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Depression in adults: drug and physical treatments

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ABSTRACT

INTRODUCTION: Depression may affect up to 10% of the population, with half of affected people having recurrence of their symptoms. In mild to moderate depression, there is no reliable evidence that any one treatment is superior in improving symptoms of depression, but the strength of evidence supporting different treatments varies. In severe depression, only prescription antidepressants and electroconvulsive therapy are known to improve symptoms. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of treatments in mild to moderate and severe depression, and in treatment-resistant depression? Which interventions reduce relapse rates? We searched: Medline, Embase, The Cochrane Library, and other important databases up to June 2009 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 88 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: antidepressant drugs (tricyclic antidepressants [including low-dose tricyclic antidepressants], selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, or venlafaxine), continuing prescription antidepressant drugs, electroconvulsive therapy, exercise, lithium augmentation, pindolol augmentation, and St John's wort.

QUESTIONS

INTERVENTIONS

DRUG AND PHYSICAL TREATMENTS IN MILD TO MODERATE OR SEVERE DEPRESSION

Beneficial

Likely to be beneficial

Unknown effectiveness

INTERVENTIONS IN TREATMENT-RESISTANT DEPRESSION

Unknown effectiveness

REDUCING RELAPSE RATES

Beneficial

Covered elsewhere in Clinical Evidence

Depression in adults: psychological treatments and care pathways

Postnatal depression

To be covered in future updates

Treatments for depression in people with a physical illness

Agomelatine

Desvenlafaxine

Key points

- Depression may affect up to 10% of the population, with half of affected people having recurrence of their symptoms.
- In mild to moderate depression, there is no reliable evidence that any one treatment is superior in improving symptoms of depression, but the strength of evidence supporting different treatments varies.

  In severe depression, only prescription antidepressants and electroconvulsive treatment are known to improve symptoms.

- Tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors, and venlafaxine improve symptoms in the short term. However, long-term studies are lacking.

  No one class or individual antidepressant has been shown to be more effective than the others in the short term, but adverse effects vary between classes.

  St John's wort may have similar efficacy compared with antidepressants, but preparations vary and drug interactions can occur.

  We don't know if exercise is beneficial in people with mild to moderate depression.

- CAUTION: Some antidepressants may induce or worsen suicidal ideation and behaviour, and agitation after initiation of treatment.
- We don't know whether adding lithium or pindolol to other antidepressant drugs reduces symptoms in people with treatment-resistant depression.
- Continuing prescription antidepressant drugs reduces the risk of relapse after recovery.

DEFINITION

Depressive disorders are characterised by persistent low mood, loss of interest and enjoyment, and reduced energy. They often impair day to day functioning. Most RCTs assessed in this review classify depression using the *Diagnostic and statistical manual of mental disorders* (DSM-IV) [1] or the *International classification of mental and behavioural disorders* (ICD-10). [2] DSM-IV divides depression into major depressive disorder or dysthymic disorder. **Major depressive disorder** is characterised by one or more major depressive episodes (i.e., at least 2 weeks of depressed mood or loss of interest accompanied by at least 4 additional symptoms of depression). **Dysthymic disorder** is characterised by at least 2 years of depressed mood for more days than not, accompanied by additional symptoms that do not reach the criteria for major depressive disorder. [1] ICD-10 divides depression into mild to moderate or severe depressive episodes. [2] Mild to moderate depression is characterised by depressive symptoms and some functional impairment. Severe depression is characterised by additional agitation or psychomotor retardation with marked somatic symptoms. [2] **Treatment-resistant depression** is defined as an absence of clinical response to treatment with a tricyclic antidepressant at a minimum dose of 150 mg daily of imipramine (or equivalent drug) for 4 to 6 weeks. [3] In this review, we use both DSM-IV and ICD-10 classifications, but treatments are considered to have been assessed in severe depression if the RCT included inpatients. **Older adults:** Older adults are generally defined as people aged 65 years or older. However, some of the RCTs of older people in this review included people aged 55 years or over. The presentation of depression in older adults may be atypical: low mood may be masked and anxiety or memory impairment may be the principal presenting symptoms. Dementia should be considered in the differential diagnosis of depression in older adults. [4] **Treating depressive disorders in adults:** Depressive disorders are generally treated with a range of drug, physical, and psychological treatments. For coverage of psychological treatments (including drug treatments *v* psychological treatments) and for coverage of combined drug and psychological treatment, see review on depression in adults: psychological treatments and care pathways. **Population:** This review does not cover intervention in women with depression in pregnancy, seasonal affective disorder, or depression owing to a physical illness such as stroke or substance abuse. See separate review on treatment of postnatal depression.

INCIDENCE/ PREVALENCE

Depressive disorders are common, with a prevalence of major depression between 5% and 10% of people seen in primary care settings. [5] Two to three times as many people may have depressive symptoms but do not meet DSM-IV criteria for major depression. Women are affected twice as often as men. Depressive disorders are the fourth most important cause of disability worldwide, and are expected to become the second most important by 2020. [6] [7] **Older adults:** Between 10% and 15% of older people have depressive symptoms, although major depression is relatively rare in older adults. [8]

AETIOLOGY/ RISK FACTORS

The causes of depression are uncertain, but are thought to include both childhood events and current psychosocial adversity. Studies suggest that genetic factors may also be important, indicating that several chromosomal regions may be involved. However, phenotypes do not seem to exhibit classic Mendelian inheritance. Psychiatric research has also focused on the role that psychosocial factors, such as social context and personality dimensions, have in depression. Many theories emphasise the importance of temperament (differences in the adaptive systems), which can increase vulnerability to mood disturbances. Impairment in social relationships, gender, socioeconomic status, and dysfunctional cognition may also have a role. It seems that integrative models, which take into account the interaction of biological and social variables, offer the most reliable way to approach the complex aetiology of depression.

PROGNOSIS

About half of people suffering a first episode of major depressive disorder experience further symptoms in the next 10 years. [9] **Older adults:** One systematic review (search date 1996, 12

prospective cohort studies, 1268 people, mean age 60 years) found that the prognosis may be especially poor in older people with a chronic or relapsing course of depression. [10] Another systematic review (search date 1999, 23 prospective cohort studies in people aged 65 years and over, including 5 identified by the first review) found that depression in older people was associated with increased mortality (15 studies; pooled OR 1.73, 95% CI 1.53 to 1.95). [11]

AIMS OF INTERVENTION

To improve mood, social and occupational functioning, and quality of life; to reduce morbidity and mortality; to prevent recurrence of depressive disorder; and to minimise adverse effects of treatment.

OUTCOMES

Symptom severity: Depressive symptoms rated by the depressed person and clinician (whether measured by dichotomous outcomes or continuous outcomes); social functioning; occupational functioning. **Quality of life**. **Admission to hospital**. **Rates of self harm**. **Relapse rates:** Relapse of depressive symptoms. **Adverse events**. RCTs often use continuous scales to measure depressive symptoms (such as the Hamilton Depression Rating Scale [HAM-D] and the Clinical Global Impression Scale [CGI]). A reduction in score of 50% or more on the HAM-D or a CGI score of 1 (very much improved) or 2 (much improved) is generally considered a clinically important response to treatment. Many RCTs express results in terms of effect size. **Older adults:** The HAM-D is not ideal for older people because it includes several somatic items that may be positive in older people who are not depressed. It has been the most widely used scale, although specific scales for older people (such as the Geriatric Depression Scale [GDS]) avoid somatic items.

METHODS

Clinical Evidence search and appraisal June 2009. The following databases were used to identify studies for this systematic review: Medline 1966 to June 2009, Embase 1980 to June 2009, and The Cochrane Database of Systematic Reviews 2009, Issue 2 (1966 to date of issue). An additional search within the Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language, at least single blinded, and containing >20 individuals of whom >80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. In this review, studies are included under the heading **older adults** if they specifically included people aged over 55 years. **Prescription antidepressant drugs versus placebo:** There is evidence that in people aged 18 years or older in primary and secondary care, prescription antidepressant drugs may be effective for treatment of all grades of depressive disorders compared with placebo. The most robust available evidence of efficacy of treatment with antidepressant drugs is in the management of moderate and severe depression as reported below. However, it has been suggested that the published literature may have inflated the effect sizes of antidepressant treatments, [12] highlighting a possible relationship between the baseline severity of depression and the difference in effectiveness between drug and placebo. [13] From April 2006, this review will only include RCT evidence comparing antidepressant drugs versus placebo that informs the question of baseline severity. **Quality issues:** We have not reported all systematic reviews that we found. Rather, we have reported those reviews that we considered to be the most contemporary, methodologically sound, and reproducible. Not all systematic reviews report their findings in full (i.e., making the analysis reproducible). Where we have found reviews that have reported transparent or full information on data, forest plots, and in which the analysis is replicable, we have selectively reported these reviews and excluded others that have not presented these data. **General reporting:** To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 38). The categorisation of the quality of the evidence (into high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *Clinical Evidence* population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of drug and physical treatments in mild to moderate or severe depression?**

OPTION PRESCRIPTION ANTIDEPRESSANT DRUGS (TRICYCLIC ANTIDEPRESSANTS [INCLUDING LOW-DOSE TRICYCLIC ANTIDEPRESSANTS], SELECTIVE SEROTONIN REUPTAKE INHIBITORS, MONOAMINE OXIDASE INHIBITORS, OR VENLAFAXINE) VERSUS PLACEBO

Contributed by Andrea Cipriani, Corrado Barbui, and John Geddes

Symptom severity

Compared with placebo Prescription antidepressants (tricyclic antidepressants, SSRIs, monoamine oxidase inhibitors, venlafaxine) seem to be more effective than placebo at improving symptoms and increasing response in adults with mild, moderate, or severe depression (moderate-quality evidence).

Compared with placebo in older adults Prescription antidepressants (tricyclic antidepressants, SSRIs, monoamine oxidase inhibitors) may be more effective than placebo at decreasing the proportion of people who fail to recover in older adults with mild, moderate, or severe depression (very low-quality evidence).

Compared with placebo in people with psychotic depression We don't know whether amitriptyline is more effective than placebo at improving symptoms in adults with psychotic depression (very low-quality evidence).

Compared with placebo in people with atypical depression Monoamine oxidase inhibitors seem to be more effective than placebo at improving symptoms in adults with atypical depression (moderate-quality evidence).

Note

Prescription antidepressant drugs are associated with adverse effects, the nature and severity of which vary by class or the individual agent used, the regimen employed, the age of the recipient, and with the use of any concomitant medication (see individual options on antidepressant drugs for details). Prescription antidepressant drugs have also been the subject of a number of alerts including increased risk of suicidal ideation and behaviour, hyponatraemia, exacerbation of psychosis, congenital defects, withdrawal effects, drug interactions, and toxic effects in overdose, among others (see individual options on antidepressant drugs for details).

For GRADE evaluation of interventions for depression in adults: drug and physical treatments, see table, p 38 .

Benefits:

We found 7 systematic reviews [14] [15] [16] [17] [18] [19] [20] All the reviews found that antidepressant drugs significantly improved depressive symptoms compared with placebo.

