3.48]
Halikas 1995	9/48	7/49		48.57%	1.31[0.53,3.24]
Total (95% CI)	**148**	**248**		**100%**	**1.38[0.74,2.59]**
Total events: 17 (Related TCAs), 18 (Atypicals)					
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.88); I^2=0%					
Test for overall effect: Z=1(P=0.32)					

Analysis 8.3. Comparison 8 Related TCAs versus Atypicals, Outcome 3 Total withdrawal rates.

Study or subgroup	Related TCAs n/N	Atypicals n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Brion 1996	66/100	94/199		92.12%	1.4[1.14,1.71]
Halikas 1995	15/49	10/49		7.88%	1.5[0.75,3.01]
Total (95% CI)	**149**	**248**		**100%**	**1.41[1.16,1.71]**
Total events: 81 (Related TCAs), 104 (Atypicals)					
Heterogeneity: Tau^2=0; Chi^2=0.04, df=1(P=0.84); I^2=0%					



ADDITIONAL TABLES

Table 1. Antidepressant dosage

Antidepressant	Fixed Dose (daily)	Varying Dose (daily)
Amitriptyline	Nugent 1979 (150mgs). Hutchinson 1991 (100mgs)	Hoyberg 1996 (upto 90mgs). Ather 1985 (up to 150mgs). Geretsegger 1995 (up to 150mgs). Kyle 1998 (up to 100mgs)
Citalopram		Kyle 1998 (up to 40mgs)
Clomipramine	Guillibert 1989 (75mgs). Pelicier 1993 (60mgs)	Smeraldi 1998 (up to 100mgs)
Dothiepin		Rahman 1991 (up to 200mgs)
Doxepin		Feighner 1985 (up to 200mgs). Gwitsman 1983 (30-100mgs/ml). Mahapatra 1997 (up to 150mgs)
Fluoxetine	La Pia 1992 (20mgs)	
Fluvoxamine		Bocksberger 1993 (up to 100mgs daily). Rahman 1991 (up to 200mgs daily)
Imipramine		Dunningham 1994 (50-200mgs). Eklund 1986 (50-100mgs). Katona 1999 (50-100mgs).
Mianserin	Brion 1996 (30mgs). La Pia (40mgs). Scadigali 1982 (60mgs)	Eklund 1986 (50-60mgs)
Mirtzpapine		Halikas 1995 (5-35mgs)
Moclobemide		Bocksberger 1993 (up to 300mgs) Dunningham 1994 (up to 450mgs).
Nomifensine	Scardigali 1982 (150mgs)	
Nortripyline		Georgotas 1986 (50-180ng/ml)
Paroxetine	Dorman 1991 (30mgs). Guillibert 1989 (30mgs). Pellicier 1993 (20mgs). Hutchinson 1991 (30mgs)	Geretsegger 1995 (up to 30mgs)
Phenelzine		Georgotas 1986 (70% MAOI inhibition rate)
Trazadone		Ather 1985 (100-300mgs). Falk 1989 (up to 400mgs). Halikas 1995 (40-280mgs). Smeraldi 1998 (up to 300mgs)

Table 1. Antidepressant dosage *(Continued)*

Venlafaxine		Mahapatra 1997 (up to 150mgs)
Viloxazine	Nugent 1979 (300mgs)	

Table 2. Patient side effect event ratios by drug class

System	Classical TCAs	SSRIs	Classical TCAs	Related TCAs
CVS	10:<1	10:<1	10:1.1	10:1.4
GIT	10:4.6	10:2.9	10:4.1	10:4.1
Neuropsych	10:4.1	10:2.3	10:7.4	10:6.5
Dermatological	10:<1	10:<1	10:1	10:<1

WHAT'S NEW

Date	Event	Description
1 November 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 4, 1999
Review first published: Issue 1, 2006

Date	Event	Description
15 February 2006	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Mottram PG, searching, reviewing, data extraction, statistics, writing
Wilson KCM, reviewing, data extraction, writing
Strobl J, reviewing and data extraction

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- Cheshire & Wirral Partnership NHS Trust R&D Funding, UK.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Antidepressive Agents [*therapeutic use]; Antidepressive Agents, Tricyclic [therapeutic use]; Depression [*drug therapy]; Randomized Controlled Trials as Topic; Serotonin Uptake Inhibitors [therapeutic use]; Treatment Refusal

MeSH check words

Aged; Aged, 80 and over; Humans; Middle Aged