The first review (search date 1995, 49 RCTs in people aged 18–70 years with mild to moderate or severe depressive disorders) included 5 RCTs in people admitted to hospital (probably with severe depressive disorders), 40 RCTs in a setting outside hospital, one RCT in both settings, and three RCTs that did not specify the setting. [14] All RCTs identified by the review were of at least 4 weeks' duration and included three-way comparisons, including two antidepressant drugs (tricyclic antidepressants [TCAs], SSRIs, or monoamine oxidase inhibitors [MAOIs]) and placebo. The review only included RCTs that measured improvement in depressive symptoms using validated scales such as the Hamilton Depression Rating Scale (HAM-D) and Montgomery–Asberg Depression Rating Scale. It found that, on average, 69% of people taking placebo had worse outcomes over a mean of 6 weeks than the average person taking antidepressant drugs (mean effect size 0.5 for change in score with antidepressant drugs *v* placebo). [14]

The second review (search date 2000, 35 RCTs, none included in the first review, 2013 people aged 18 years or older with all grades of depression, some with a physical illness) compared low-dose (75–100 mg/day) TCAs (amitriptyline, clomipramine, doxepin, dosulepin [dothiepin], imipramine, lofepramine, trimipramine) versus placebo. [15] It found that low-dose TCAs significantly increased the proportion of people who responded at 4 weeks and at 3 to 12 months compared with placebo (response defined as 50% or greater reduction in symptoms measured on a validated scale; at 4 weeks: 274/603 [45%] with TCAs *v* 159/557 [28%] with placebo; RR 1.65, 95% CI 1.36 to 2.00; at 3–12 months: 40/76 [53%] with TCAs *v* 18/77 [23%] with placebo; RR 2.14, 95% CI 1.41 to 3.26; results not intention to treat). The significant difference in response rates between low-dose TCAs and placebo was not maintained when an intention-to-treat analysis based on the worst case scenario was performed.

The third review (search date 1998, 150 RCTs, 16,000 people or greater with major depression) compared newer antidepressants (SSRIs [43 RCTs], MAOIs, or venlafaxine) versus placebo for at least 6 weeks. [16] Response was defined as a 50% reduction in depression rating scale score or a Clinical Global Impression Scale (CGI) score of 1 (very much improved) or 2 (much improved).

The review found that newer antidepressants significantly increased the proportion of people who responded compared with placebo (51% with newer antidepressants *v* 31% with placebo; RR 1.6, 95% CI 1.5 to 1.7). The third review [16] also performed a separate analysis of results for people in primary care. [21] It found that results remained significant; the average response rate was 63% with newer agents, 35% with placebo, and 60% with TCAs (RR for SSRIs *v* placebo 1.6, 95% CI 1.2 to 2.1).

The fourth review (search date 1997, 15 RCTs, none included in the other reviews, some comparing two antidepressants *v* placebo, 1871 people aged 18 years or older) compared antidepressant and other drugs (TCAs [5 RCTs], SSRIs [4 RCTs], MAOIs [3 RCTs], other [2 RCTs]) versus placebo in people with dysthymia (chronic mild depressive disorders). [17] It found that antidepressant or other drugs significantly increased the proportion of people who responded to treatment over 4 to 12 weeks compared with placebo (response defined as a 50% reduction in HAM-D score or scoring 1 or 2 on item 2 of the CGI score; RR 1.9, 95% CI 1.6 to 2.3; NNT 4, 95% CI 3 to 5).

The fifth review found that SSRIs plus pindolol (7.5–15.0 mg/day) significantly increased the proportion of people with early clinical response compared with SSRIs plus placebo (search date 2001, 5 RCTs, 405 people aged >18 years with depressive illness; proportion with early clinical response: 66/187 [35%] people with SSRIs plus pindolol *v* 32/187 [17%] people with SSRIs plus placebo; OR 2.8, 95% CI 1.4 to 5.7; NNT 6, 95% CI 4 to 20). [18] The review found no significant difference between SSRIs plus pindolol and SSRIs plus placebo in late clinical response (7 RCTs, 187 people aged >18 years with depressive illness; proportion with late clinical response: 142/208 [68%] people with SSRIs plus pindolol *v* 124/206 [60%] people with SSRIs plus placebo; OR 1.4, 95% CI 0.8 to 2.7). [18]

The sixth review (search date 2004, 15 RCTs, 2753 people aged 18 years or older in primary care for depression) compared TCAs versus placebo (10 RCTs), SSRIs versus placebo (3 RCTs), and TCAs and SSRIs versus placebo (2 RCTs). [19] The review found that both TCAs and SSRIs were significantly more effective at treating depression compared with placebo (TCA *v* placebo: SMD for depression scores –0.42, 95% CI –0.55 to –0.30; RR for improvement 1.26, 95% CI 1.12 to 1.42; 323/535 [60%] with TCAs *v* 216/460 [47%] with placebo; SSRI *v* placebo: RR for improvement 1.37, 95% CI 1.21 to 1.55; 310/552 [56%] with SSRIs *v* 231/562 [41%] with placebo). There were several definitions used to describe "improvement": 4 definitions used >50% reduction in the Montgomery–Asberg Depression Rating Scale (MADRS), >50% reduction in HAM-D, >7 on the HAM-D scale, and 4 points or greater on HAM-D; and three definitions used global evaluation of improvement.

The seventh review (search date 2004) was a high-quality systematic review undertaken as part of a guideline development process. [20] The guideline, initially published in 2004, was amended in 2007 and further updated in 2009 at which time some, but not all, of the included analyses were updated (to search date 2009). [22] The review found that TCAs significantly improved depressive symptoms compared with placebo whether measured by dichotomous outcomes or by continuous outcomes (dichotomous: not achieving response [50% reduction in depression symptoms as measured by standardised rating scale], 34 RCTs, 4717 people; RR 0.70, 95% CI 0.66 to 0.75; continuous: mean depression scores at end point, 22 RCTs, 2445 people; SMD –0.48, 95% CI –0.37 to –0.59). The review found that SSRIs significantly improved depressive symptoms compared with placebo, whether measured by dichotomous outcomes or continuous outcomes (dichotomous: not achieving at least 50% reduction in depression scores measured by the Hamilton Depression Rating Scale, 17 RCTs, 3143 people; RR 0.73, 95% CI 0.69 to 0.78; continuous: mean end point scores measured by the Hamilton Depression Rating Scale, 16 RCTs, 2223 people; SMD –0.34, 95% CI –0.47 to –0.22). The results were similar when only RCTs lasting 8 weeks or longer were assessed, with SSRIs significantly more effective than placebo (not achieving at least 50% reduction in depression scores measured by the Hamilton Depression Rating Scale, 8 RCTs, 1764 people; RR 0.72, 95% CI 0.66 to 0.79). The results were similar when analysed by severity of illness: moderate depression (3 RCTs, 729 people; RR 0.75, 95% CI 0.65 to 0.87; 2 RCTs, 386 people; SMD –0.28, 95% CI –0.48 to –0.08); severe depression (5 RCTs, 619 people; RR 0.63, 95% CI 0.54 to 0.73; 4 RCTs, 344 people; SMD –0.61, 95% CI –0.83 to –0.40); and very severe depression (6 RCTs, 866 people; RR 0.72, 95% CI 0.65 to 0.8; 5 RCTs, 726 people; SMD –0.39, 95% CI –0.54 to –0.24). The review found insufficient evidence to determine whether there was a clinically significant difference between SSRIs and placebo in increasing the likelihood of achieving remission as measured by the HRSD (3 RCTs, 468 people; RR 0.80, 95% CI 0.61 to 1.06). [20] The analysis of SSRIs as a class versus placebo did not include escitalopram, the most recently marketed SSRI. [20] The update of the guideline considered escitalopram separately versus placebo, but results were not substantially qualitatively different from other SSRIs. [22] The review also reported on moclobemide and phenelzine. It reported that none of the included studies described participants as having depression with atypical features. The review found that, compared with placebo, moclobemide significantly reduced symptoms of depression by the end of treatment as measured by

the HRSD (3 RCTs, 490 people; SMD –0.6, 95% CI –1.13 to –0.07) and significantly increased the likelihood of achieving at least a 50% reduction in symptoms as measured by the HRSD (3 RCTs, 606 people; RR 0.7, 95% CI 0.5 to 0.99). It found no placebo-controlled RCTs of phenelzine. [20] [22]

In older adults:
We found two systematic reviews [23] [24] and two subsequent RCTs. [25] [26]

The first systematic review [23] compared antidepressant drugs versus placebo. The review found that TCAs, SSRIs, or MAOIs significantly reduced the proportion of people who failed to recover over 4 to 7 weeks compared with placebo (search date 2000, 17 RCTs, 1326 people aged >55 years, with mild to moderate or severe depression; numbers failing to recover: 125/245 [51%] with TCAs *v* 167/223 [75%] with placebo; RR 0.68, 95% CI 0.59 to 0.78; NNT 4, 95% CI 4 to 5; 261/365 [72%] with SSRIs *v* 310/372 [83%] with placebo; RR 0.86, 95% CI 0.79 to 0.93; NNT 9, 95% CI 9 to 10; 34/58 [59%] with MAOIs *v* 57/63 [90%] with placebo; RR 0.64, 95% CI 0.50 to 0.81; NNT 4, 95% CI 3 to 4). [23]

The second systematic review (search date 2007, 22 RCTs) compared antidepressant drugs versus placebo in depressed people in later life. [24] It did not pool data, and did not report methodological or numerical data on included RCTs, or report on the antidepressant used. It reported that "some of the trials have shown efficacy of antidepressants against placebo (18 RCTs) whilst others have not (4 RCTs)" (absolute data and statistical analysis not reported). [24]

The first subsequent RCT (264 people, 12 weeks' duration) compared escitalopram versus placebo in depressed people aged 60 years or older. [25] The primary end point was the mean change from baseline to week 12 in the MADRS total score. The RCT found no significant difference between escitalopram and placebo in response measured by MADRS (mean difference –1.34, 95% CI –3.84 to +1.15; P = 0.29). [25]

The second subsequent RCT (525 people, 10 weeks' duration) compared two different low doses of controlled released (CR) paroxetine (CR 25 mg, 177 people; CR 12.5 mg, 168 people) versus placebo (180 people) in depressed people aged 60 years or older. [26] It found that, compared with placebo, a significantly higher proportion of people achieved remission (HAM-D score 7 or less at end point) with paroxetine CR 25 mg, but not with paroxetine CR 12.5 mg (remission: 41% with paroxetine CR 25 mg *v* 31% with paroxetine CR 12.5 mg *v* 28% with placebo; paroxetine CR 25 mg *v* placebo, OR 1.83, 95% CI 1.17 to 2.87; P = 0.008; CR 12.5 mg *v* placebo, reported as not significant; P value and absolute numbers not reported). [26]

Psychotic depression:
We found one systematic review (search date 2004, 10 RCTs, 548 people) that compared the effectiveness of drug treatments for people with psychotic depression. [27] The review found no significant difference for treatment of psychotic depression with amitriptyline compared with placebo (1 RCT; RR 8.40, 95% CI 0.50 to 147.87; P = 0.14).

Atypical depression:
We found one systematic review (search date 2004, 8 RCTs, 792 people with atypical depression), which compared the clinical effectiveness of drug treatments. [28] The review found that MAOIs significantly improved atypical depression compared with placebo (4 RCTs, 250 people; mean effect size 0.45, 95% CI 0.35 to 0.60). However, this review found an asymmetrical distribution for comparisons between MAOIs and placebo, possibly owing to one study that showed a very high response rate difference between phenelzine and placebo (25/30 [83%] with phenelzine *v* 5/26 [19%] with placebo). It must be noted that this high response rate difference does not correlate with a relatively large sample size. Furthermore, this finding is by contrast with the lower response rate differences in the other three studies comparing the efficacy of MAOIs and placebo in people with atypical depression (first study: 24/34 [71%] with phenelzine *v* 13/47 [28%] with placebo; second study: 12/17 [71%] with phenelzine *v* 7/24 [29%] with placebo; third study: 21/36 [58%] with phenelzine *v* 10/36 [28%] with placebo). [28]

Harms:

The first review gave no information on adverse effects. [14] The second review found that people taking low-dose TCAs were 111% (95% CI 35% to 228%) more likely than people taking placebo to withdraw because of adverse effects. [15] However, it found no significant difference between low-dose TCAs and placebo in the proportion of people who withdrew for any cause (RR 1.08, 95% CI 0.93 to 1.26). People taking low-dose TCAs were 63% (95% CI 36% to 95%) more likely to experience at least one adverse effect than were people taking placebo. The third review found that significantly more people taking SSRIs than placebo withdrew because of adverse effects (ARI 5.5%, 95% CI 3.4% to 7.6%). [16] The review gave no information on adverse effects of MAOIs, TCAs, or venlafaxine compared with placebo. The fourth review found that, compared with placebo,

TCAs significantly increased the proportion of people who had constipation, dizziness, and dry mouth (constipation: 2 RCTs; 78/239 [33%] with TCAs *v* 27/244 [11%] with placebo; RR 2.95, 95% CI 1.97 to 4.41; dizziness: 59/239 [25%] with TCAs *v* 32/244 [13%] with placebo; RR 1.89, 95% CI 1.28 to 2.79; dry mouth: 163/239 [68%] with TCAs *v* 45/244 [18%] with placebo; RR 3.70, 95% CI 2.80 to 4.88). [17] It found that, compared with placebo, SSRIs significantly increased the proportion of people who had sweating, sexual dysfunction, insomnia, and dry mouth (sweating: 2 RCTs; 41/311 [13%] with SSRIs *v* 12/308 [4%] with placebo; RR 3.40, 95% CI 1.81 to 6.36; sexual dysfunction: 22/153 [14%] with SSRIs *v* 9/156 [6%] with placebo; RR 2.49, 95% CI 1.18 to 5.23; insomnia: 68/292 [23%] with SSRIs *v* 48/292 [16%] with placebo; RR 1.42, 95% CI 1.02 to 1.98; dry mouth: 52/292 [18%] with SSRIs *v* 34/292 [12%] with placebo; RR 1.56, 95% CI 1.05 to 2.31). The review found insufficient evidence from one RCT to compare the adverse effects of MAOIs versus placebo. [17] The fifth review found no differences in tolerability or adverse events between SSRIs plus pindolol compared with SSRIs plus placebo (tolerability: OR 1.3, 95% CI 0.8 to 2.3, adverse events: OR 1.3, 95% CI 0.7 to 2.1). Small sample size may limit these findings. [18] The sixth review found that people taking either TCAs or SSRIs were significantly more likely than people taking placebo to withdraw because of adverse effects (81/692 [12%] with TCAs *v* 30/578 [5%] with placebo; RR 2.35, 95% CI 1.59 to 3.46; 30/576 [5.2%] with SSRIs *v* 15/573 [2.6%] with placebo; RR 2.01, 95% CI 1.10 to 3.70). [19]

In terms of acceptability, the seventh review found evidence suggesting that there was a statistically significant difference favouring placebo over SSRIs in reducing the likelihood of leaving treatment early (39 RCTs, 7274 people; RR 0.94, 95% CI 0.88 to 0.99). [20] [22] However, the review concluded that the size of this difference was unlikely to be of clinical importance, and in RCTs lasting 8 weeks or longer there was no significant difference between SSRIs and placebo in all-cause withdrawal rate (13 RCTs, 3069 people; RR 0.95, 95% CI 0.83 to 1.09). By contrast, there was a significant and clinically important difference favouring placebo over SSRIs in reducing the likelihood of leaving treatment early because of adverse effects and in reducing the number of people reporting adverse effects (likelihood of leaving treatment early because of adverse effects: 39 RCTs, 7460 people; RR 2.45, 95% CI 2.08 to 2.89; number of people reporting adverse effects: 11 RCTs, 2290 people; RR 1.19, 95% CI 1.13 to 1.25). The review found no significant difference between TCAs and placebo in all-cause withdrawal rate (84 RCTs, 9901 people; RR 0.99, 95% CI 0.92 to 1.06). However, there was a significant difference favouring placebo over TCAs in reducing the likelihood of leaving treatment early because of adverse effects (65 RCTs, 8173 people; RR 4.02, 95% CI 3.46 to 4.67) and in reducing the proportion of people reporting adverse effects (30 RCTs, 4523 people; RR 1.40, 95% CI 1.26 to 1.58). [20] [22]

For further information on harms of class of drug or individual agent see harms of tricyclic antidepressants, p 9 , SSRIs, p 11 , monoamine oxidase inhibitors, p 18 , and venlafaxine, p 19 .

In older adults:
The systematic reviews did not report on adverse events. [23] [24] The first subsequent RCT reported that discontinuation rates resulting from adverse events were 6% in the placebo group and 11% in the escitalopram group (statistical analysis between groups not reported). [25] Treatment emergent adverse events reported by 10% or more of people in the escitalopram group were: headache, nausea, diarrhoea, and dry mouth (headache: 19.2% with escitalopram *v* 9.7% with placebo; nausea: 15.4% with escitalopram *v* 6.0% with placebo; diarrhoea: 14.6% with escitalopram *v* 3.7% with placebo; dry mouth: 10.8% with escitalopram *v* 5.2% with placebo; statistical analysis between groups not reported). [25] In the second subsequent RCT, adverse event withdrawal rates were 6% with paroxetine CR 12.5 mg, 8% with paroxetine CR 25 mg, and 7% with placebo (results presented graphically; absolute numbers and statistical analysis not reported). [26]

We found one systematic review (search date 2005) of hyponatraemia associated with SSRIs in older adults. [29] The review included observational data including case reports, chart reviews, and case-control studies. The review stated that the reported incidence of SSRI-associated hyponatraemia has been variable, ranging from 0.5% to 32%, and was most often observed in older adults. The review reported that in published reports, hyponatraemia developed within the first few weeks of treatment (median time of onset 13 days, range 3–120 days) and resolved within 2 weeks of therapy being discontinued (most cases resolving within 2 weeks, range from 2 days to 6 weeks). The review concluded that practitioners should be alert for this potentially life-threatening event in older people. [29] See harms of SSRIs, p 11 .

Psychotic depression:
The systematic review gave no information on adverse effects. [27]

Atypical depression:
The systematic review gave no information on adverse effects. [28]

Comment:

It has long been argued that placebo-controlled trials are required to adequately demonstrate the efficacy of novel antidepressant drugs. [30] In both the US and Europe, regulatory authorities require placebo-controlled evidence for marketing authorisation. The selective publication of antidepressant versus placebo trials and its influence on apparent efficacy is well recognised [12] and there is currently controversy surrounding this topic. [13] [31] [32] Placebo-controlled trials are mainly designed for regulatory approval purposes and, to meet both ethical and safety requirements, tend to recruit patients from the mild end of the disease spectrum who have a greater chance of spontaneously improving or having a placebo response. [33] In recent years, response to placebo across antidepressant trials has varied and has clearly increased in the past two decades, with a similar increase occurring in the fraction of patients responding to active medication. [34] Inflation of baseline severity is likely to be a cause of the temporal trend towards increasing placebo response rates, which increases the proportion of failed trials. There is evidence showing that trial design might influence the benefit that participants may obtain from pharmacological interventions and that the chance of improvement in response to antidepressants in clinical practice may not be the same as the improvement in clinical trials involving placebo. [35] One meta-analysis found that studies in which people knew that they got only active treatments showed higher response rates than when they knew they might get a placebo tablet, suggesting that placebo response is not simply an issue related to an effect of distraction, but that it is an integral part of treatment. [35] There is some evidence that the placebo response is greatest with mild depression, and the drug–placebo difference becomes greater with increasing degrees of severity of depression. [13] However, the lack of data at an individual patient level cannot allow researchers to draw firm conclusions on this hypothesis, because any effect of disease severity might be diluted in summary analyses by group of patients.

Two additional clinical issues should also be borne in mind when prescribing antidepressants for depression. First, there are non-mood-related benefits of prescribing antidepressants, for example in helping patients to sleep better and in dealing with anxiety-related symptoms. Improving these factors may help patients to cope with their daily lives, thereby contributing to a reduction in depression symptoms. Second, the placebo response may also be short-lived, with more people on placebo relapsing compared with those on antidepressants. Longer trials are required to be able to fully elucidate the contributions of placebo and treatment to clinical response.

One systematic review (search date 2003) systematically reviewed the literature on drug interactions with antidepressants. [36] The review found 904 eligible interactions, involving 9509 patients, for a total of 598 summary interactions. For 510 (85%) interactions, the quality of evidence was poor; it was fair for 67 (11%) interactions and good for 10 (2%) interactions. There were no interactions with excellent quality of evidence. The review found 145 (24%) interactions of major clinical significance (predominantly hypertensive emergencies and serotonin syndrome). Most interacting drugs had central nervous system activity, so caution is needed when combining antidepressants with other central nervous system drugs. The review reported that monoamine oxidase inhibitors (MAOIs) seemed to be the most problematic family in terms of potential for serious drug interactions. [36]

For mild to moderate depression, most RCTs were short term and focused exclusively on improvement in depressive symptoms. Longer-term RCTs that could provide more data on the sustainability of benefits and the potential adverse effects are lacking. Although effects on depressive symptoms are clear, effects on functional status and health-related quality-of-life outcomes are not well described. Most RCTs analysed results using "last observation carried forward"; this method may bias the estimate of treatment efficacy. A "pure" intention-to-treat analysis, following participants for the whole trial duration even if they withdraw, would be more conservative and would replicate what happens in clinical practice.

Many of the RCTs were sponsored by the drug manufacturer, and sponsorship has been shown to be a potential factor influencing the outcomes of RCTs [37] and their reporting. [12] In one study, studies from the FDA were reviewed for some antidepressant agents (bupropion, citalopram, duloxetine, escitalopram, fluoxetine, mirtazapine, nefazodone, paroxetine, sertraline, and venlafaxine). [12] The study conducted a systematic literature search to identify matching publications, comparing the published outcomes with the FDA outcomes and the effect size derived from the published reports with the effect size derived from the entire FDA data set. The study found 74 trials with a total sample of 12,564 people. Of these 74 FDA registered studies, the study did not find evidence of publication for 23 RCTs (31%) including 3449 people (27% of the overall sample size). Data from an additional 1843 people (15%) were reported in journal articles in which the highlighted finding conflicted with the FDA-defined primary outcome. Overall, 48 of the 51 published studies were reported to have positive results (i.e., 94% of the trials conducted were positive); by contrast, according to the FDA, only 38 of the 74 registered studies had positive results (i.e., 51% of RCTs). Among these 38 studies with positive results, 37 were published and one was not published. Apart from three exceptions, among the studies viewed by the FDA as having negative or questionable results, 22 were not published and 11 were published in a way possibly (in the opinion of the authors of

the review) conveying a positive outcome. The study reported that for each of the 12 drugs, the effect size derived from the journal articles exceeded the effect size derived from the FDA reviews. The magnitude of the increases in effect size between the FDA reviews and the published reports ranged from 11% to 69%, with a median increase of 32%. [12]

In older adults:
The reviews comparing antidepressant drugs versus placebo in older people were limited by the diversity of populations included and by the brevity of the RCTs. [23] [24] Metabolic and physical changes with age mean that older people may be more prone to adverse effects such as falls. Because older people often take more medications, they may be at greater risk of drug interactions.

Clinical guide:
The concept of atypical depression as a distinct subtype is based on reported preferential response to one class of antidepressants — MAOIs. The preferential response of atypical depression to MAOIs is now part of accepted wisdom in clinical psychiatry, even though the use of varying definitions of atypical depression before the inclusion of operational criteria in *Diagnostic and statistical manual of mental disorders* (DSM-IV) makes it difficult to rely only on these findings.

OPTION TRICYCLIC ANTIDEPRESSANTS VERSUS EACH OTHER AND OTHER PRESCRIPTION ANTIDEPRESSANT DRUGS (SELECTIVE SEROTONIN REUPTAKE INHIBITORS, MONOAMINE OXIDASE INHIBITORS, OR VENLAFAXINE)

Contributed by Andrea Cipriani, Corrado Barbui, and John Geddes

Symptom severity
Tricyclic antidepressants compared with each other We don't know whether amitriptyline is more effective than other tricyclic antidepressants (analysis also included other related antidepressants) at improving symptoms in adults with major depression (low-quality evidence).

Tricyclic antidepressants compared with SSRIs Tricyclic antidepressants and SSRIs seem to be equally effective at improving symptoms in adults with depression (high-quality evidence).

Tricyclic antidepressants compared with monoamine oxidase inhibitors (MAOIs) Tricyclic antidepressants and moclobemide or phenelzine seem to be equally effective at improving symptoms in adults with depression. Imipramine seems less effective than MAOIs (moclobemide and phenelzine in analysis) at improving symptoms in people with atypical depression (moderate-quality evidence).

Tricyclic antidepressants compared with venlafaxine Tricyclic antidepressants and venlafaxine seem to be equally effective improving symptoms in adults with depression (moderate-quality evidence).

Tricyclic antidepressants compared with St John's wort We don't know whether tricyclic antidepressants are more effective than St John's wort at improving symptoms in adults with mainly mild to moderate depression (very low-quality evidence).

Low-dose tricyclic antidepressants compared with standard-dose tricyclic antidepressants We don't know whether low-dose tricyclic antidepressants are more effective than standard-dose tricyclic antidepressants at increasing the proportion of people who respond to treatment at 6 to 8 weeks (low-quality evidence).

Tricyclic antidepressants plus benzodiazepines compared with tricyclic antidepressants alone Antidepressants (primarily tricyclic antidepressants) plus benzodiazepines may be more effective than antidepressants (primarily tricyclic antidepressants) alone at increasing response (50% reduction on symptom rating scale) at 1 week but not at 6 weeks in adults with major depression (very low-quality evidence).

Tricyclic antidepressants compared with other antidepressants in people with psychotic depression Imipramine may be more effective than fluvoxamine at improving symptoms in adults with psychotic depression (low-quality evidence).

For GRADE evaluation of interventions for depression in adults: drug and physical treatments, see table, p 38 .

Benefits:

Tricyclic antidepressants versus each other:
Although amitriptyline was not the first tricyclic antidepressant developed or the most widely prescribed, it is the standard drug against which new antidepressants are compared with respect to both efficacy and tolerability. We found one systematic review (search date 2005) that compared amitriptyline versus other tricyclic antidepressants (TCAs) and related antidepressants (including heterocyclic antidepressants). [38] Most of the included RCTs enrolled people with major depression. In an analysis of dichotomous outcomes, the review found no significant difference between amitriptyline and tricyclic and other related antidepressants in response, although amitriptyline had

slightly higher response rates (84 RCTs; 1132/2739 [41%] with amitriptyline *v* 1036/2637 [39%] with tricyclic and other related antidepressants; OR 1.11, 95% CI 0.99 to 1.25; P = 0.068). However, there was significant heterogeneity among RCTs (P = 0.03) and the control group also included treatments other than TCAs (e.g., mianserin, trazodone). In an analysis of continuous outcomes, the review found a borderline significant difference in efficacy between amitriptyline and tricyclic and other related antidepressants in favour of amitriptyline (29 RCTs, 1360 people; SMD 0.18, 95% CI 0 to 0.35; P = 0.044). However, the size of this difference was unlikely to be of clinical importance, there was significant heterogeneity among RCTs (P = 0.00016), and the control group also included treatments other than TCAs (e.g., mianserin, trazodone). In subgroup analysis, the review found that amitriptyline was significantly more effective than other TCAs among inpatients (OR 1.20, 95% CI 1.02 to 1.42), but found no significant difference between groups among outpatients (OR 0.98, 95% CI 0.81 to 1.17; absolute numbers and further details not reported). [38]

Tricyclic antidepressants versus SSRIs:
See benefits of SSRIs, p 11 .

Tricyclic antidepressants versus monoamine oxidase inhibitors:
See benefits of monoamine oxidase inhibitors, p 18 .

Tricyclic antidepressants versus venlafaxine:
See benefits of venlafaxine versus other prescription antidepressant drugs, p 19 .

Tricyclic antidepressants versus St John's wort:
See benefits of St John's wort, p 23 .

Low-dose tricyclic antidepressants versus standard-dose tricyclic antidepressants:
We found one systematic review that found no significant difference between low-dose TCAs and standard-dose TCAs in the proportion of responders at 6 to 8 weeks (search date 2000, 6 RCTs, 551 people; response: RR 1.11, 95% CI 0.76 to 1.61). [15] It is likely that these RCTs were designed to show equivalence between treatments rather than superiority of one over another, so the clinical relevance of this result is unclear.

Tricyclic antidepressants plus benzodiazepines versus tricyclic antidepressants alone:
We found one systematic review (search date 1999, 9 RCTs, 679 people aged 18–73 years with major depression) comparing combination treatment with antidepressant drugs (primarily TCAs) plus benzodiazepines versus antidepressant drugs alone. [39] It found that combination treatment was significantly more likely to produce a response within 1 week compared with antidepressant drugs alone (RR of >50% reduction on symptom rating scale 1.64, 95% CI 1.19 to 2.27), although this difference was not apparent at 6 weeks.

Psychotic depression:
We found one systematic review (search date 2004, 10 RCTs, 548 people) that compared the effectiveness of drug treatments for people with psychotic depression. [27] One RCT included in this review compared imipramine versus fluvoxamine (an SSRI). The RCT found that imipramine was significantly more effective than fluvoxamine (RR 2.10, 95% CI 1.06 to 4.17; P = 0.03). [27]

Harms:

Tricyclic antidepressants versus each other:
The review found no significant difference between amitriptyline and tricyclic and related antidepressants in withdrawal rates (113 RCTs, 9156 people; OR 1.07, 95% CI 0.96 to 1.19; P = 0.21). [38] The review found that the proportion of people who experienced adverse effects "significantly favoured control tricyclic or related antidepressant over amitriptyline" (42 RCTs, 3310 people; OR 0.67, 95% CI 0.58 to 0.78; P <0.00001; significant heterogeneity among RCTs [P = 0.006]). [38]

Tricyclic antidepressants versus SSRIs:
See harms of SSRIs, p 11 .

Tricyclic antidepressants versus monoamine oxidase inhibitors:
See harms of monoamine oxidase inhibitors, p 18 .

Tricyclic antidepressants versus venlafaxine:
See harms of venlafaxine, p 19 .

Tricyclic antidepressants versus St John's wort:
See harms of St John's wort, p 23 .

Low-dose tricyclic antidepressants versus standard-dose tricyclic antidepressants:
The review found that people taking low-dose TCAs were 55% (95% CI 24% to 73%) less likely than people taking standard-dose TCAs to withdraw because of adverse effects. [15] However, it found no significant difference between low-dose and standard-dose TCAs in the proportion of people who withdrew for any cause (RR 0.95, 95% CI 0.75 to 1.20).

Tricyclic antidepressants plus benzodiazepines versus tricyclic antidepressants alone:
The review found that TCAs plus benzodiazepines significantly reduced the proportion of people who withdrew from the trial because of adverse effects compared with antidepressants alone (23/342 [7%] with TCAs plus benzodiazepines *v* 46/337 [14%] with TCAs alone; RR 0.53, 95% CI 0.32 to 0.86). [39]

Psychotic depression:
The systematic review gave no information on adverse effects. [27] We found a second systematic review (search date 2005) investigating the potential risk of antidepressant exacerbation of psychosis in people with unipolar major depressive disorder with psychotic features, which included participants from controlled, open, and retrospective studies. [40] The people in the studies were divided into two groups; those with acute monotherapy with antidepressants, and those with acute treatment therapy including an antipsychotic medication (i.e., antipsychotic monotherapy or antidepressant plus antipsychotic [combination] treatment). Twenty studies provided sufficient adverse event reporting. The studies included 78 people using TCAs, 93 people using a serotoninergic antidepressant, and 6 people using a monoamine oxidase inhibitor (MAOI; 177 people in total). Fifteen people were determined to have had psychosis exacerbation while undergoing active treatment with antidepressant alone. One-hundred and twenty-nine subjects were on either antipsychotic monotherapy or combination treatment. Two people were identified as having psychosis exacerbation, both of whom were in the combination group. The review reported that people assigned to antidepressant monotherapy were significantly more likely to experience psychosis exacerbation (OR 5.88, CI not reported; P = 0.01), but not when only randomised and blinded trials were considered (absolute numbers and further details not reported). [40] The review reported that people on TCAs were more likely to experience psychosis exacerbation than people on serotoninergic antidepressants (OR 10.51, CI not reported; P = 0.01; further details not reported). The review reported that 8/78 [10%]) people on TCAs and 6/6 (100%) people on MAOIs experienced psychosis exacerbation, as opposed to 1/93 (1%) people on SSRIs. It reported that tricyclic monotherapy was also more likely to be temporally associated with psychosis exacerbation than treatment including an antipsychotic (OR 7.26, CI not reported; P = 0.007; absolute numbers and further details not reported). [40] However, these data included non-RCT data, and the review noted that limitations of the analysis included the small number of placebo-controlled trials, the numerous studies identified in which these data were missing, the fact that the studies were powered to measure outcomes and not to determine the rate of psychosis exacerbation, and that the majority of studies were in inpatients.

Comment:

All TCAs, apart from lofepramine, are toxic in overdose with seizures and arrhythmias being a particular concern. [20] Overdose of TCAs or elevated plasma levels as a result of interactions with other drugs, liver disease, and age is associated with serious hypotension, and atrial and ventricular arrhythmias may arise even to the extent of complete AV block, which in a number of cases may be fatal. [20] This toxicity, and the perceived poor tolerability of these drugs in general, have led to a decline in their use over the past decade.

OPTION SELECTIVE SEROTONIN REUPTAKE INHIBITORS VERSUS EACH OTHER AND OTHER PRESCRIPTION ANTIDEPRESSANT DRUGS (TRICYCLIC ANTIDEPRESSANTS, MONOAMINE OXIDASE INHIBITORS, OR VENLAFAXINE)

Contributed by Andrea Cipriani, Corrado Barbui, and John Geddes

Symptom severity

SSRIs compared with each other No one individual SSRI seems to be consistently more effective than all other SSRIs at improving symptoms in adults with depression. However, some SSRIs seem to be more effective than other SSRIs at improving symptoms when compared on an individual pairwise analysis (moderate-quality evidence).

SSRIs compared with tricyclic antidepressants (TCAs) SSRIs and TCAs seem equally effective at improving symptoms in adults with depression (high-quality evidence).

SSRIs compared with monoamine oxidase inhibitors (MAOIs) SSRIs and moclobemide or phenelzine seem equally effective at improving symptoms in adults with depression or atypical depression (defining atypical depression as a depressive subtype that is preferentially responsive to MAOI treatment) (high-quality evidence).

SSRIs compared with venlafaxine SSRIs and venlafaxine seem equally effective at improving symptoms in people with depression (moderate-quality evidence).

SSRIs compared with St John's wort We don't know whether SSRIs are more effective than St John's wort at improving symptoms in adults with mainly mild to moderate depression (very low-quality evidence).

SSRIs plus benzodiazepines compared with SSRIs alone We don't know whether fluoxetine plus clonazepam is more effective than fluoxetine alone at improving the proportion of people who respond (measured by Clinical Global Impression score; much or very much improved) at 6 weeks (very low-quality evidence).

SSRIs compared with each other or other antidepressants in people with psychotic depression Imipramine may be more effective than fluvoxamine and sertraline may be more effective than paroxetine at improving symptoms in people with psychotic depression, but we don't know whether fluvoxamine is more effective than venlafaxine. However, studies were small, ranging from 22 people to 48 people (low-quality evidence).

For GRADE evaluation of interventions for depression in adults: drug and physical treatments, see table, p 38 .

Benefits:

SSRIs versus each other:

We found one systematic review (search date 2007, 117 RCTs, 25,928 people [65% women]) comparing the following selected antidepressants at therapeutic dose range for the acute treatment of unipolar major depression in adults: bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, mirtazapine, paroxetine, reboxetine, sertraline, and venlafaxine. [43] We have only reported data on SSRIs versus each other here (see comments below). Overall for all included RCTs, the mean study duration was 8 weeks and mean sample size was 110 participants per group. The overall mean baseline score at study entry was 23.47 measured by Hamilton Depression Rating Scale (HDRS)-17 and 30.09 measured by Montgomery–Asberg Depression Rating Scale (MADRS). The primary end points were response (defined as the proportion of people with a reduction of at least 50% from baseline measured by HDRS or MADRS or who were much or very much improved measured by Clinical Global Impression Scale [CGI] at 8 weeks) and withdrawal rates (acceptability, defined as the proportion of people who terminated the study early for any reason during the first 8 weeks). The full dataset of all comparisons is available online (http://www.psychiatry.univr.it/docs/Research%20Activities/MANGA_Dataset_DEF.xls). The review reported direct comparisons of individual agents and also multiple treatments meta-analysis (MTM; see comment below).

In the analysis of direct comparisons, no individual SSRI was consistently superior to all other SSRIs in terms of efficacy, although some individual pairwise comparisons were significant (see table 1, p 35). [43] For efficacy for direct comparisons, citalopram was significantly superior to paroxetine, escitalopram was significantly superior to citalopram, and sertraline was significantly superior to fluoxetine (see table 1, p 35). For the MTM analysis (including direct and indirect comparisons) for efficacy, escitalopram was significantly superior to fluoxetine, fluvoxamine, and paroxetine, and sertraline was significantly superior to fluoxetine and paroxetine (see table 1, p 35). It should be noted that between the direct and MTM analysis, sometimes a comparison was significant when calculated by one method (direct analysis or MTM) but not by the other (e.g., escitalopram *v* citalopram), and sometimes the direction of effect changed depending on the method of analysis used (e.g., fluvoxamine *v* sertraline). The review suggested, based on evidence from direct and indirect comparisons including all the 12 second-generation antidepressants it examined, that escitalopram and sertraline might be the best choice when starting treatment for moderate to severe major depression because they have the best balance between efficacy and acceptability. However, the review noted that these findings only apply to acute phase treatment (8 weeks), and it did not examine other important outcomes such as adverse events, toxic events, discontinuation symptoms, or social functioning. [43]

SSRIs versus tricyclic antidepressants:

We found three systematic reviews in people with mild to moderate or severe depression comparing SSRIs versus tricyclic antidepressants (TCAs). [20] [38] [44] The reviews found no significant difference in overall effectiveness between TCAs and SSRIs.

The first review (search date 2004) found evidence suggesting that there is no clinically significant difference between SSRIs and TCAs in reducing depression symptoms as measured by the HRSD or MADRS (49 RCTs, 4073 people; SMD +0.05, 95% CI –0.01 to +0.12). [20]

The second review (search date 2005) compared amitriptyline versus SSRIs. [38] The review found no significant difference between groups in continuous measures of depression (24 RCTs, 2659 people; SMD +0.09, 95% CI –0.01 to +0.19; P = 0.086). [38] Similarly, when measuring dichotomous outcomes, it found no significant difference between amitriptyline and SSRIs in the proportion of

people who responded (20 RCTs, 2046 people; OR 1.14, 95% CI 0.95 to 1.36; P = 0.16). In subgroup analysis, the review found no significant difference in effectiveness between amitriptyline and SSRIs whether treated as an inpatient (OR 1.30, 95% CI 0.87 to 1.96) or outpatient (OR 1.08, 95% CI 0.86 to 1.35; absolute numbers and further details not reported).

The third review (search date 2004) compared fluoxetine versus TCAs including amitriptyline, clomipramine, desipramine, dosulepin (dothiepin), doxepin, imipramine, and lofepramine. [44] The review defined response rate as the number of people showing a reduction of at least 50% in the HDRS. The review found no significant difference between fluoxetine compared with TCAs as a class for treatment of depression (failure to respond: 481/1008 [48%] with fluoxetine *v* 504/1032 [49%] with TCAs; OR 0.95, 95% CI 0.80 to 1.14; P = 0.6). However, in head to head comparisons, only dosulepin was found to be significantly more effective than fluoxetine (2 RCTs, 144 people; failure to respond: 42/72 [58%] with fluoxetine *v* 29/72 [40%] with dosulepin; OR 2.09, 95% CI 1.08 to 4.05). [44]

SSRIs versus monoamine oxidase inhibitors:
We found two systematic reviews. [20] [28] The first systematic review (search date 2003) compared moclobemide or phenelzine versus SSRIs. [20] Only one RCT (40 people) reported by the review included people described as having depression with additional atypical features. The review found no significant difference between moclobemide or phenelzine and SSRIs in reducing symptoms of depression by the end of treatment as measured by the HRSD (moclobemide: 7 RCTs, 557 people; SMD –0.06, 95% CI –0.22 to +0.11; phenelzine: 1 RCT, 40 people [with additional atypical features]; SMD +0.27, 95% CI –0.35 to +0.90). It found no significant difference between moclobemide or phenelzine and SSRIs in increasing the likelihood of achieving at least a 50% reduction in symptoms by the end of treatment as measured by the HRSD or MADRS (moclobemide: 6 RCTs, 511 people; RR 0.91, 95% CI 0.77 to 1.08; phenelzine: 1 RCT, 40 people [with additional atypical features]; RR 0.75, 95% CI 0.19 to 2.93). [20]

The second systematic review (search date 2004) compared the clinical effectiveness of drug treatments for people with atypical depression (defining atypical depression as a depressive subtype that is preferentially responsive to monoamine oxidase inhibitor [MAOI] treatment). [28] The review found that MAOIs (phenelzine and moclobemide) were not significantly more effective for treatment of atypical depression in terms of response rate and treatment effect size compared with SSRIs (response rate: 3 RCTs, 265 people; 85/127 [67%] with MAOIs *v* 90/138 [65%] with SSRIs; treatment effect size: 3 RCTs, 265 people; +0.02, 95% CI –0.10 to +0.14). [28]

SSRIs versus venlafaxine:
See benefits of venlafaxine, p 19 .

SSRIs versus St John's wort:
See benefits of St John's wort, p 23 .

SSRIs plus benzodiazepines versus SSRIs alone:
We found no systematic review, but found one RCT. [45] The RCT compared fluoxetine (20–40 mg/day) plus clonazepam (0.5–1.0 mg/day) for 18 weeks versus fluoxetine plus placebo. [45] It found no significant difference between fluoxetine plus clonazepam and fluoxetine alone in the proportion of people who responded at 6 weeks (50 people aged 18–70 years with moderate to severe depression for at least 1 month and a HAM-D score of 18–26; response defined as CGI score of 1 [very much improved] or 2 [much improved]: 76% with fluoxetine plus clonazepam *v* 56% with fluoxetine alone; reported as not significant; CI not reported). The RCT is likely to have been underpowered to detect a clinically important difference in outcomes.

Psychotic depression:
We found one systematic review (search date 2004, 3 RCTs, 101 people with psychotic depression), which compared SSRIs with each other or other antidepressants. [27] The first RCT included in the review found that imipramine was significantly more effective than fluvoxamine for treating psychotic depression (1 RCT, 48 people; 16/25 [64%] with imipramine *v* 7/23 [30%] with fluvoxamine; RR 2.10, 95% CI 1.06 to 4.17; P = 0.03). The second RCT included in the review found that sertraline was significantly more effective than paroxetine (1 RCT, 32 people; 13/18 [72%] with sertraline *v* 3/14 [21%] with paroxetine; RR 3.37, 95% CI 1.19 to 9.57; P = 0.02). The third RCT included in the review found no significant difference between fluvoxamine and venlafaxine for treating psychotic depression (1 RCT, 22 people; 9/11 [82%] with fluvoxamine *v* 6/11 [55%] with venlafaxine; RR 1.50, 95% 0.82 to 2.75; P = 0.2). [27]

Harms:

SSRIs versus each other:
The review found that, for direct comparisons, there was little difference between SSRIs in terms of acceptability (see table 1, p 35). [43] For acceptability for the multiple treatments meta-analysis

(MTM) analyses, citalopram was significantly superior to fluvoxamine, escitalopram was significantly superior to fluvoxamine and paroxetine, and sertraline was significantly superior to fluvoxamine and paroxetine (see table 1, p 35). The review did not report on other adverse effects. [43]

Common adverse events with SSRIs versus tricyclic antidepressants:
The second systematic review compared treatment discontinuation rates with amitriptyline versus SSRIs in people aged 18 years or older with depression. [38] It found that amitriptyline was significantly less well tolerated than SSRIs (withdrawals: 46 RCTs, 5770 people; OR 0.84, 95% CI 0.75 to 0.95). In addition, the proportion of people who experienced adverse effects "significantly favoured SSRIs in comparison with amitriptyline" (12 RCTs, 2155 people; OR 0.65, 95% CI 0.55 to 0.76). [38] Another systematic review (search date 1996) compared adverse events with SSRIs versus TCAs in people aged 18 years or older with all severities of depression (see table 2, p 37). [46] It found that, compared with SSRIs, about twice as many people taking TCAs had dry mouth, constipation, and dizziness, but that slightly more people taking SSRIs had nausea, diarrhoea, anxiety, agitation, insomnia, nervousness, and headache. The third systematic review (search date 2004) comparing fluoxetine versus all other antidepressants found that, in terms of people who withdrew during the trial for any cause, fluoxetine was better tolerated than TCAs (OR 0.78, 95% CI 0.68 to 0.89). [44] In particular, fluoxetine was better tolerated than amitriptyline (OR 0.64, 95% CI 0.47 to 0.85) and imipramine (OR 0.79, 95% CI 0.63 to 0.99). An advantage in terms of tolerability, although not statistically significant, was found in favour of fluoxetine over lofepramine (OR 0.51, 95% CI 0.25 to 1.03) and nortriptyline (OR 0.68, 95% CI 0.45 to 1.03); by contrast, dosulepin was better tolerated than fluoxetine (OR 1.44, 95% CI 0.98 to 2.12). In terms of adverse effect profile, data from 26 RCTs included in the previous systematic review showed that 50.9% of people treated with fluoxetine experienced adverse effects during the study compared with 60.3% of people who received a TCA (RR 0.84, 95% CI 0.76 to 0.94). [47] However, the analysis of individual TCAs showed that relative risk for adverse effects significantly favoured fluoxetine compared with amitriptyline and clomipramine, but not compared with the other TCAs included in the analysis. In this review, significant differences were reported as numbers needed to treat (positive NNTs indicating a significant advantage for fluoxetine, negative NNTs indicating a significant advantage for comparison). TCAs were associated with less insomnia, anxiety, nausea, anorexia, and weight loss compared with fluoxetine (insomnia: 65 RCTs; NNT –33, 95% CI –52 to –24; anxiety: 65 RCTs; NNT –105, 95% CI –1000 to –55; nausea: 65 RCTs; NNT –13, 95% CI –16 to –10; anorexia: 65 RCTs; NNT –100, 95% CI –434 to –56; weight loss: 6 RCTs; NNT –23, 95% CI –55 to –14). TCAs were associated with more sedation, dizziness, dry mouth, blurred vision, constipation, and weight gain compared with fluoxetine (sedation: 65 RCTs; NNT 21, 95% CI 16 to 30; dizziness: 10 RCTs; NNT 13, 95% CI 10 to 18; dry mouth: 10 RCTs; NNT 25, 95% CI 17 to 53; blurred vision: 65 RCTs; NNT 100, 95% CI 51 to 666; constipation: 65 RCTs; NNT 12, 95% CI 10 to 14; weight gain: 65 RCTs; NNT 39, 95% CI 30 to 59).

Adverse effects with different SSRIs:
The overall incidence of adverse events is similar among antidepressants: discontinuation rates attributed to adverse events are similar, but available evidence suggests that the profiles of adverse effects differed among drugs. [48] One systematic review reported the mean incidence and 95% CIs for specific adverse events that were commonly reported in included RCTs (mean incidence: citalopram: diarrhoea 6.8, 95% CI 1.8 to 11.8; headache 5, 95% CI 0 to 24.1; insomnia 6.4, 95% CI 1.6 to 11.2; nausea 11.9, 95% CI 0 to 24.8; escitalopram: diarrhoea 8.9, 95% CI 1.6 to 16.1; headache 14.1, 95% CI 0 to 29.9; insomnia 8.7, 95% CI 1.3 to 16.2; nausea 14.8, 95% CI 6.1 to 23.5; fluoxetine: diarrhoea 11.7, 95% CI 6.8 to 16.6; dizziness 7.2, 95% CI 4.3 to 10.0; headache 16.6, 95% CI 10.2 to 23.0; insomnia 13.7, 95% CI 10.0 to 17.4; nausea 18.6, 95% CI 15.1 to 22.1; fluvoxamine: headache 14.5, 95% CI 0 to 41.5; nausea 22.2, 95% CI 0 to 46.8; paroxetine: diarrhoea 9.2, 95% CI 5.6 to 12.9; dizziness 10.6, 95% CI 7.5 to 13.7; headache 21.2, 95% CI 11.1 to 31.3; insomnia 14.3, 95% CI 8.6 to 20.1; nausea 18.3, 95% CI 11.1 to 25.6; sertraline: diarrhoea 15.4, 95% CI 10.2 to 20.6; dizziness 7.5, 95% CI 4.6 to 10.4; headache 20.2, 95% CI 12.8 to 27.6; insomnia 15.0, 95% CI 8.7 to 21.3; nausea 19.5, 95% CI 14.4 to 24.6). [48] The method and extent of assessment of adverse events varied among studies, and the pooled incidence should be interpreted with caution. One systematic review, which compared fluoxetine versus all other antidepressants, found that fluoxetine was associated with less constipation (8 RCTs; NNT 42, 95% CI 24 to 141), but more sweating (8 RCTs; NNT –58, 95% CI –400 to –32) and weight loss (4 RCTs; NNT –15, 95% CI –38 to –9) than paroxetine, and more nausea than fluvoxamine (1 RCT; NNT –5, 95% CI –71 to –2). [44] One large cohort study of people receiving 4 different SSRIs (fluvoxamine [983 people], fluoxetine [692 people], sertraline [734 people], and paroxetine [13,741 people]) in primary care in the UK found that reports of common adverse events (nausea/vomiting, malaise/lassitude, dizziness, and headache/migraine) varied between SSRIs (fluvoxamine 78/1000 participant months; fluoxetine 23/1000 participant months; RR *v* fluvoxamine 0.29, 95% CI 0.27 to 0.32; paroxetine 28/1000 participant months; RR *v* fluvoxamine 0.35, 95% CI 0.33 to 0.37; sertraline 21/1000 participant months; RR *v* fluvoxamine 0.26, 95% CI 0.25 to 0.28). [49] Only 52% of people responded to the questionnaire, although this response rate was similar for all 4 drugs. A study of spontaneous

reports to the UK Committee on Safety of Medicines found similar safety profiles among the same 4 SSRIs. [50]

Another systematic review (search date 2005) examined hyponatraemia as a complication of SSRIs in older people. [51] The review retrieved scant research on the phenomenon of hyponatraemia in association with SSRI use, the majority being case reports or observational evidence. Because of the nature of the literature located, no aggregation of data was made. The review reported that no clear evidence exists to adequately explain the pathophysiological relationship between hyponatraemia with SSRIs and ageing. It noted that hyponatraemia is a common electrolyte disturbance in older adults, occurring in approximately 7% of healthy older people who are not taking SSRIs. The multiple drugs prescribed for older people may increase risk. The review reported that diuretics have been implicated as contributors to this adverse drug reaction, but hyponatraemia is also widely reported in people who are not taking diuretics. [51] It suggested that older adults may be more at risk because of age-related changes in fluid regulation, including reduction in total body water, diminished renal blood flow and glomerular filtration rate, and age-related impairment of tubular concentrating and diluting capacity. It reported that hyponatraemia had been reported in association with most SSRIs (including fluoxetine, paroxetine, citalopram, sertraline, and fluvoxamine) and it has also been reported with reboxetine, venlafaxine, and mirtazapine. [51] It reported that the onset of hyponatraemia was consistently found to occur within a 2- to 3-week period following the start of the drug regimen, with occasional outliers. [51] See harms of prescription antidepressant drugs versus placebo, p 4 .

A further systematic review (search date 2006) was carried out to quantify congenital malformation rates associated with the use of paroxetine. [52] Both case-control and cohort studies were considered for inclusion and were required to have reported first-trimester (0–14 weeks of gestational age) exposure to paroxetine and to have had a control group of pregnant women not exposed to paroxetine. The outcome measures (considered only for live births) were major malformations or cardiac malformations. Seven studies met the inclusion criteria (including reports, articles, abstracts, and letters on nested case-control, prospective controlled, population-based cohort, retrospective cohort, and prospective recording registry studies). The summary odds ratio for all of the included paroxetine studies for major malformations was 1.31, 95% CI 1.03 to 1.67, for cardiac malformations 1.72, 95% CI 1.22 to 2.42, and for non-cardiac major malformations 1.29, 95% CI 0.86 to 1.92. In 4 studies that used women exposed to antidepressants other than paroxetine as the control group, the odds ratio was 1.30, 95% CI 0.93 to 1.80 for all major malformations; 1.70, 95% CI 1.17 to 2.46 for cardiac malformations, and 1.44, 95% CI 0.95 to 2.19 for non-cardiac major malformations. Women using antidepressants (either paroxetine or other antidepressants) during pregnancy had a significantly higher mean number of ultrasounds, amniocentesis, and echocardiograms than women not receiving antidepressants (all analyses; $P < 0.001$). Infants of women who received any SSRI had an odds ratio of 2.1, 95% CI 1.5 to 2.9, to have undergone echocardiograms in the first year of life compared with infants of women not receiving antidepressants. The review concluded that on the basis of the results of the meta-analysis, first-trimester exposure to paroxetine seems to be associated with a significant increase in the risk for cardiac malformation. However, a detection bias could not be ruled out as contributing to the apparent increased detection of cardiovascular malformation of children exposed *in utero* to paroxetine. [52]

The MHRA issued an alert with regards to a possible increased risk of congenital cardiac defects in association with fluoxetine in early pregnancy (www.mhra.gov.uk), and there has been an FDA alert with regards to an association with neonatal persistent pulmonary hypertension in infants born to mothers who took SSRIs during pregnancy (www.fda.gov).

Withdrawal effects with SSRIs:

We found one RCT in people aged 18 years or older (mean age 30–40 years) comparing abrupt discontinuation of fluoxetine (96 people) versus continued treatment (299 people) in people who had been taking the drug for 12 weeks. [53] It found that abrupt discontinuation was associated with increased dizziness, dysmenorrhoea, rhinitis, and somnolence (dizziness: 7% with abrupt discontinuation *v* 1% with continued treatment; dysmenorrhoea: 3% with abrupt discontinuation *v* 0% with continued treatment; rhinitis: 10% with abrupt discontinuation *v* 3% with continued treatment; somnolence: 4% with abrupt discontinuation *v* 0% with continued treatment). However, there was a high withdrawal rate in this RCT because of the return of symptoms of depression (39%), so these may be underestimates of the true rate of withdrawal symptoms. Between 1987 and 1995, the rate of spontaneous reports of suspected withdrawal reactions (per million defined daily doses) to the World Health Organization Collaborating Centre for International Drug Monitoring was higher for paroxetine than for sertraline and fluoxetine. [54] The most common withdrawal effects were dizziness, nausea, paraesthesia, headache, and vertigo.

SSRIs versus monoamine oxidase inhibitors:
One review reported on acceptability and tolerability. [20] There was evidence suggesting that there were no clinically important differences between moclobemide and SSRIs in all-cause withdrawal rate, reducing the likelihood of leaving treatment because of adverse effects, or in the number of people reporting adverse effects (all-cause withdrawal rate: 8 RCTs, 702 people; RR 0.96, 95% CI 0.79 to 1.26; likelihood of leaving treatment because of adverse effects: 7 RCTs, 660 people; RR 0.96, 95% CI 0.59 to 1.57; number of people reporting adverse effects: 6 RCTs, 519 people; RR 0.90, 95% CI 0.79 to 1.03). The review reported that there was insufficient evidence on the effects of phenelzine and SSRIs in terms of acceptability and tolerability measures. [20]

Adverse events with SSRIs versus other newer antidepressants:
One systematic review (search date 2007) analysed adverse events data from 80 comparative RCTs and 42 additional studies of both experimental and observational designs. [55] Overall, second-generation antidepressants (SSRIs and other newer antidepressants, such as bupropion, duloxetine, mirtazapine, nefazodone, trazodone, and venlafaxine) had similar adverse events profiles. Constipation, diarrhoea, dizziness, headache, insomnia, nausea, sexual adverse events, and somnolence were commonly and consistently reported adverse events (about 60% of people reported at least 1 adverse event). [55] The review reported that nausea and vomiting were the most common reasons for discontinuation in efficacy studies. It found that mirtazapine and paroxetine resulted in higher mean weight gain than did fluoxetine, paroxetine, trazodone, and venlafaxine, or fluoxetine and sertraline, respectively (mean weight gain for mirtazapine compared with comparator drug after 6–8 weeks, 0.8–3.0 kg), while paroxetine led to higher rates of sexual dysfunction than did fluoxetine, fluvoxamine, nefazodone, or sertraline. It reported higher mean incidence of diarrhoea with sertraline than with bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, and venlafaxine (11% with sertraline *v* 8% with comparator drug); higher mean incidence of somnolence with trazodone than with bupropion, fluoxetine, mirtazapine, paroxetine, or venlafaxine (42% with trazodone *v* 25% with comparator drug); and venlafaxine resulted in higher incidence of nausea and vomiting than did SSRIs as a class (33% with venlafaxine *v* 22% with comparator drug; statistical analysis not reported). [55] Evidence on the comparative risk for rare but severe adverse events, such as seizures, cardiovascular events (events relating to systolic and diastolic blood pressure and pulse or heart rate), hyponatraemia, hepatotoxicity, and the serotonin syndrome, was insufficient to draw firm conclusions.

Another systematic review (search date 2008) reviewed data examining the relationships between depression, antidepressants, and CVD. [56] This review did not provide point estimates for risks of adverse effects, but is included in this*Clinical Evidence* review because it provides an updated summary of available evidence on this important topic. Regarding the link between depression, antidepressants, and cardiovascular disorders, the review suggested that depression seems to be an independent risk factor for the development of coronary disease and for cardiac death after MI and stroke (a possible hypothesised mechanism being increased platelet reactivity). [56] The review concluded that some antidepressants (including sertraline, citalopram, and mirtazapine) seemed to be safe to use after MI. [56] It also suggested that some antidepressants may even reduce mortality, even though response to treatment may be a prerequisite for this beneficial effect. The review reported that most TCAs and mirtazapine caused significant orthostatic hypotension in normal clinical doses. It suggested that reboxetine, duloxetine, and venlafaxine were associated with small increases in blood pressure and SSRIs (as a class) were linked to an increased risk of bleeding. It noted that there was an urgent need for large, controlled prospective studies examining the effect of different antidepressants on physical outcomes and mortality in CVD and after MI and stroke. [56]

Adverse events with SSRIs versus venlafaxine:
See harms of venlafaxine, p 19 .

Adverse events with SSRIs versus St John's wort:
See harms of St John's wort, p 23 .

Adverse events with SSRIs plus benzodiazepines:
The RCT found that 30% of people taking fluoxetine plus clonazepam had decreased appetite. [45] It also found that 28% of people taking fluoxetine alone had headache and 24% had sleep disturbance.

Psychotic depression:
The systematic review gave no information on adverse effects. [27]

Suicide with SSRIs:
Antidepressant drugs currently carry warnings of the possibility of increased suicidal ideation and behaviour during treatment, especially in younger people. There is a longstanding belief that an-

tidepressants might have an early activating effect that might give depressed patients the energy to follow through on suicidal impulses before the mood improvement also provided by antidepressant treatment takes effect. Concern about the possibility of an increased risk of suicide with antidepressants goes back to 1991. However, it has to be borne in mind that depression is a serious illness that itself is a strong predictor of suicide. A meta-analysis using data on individual patients from placebo-controlled antidepressant trials was carried out by the FDA. [57] The FDA asked pharmaceutical companies marketing selected antidepressants (bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, and venlafaxine) for datasets from all completed, double-blind randomised placebo-controlled trials (with at least 20 participants in each treatment arm), using any of these antidepressants in adults for any indication (not only depression). Events were classified into 7 mutually exclusive categories (completed suicide; suicide attempt; preparatory acts towards imminent suicidal behaviour; suicidal ideation; self-injurious behaviour, intent unknown; not enough information [fatal]; not enough information [non-fatal]). Overall, there were 8 reported completed suicides, 134 suicide attempts, 10 reports of preparations without attempted suicide, and 378 reports of suicidal ideation alone (i.e., suicidal ideation without any action). The incidence rates for suicidality in those with major depression were higher than in the other indication groups. Because of the large number of participants, the study sponsors (and not the FDA) adjudicated events. The review included data on 372 RCTs and 99,231 people. [57]

By contrast with the results of the review of paediatric studies on suicide and antidepressants by the FDA, pooled estimates for the adult population did not show an increased risk of suicidality (suicidality risk for active drug *v* placebo, ideation or worse, all adults, all diagnoses: OR 0.85, 95% CI 0.71 to 1.02). [57] The suicidality risk (ideation or worse) for active drug relative to placebo in all adults with major depression was very similar (OR 0.85, 95% CI 0.67 to 1.07). However, the overall sample analysis found that the association between antidepressant drugs and the incidence of reported suicidal behaviour was strongly related to age. The risk was significantly raised in people aged under 25 years (suicidal behaviour risk for active drug *v* placebo, preparation or worse, adults with psychiatric disorders: OR 2.30, 95% CI 1.04 to 5.09), not affected in those aged 25 to 64 years (suicidal behaviour risk for active drug *v* placebo, preparation or worse, adults with psychiatric disorders: OR 1.03, 95% CI 0.68 to 1.58), and significantly reduced in those aged 65 years and older (suicidal behaviour risk for active drug *v* placebo, preparation or worse, adults with psychiatric disorders: OR 0.06, 95% CI 0.01 to 0.58). These figures did not change substantially when the analysis was carried out for preparation or worse only in people with major depressive disorder aged under 25 years. The analysis also found differences in risk between drugs. The suicidality risk for active drug relative to placebo (ideation or worse) in adults with psychiatric disorders by drug found that fluoxetine and sertraline scored better than placebo (suicidality risk: active drug *v* placebo, adults with psychiatric disorders: fluoxetine; OR 0.71, 95% CI 0.52 to 0.99; sertraline: OR 0.51, 95% CI 0.29 to 0.91), while citalopram and escitalopram did not show a favourable profile, even though the difference versus placebo was not statistically significant (suicidality risk: active drug *v* placebo, adults with psychiatric disorders; citalopram: OR 2.11, 95% CI 0.90 to 4.94; escitalopram: OR 2.44, 95% CI 0.90 to 6.63). [57]

Comment:

SSRIs versus each other — multiple treatments meta-analysis:

Even though current clinical practice guidelines on the treatment of depressive disorder recommend that an SSRI should be the first-line option when drug therapy is indicated for a depressive episode, [20] some systematic reviews have found that certain antidepressants are more efficacious than other drugs both within and between classes. However, these differences are inconsistent across different systematic reviews and more recently, some new statistical approaches have been developed to overcome this problem. Multiple treatments meta-analysis (MTM) is a statistical technique that allows both direct and indirect comparisons to be undertaken, even when two of the treatments have not been directly compared. In other words, it is a generalisation of standard pair-wise meta-analysis for A versus B trials, to data structures that include, for example, A versus B, B versus C, and A versus C trials. MTM (also known as network meta-analysis) can summarise RCTs of several different treatments providing point estimates (together with 95% CIs) for their association with a given end point, as well as an estimate of incoherence (i.e., a measure of how well the entire network fits together, with small values suggesting better internal agreement of the model). MTM has already been used successfully in other fields of medicine and two fruitful roles for MTM have been identified. First, to strengthen inferences concerning the relative efficacy of two treatments, by including both direct and indirect comparisons to increase precision and combine both direct and indirect evidence; second, to facilitate simultaneous inference regarding all treatments in order, for example, to select the best treatment. Considering how important comparative efficacy could be for clinical practice and policy making, it is useful to use all the available evidence to estimate potential differences in efficacy among treatments.

SSRIs versus each other — other antidepressants reported in multiple treatments meta-analysis:
The review [43] included 12 new-generation antidepressants, some of which are not included in this *Clinical Evidence* review. Based on the MTM analysis of all the included antidepressants, the review concluded that mirtazapine, escitalopram, venlafaxine, and sertraline were significantly more efficacious than duloxetine (OR 1.39, 1.33, 1.30, and 1.27, respectively), fluoxetine (1.37, 1.32, 1.28, and 1.25, respectively), fluvoxamine (1.41, 1.35, 1.30, and 1.27, respectively), paroxetine (1.35, 1.30, 1.27, and 1.22, respectively), and reboxetine (2.03, 1.95, 1.89, and 1.85, respectively). [43] It also concluded that reboxetine was significantly less efficacious than all the other antidepressants tested. [43] The review reported that escitalopram and sertraline showed the best profile of acceptability, leading to significantly fewer discontinuations than did duloxetine, fluvoxamine, paroxetine, reboxetine, and venlafaxine. [43] The review did not conduct a formal cost-effectiveness analysis, but noted that only two of the antidepressants included were still on patent in the US and in Europe, namely, escitalopram and duloxetine.

Fluoxetine dose:
We found one systematic review (search date 2000, 103 RCTs) that assessed the effects of fluoxetine dose on outcomes in RCTs comparing fluoxetine versus tricyclic, heterocyclic, and related antidepressants, SSRIs, and newer antidepressants in people with depression. [58] The review found that the weighted rate of fluoxetine responders was higher in RCTs where fluoxetine was the experimental drug (70%) compared with RCTs where fluoxetine was the control drug (58%), possibly reflecting the use of higher doses of fluoxetine in RCTs where fluoxetine was the experimental drug. The review did not assess the proportion of responders with other antidepressants and did not adjust for possible confounders. See comment on prescription antidepressant drugs versus placebo, p 4 .

OPTION MONOAMINE OXIDASE INHIBITORS VERSUS OTHER PRESCRIPTION ANTIDEPRESSANT DRUGS (TRICYCLIC ANTIDEPRESSANT DRUGS, SELECTIVE SEROTONIN REUPTAKE INHIBITORS, OR VENLAFAXINE) IN ATYPICAL DEPRESSIVE DISORDERS

Contributed by Andrea Cipriani, Corrado Barbui, and John Geddes

Symptom severity
Monoamine oxidase inhibitors (MAOIs) compared with tricyclic antidepressants (TCAs) Moclobemide or phenelzine and TCAs seem to be equally effective at improving symptoms in adults with depression. MAOIs (moclobemide and phenelzine in analysis) seem to be more effective than imipramine at improving symptoms in people with atypical depression (moderate-quality evidence).

Monoamine oxidase inhibitors compared with SSRIs Moclobemide or phenelzine and SSRIs seem to be equally effective at improving symptoms in adults with depression or atypical depression (defining atypical depression as a depressive subtype that is preferentially responsive to MAOI treatment) (high-quality evidence).

For GRADE evaluation of interventions for depression in adults: drug and physical treatments, see table, p 38 .

Benefits:

Monoamine oxidase inhibitors versus tricyclic antidepressants:
We found two systematic reviews. [20] [28]

The first systematic review (search date 2004) compared moclobemide or phenelzine versus tricyclic antidepressants (TCAs). [20] Only one RCT (285 people) identified by the review included people described as having depression with additional atypical features (67% of participants).The review found no significant difference between moclobemide or phenelzine and TCAs in reducing the symptoms of depression by the end of treatment as measured by the Hamilton Depression Rating Scale (HDRS) (moclobemide: 6 RCTs, 665 people; SMD +0.04, 95% CI –0.11 to +0.19; phenelzine: 6 RCTs, 594 people; SMD –0.07, 95% CI –0.40 to +0.27). It found no significant difference between moclobemide and TCAs in increasing the likelihood of achieving at least a 50% reduction in symptoms by the end of treatment as measured by the HRSD or Montgomery–Asberg Depression Rating Scale (MADRS) (7 RCTs, 1559 people; RR 1.07, 95% CI 0.96 to 1.21). [20] [22] One RCT identified by the review found that phenelzine was significantly more effective than imipramine/desipramine at reducing the proportion of people not achieving at least a 50% reduction in depression score as measured by the HDRS (1 RCT, 285 people [including 67% people with additional atypical features]; OR 0.66, 95% CI 0.52 to 0.83). [20] [22]

The second review (search date 2004, 4 RCTs, 236 people with atypical depression) found that monoamine oxidase inhibitors (MAOIs) were significantly more effective for treating atypical depres-

sion compared with imipramine (effect size 0.27, 95% CI 0.16 to 0.42; response rates: 83/116 [71%] with MAOIs *v* 55/120 [46%] with imipramine). [28]

Monoamine oxidase inhibitors versus SSRIs:
See benefits of SSRIs, p 11 .

Harms:

Monoamine oxidase inhibitors versus tricyclic antidepressants:
The first review found that, compared with people taking TCAs, people taking moclobemide were significantly less likely to leave treatment early because of adverse effects (12 RCTs, 1632 people; RR 0.46, 95% CI 0.34 to 0.64) and to report adverse effects (6 RCTs, 953 people; RR 0.83, 95% CI 0.76 to 0.91), although the review reported that the latter result was unlikely to be of clinical importance. [20] It found no significant difference between phenelzine and TCAs in people leaving the study because of adverse effects (6 RCTs, 234 people; RR 0.58, 95% CI 0.21 to 1.61) or in those reporting adverse effects (1 RCT, 60 people; RR 0.97, 95% CI 0.87 to 1.09). [20] The second review gave no information on adverse effects. [28]

Monoamine oxidase inhibitors versus SSRIs:
See harms of SSRIs, p 11 .

Comment:

See comment on prescription antidepressant drugs versus placebo, p 4 .

Clinical guide:
MAOIs are one of the oldest classes of antidepressants. MAOIs act by inhibiting the activity of monoamine oxidase, preventing the breakdown of monoamine neurotransmitters. There are two isoforms of monoamine oxidase, MAO-A and MAO-B. The early MAOIs inhibited monoamine oxidase irreversibly. When they react with monoamine oxidase, they permanently deactivate it, and the enzyme cannot function until it has been replaced by the body, which can take about 2 weeks. A few newer MAOIs, notably moclobemide, are reversible, meaning that they can inhibit the enzyme for a time, allowing the enzyme to function once more. In addition, older MAOIs inhibit both MAO-A and MAO-B equally, but moclobemide targets only MAO-A. MAOIs are mostly used for atypical depression, but are used less frequently because they usually require specific dietary restrictions because they can, when combined with certain foods, cause a sudden large increase in blood pressure or hypertensive crisis.

OPTION VENLAFAXINE VERSUS OTHER PRESCRIPTION ANTIDEPRESSANT DRUGS (TRICYCLIC ANTIDEPRESSANT DRUGS, SELECTIVE SEROTONIN REUPTAKE INHIBITORS, OR MONOAMINE OXIDASE INHIBITORS)

Contributed by Andrea Cipriani, Corrado Barbui, and John Geddes

Symptom severity
Venlafaxine compared with tricyclic antidepressants (TCAs) Venlafaxine and TCAs seem to be equally effective at improving symptoms in adults with depression (moderate-quality evidence).

Venlafaxine compared with SSRIs Venlafaxine and SSRIs seem to be equally effective at improving symptoms in people with depression (moderate-quality evidence).

For GRADE evaluation of interventions for depression in adults: drug and physical treatments, see table, p 38 .

Benefits:

Venlafaxine versus tricyclic antidepressants:
We found two systematic reviews. [42] [20]

The first systematic review (search date 2007, 18 RCTs, 2769 people) compared venlafaxine versus tricyclic antidepressants (TCAs). [42] The review included published data and also unpublished data provided by the manufacturer. Of 16 RCTs comparing tricyclics versus venlafaxine, approximately a third (5 RCTs) were unpublished. Fifteen RCTs were included in the analysis of response (6 RCTs, imipramine; 3 RCTs, clomipramine; 2 RCTs, amitriptyline; 2 RCTs, dosulepin [dothiepin]; 1 RCT, amineptine; 1 RCT, maprotiline). The review found no significant difference between venlafaxine and TCAs in response (15 RCTs; OR 1.22, 95% CI 0.96 to 1.54; results presented graphically; absolute numbers not reported). Seven RCTs provided data for the analysis of remission (2 RCTs, clomipramine: 1 RCT of amitriptyline, dosulepin, amineptine, maprotiline, and nortriptyline). The review found no significant difference between venlafaxine and TCAs in remission (7 RCTs; OR 1.06, 95% CI 0.74 to 1.63; results presented graphically; absolute numbers not reported). [42] The review did not report which RCTs had been included in each individual analysis.

The second review (search date 2004) was a high-quality systematic review undertaken as part of a guideline development process. [20] The guideline, initially published in 2004, was amended in 2007 and further updated in 2009 at which time some, but not all, of the included analyses were updated (to search date 2009). [22] The review found no significant difference between venlafaxine and TCAs with regards to the proportion of people not achieving at least a 50% reduction in depression score as measured by the HRSD or Montgomery–Asberg Depression Rating Scale (MADRS) (6 RCTs, 773 people; RR 0.91, 95% CI 0.71 to 1.17). It found no significant difference between venlafaxine and TCAs with regards to reducing the symptoms of depression by the end of treatment as measured by the HRSD or MADRS (6 RCTs, 744 people; SMD –0.12, 95% CI –0.27 to +0.02). [20] [22]

Venlafaxine versus SSRIs:
We found three systematic reviews. [43] [42] [20]

The first review compared venlafaxine versus individual SSRIs using both a direct comparisons analysis and multiple treatments meta-analysis (MTM; see SSRIs versus each other and other prescription antidepressant drugs, p 11). [43] In direct comparisons analysis for efficacy, the review found that venlafaxine was significantly superior than fluoxetine and fluvoxamine, and found no significant difference compared with citalopram, escitalopram, paroxetine, or sertraline (see table 1, p 35). In MTM comparisons for efficacy, venlafaxine was significantly superior to fluoxetine, fluvoxamine, and paroxetine (see table 1, p 35).

The second systematic review (search date 2007, 34 RCTs, 7155 people) compared venlafaxine versus SSRIs as a group. [42] The review included published data and also unpublished data provided by the manufacturer. Of the 34 RCTs comparing venlafaxine versus SSRIs, approximately one third (10 RCTs) were unpublished, and data were supplied by the manufacturer. Of 29 RCTs providing data for the analysis of response, venlafaxine was compared with fluoxetine in 15 RCTs, with paroxetine in 7 RCTs, with sertraline in three RCTs, with citalopram in two RCTs, and with escitalopram in two RCTs. The review found that venlafaxine significantly improved treatment response and remission compared with SSRIs (response: 29 RCTs; OR 1.15, 95% CI 1.02 to 1.29; remission: 23 RCTs; OR 1.25, 95% CI 1.08 to 1.51; results presented graphically; absolute numbers not reported). In the result for remission, there was significant heterogeneity among RCTs (P = 0.03). The review did not report which RCTs had been included in each individual analysis.

The third review (search date 2004) was a high-quality systematic review undertaken as part of a guideline development process. [20] The guideline, initially published in 2004, was amended in 2007 and further updated in 2009 at which time some, but not all, of the included analyses were updated (to search date 2009). [22] It compared venlafaxine versus SSRIs as a group. It found no significant difference between venlafaxine and SSRIs in the proportion of people achieving a 50% reduction in symptoms of depression (16 RCTs, 3268 people; RR 0.92, 95% CI 0.84 to 1.005; P = 0.06) or in remission (19 RCTs, 3692 people; RR 0.95, 95% CI 0.9 to 1.002; P = 0.06). It found that venlafaxine significantly reduced symptoms compared with SSRIs by the end of treatment (13 RCTs, 2741 people; SMD –0.10, 95% CI –0.17 to –0.02). However, it reported that the size of the difference was unlikely to be of clinical importance. [20] [22]

Harms:

Venlafaxine versus tricyclic antidepressants:
The first review reported that the overall withdrawal rate and withdrawal rate due to adverse effects were lower with venlafaxine than with TCAs, the extent of which varied by the analysis undertaken (overall withdrawal rate: 15 RCTs; OR 0.77, 95% CI 0.65 to 0.90, pooled risk difference –0.03, 95% CI –0.07 to 0; withdrawal rate due to adverse effects: OR 0.76, 95% CI 0.61 to 0.94, pooled risk difference –0.01, 95% CI –0.04 to +0.01; absolute numbers not reported for either analysis). [42]

The second review found no significant difference between venlafaxine and TCAs in the proportion of people leaving the study early, leaving the study early because of adverse effects, or in the proportion of people reporting adverse effects (people leaving the study early: 6 RCTs, 773 people; RR 0.89, 95% CI 0.73 to 1.10; people leaving the study early because of adverse effects: 6 RCTs, 773 people; RR 0.77, 95% CI 0.53 to 1.12; people reporting adverse effects (5 RCTs, 627 people; RR 0.96, 95% CI 0.89 to 1.05). [20] [22]

Venlafaxine versus SSRIs:
The first review reported on treatment acceptability (see SSRIs versus each other and other prescription antidepressant drugs, p 11). [43] In terms of acceptability in direct comparisons, it found no significant difference between venlafaxine and any individual SSRI, while in MTM comparisons for acceptability, it found that venlafaxine was significantly inferior to escitalopram and sertraline (see table 1, p 35). [43]

In the second review, which compared venlafaxine versus SSRIs as a group, 31 RCTs provided data for the assessment of overall withdrawal rate, 30 RCTs provided data for withdrawal rate due to adverse effects, and 25 RCTs provided data for withdrawals due to inefficacy. [42] The review found no significant difference between venlafaxine and all SSRIs in overall withdrawal rate (OR 1.06, 95% CI 0.95 to 1.19; P = 0.26; absolute numbers not reported). It found that the withdrawal rate due to adverse effects was significantly higher with venlafaxine compared with SSRIs (OR 1.45, 95% CI 1.23 to 1.70; P <0.0001). [42]

The third review found no significant difference between venlafaxine and SSRIs in the proportion of people leaving the study early or in the proportion of people reporting adverse effects (people leaving the study early: 15 RCTs, 3117 people; RR 0.99, 95% CI 0.87 to 1.12; people reporting adverse effects: 15 RCTs, 2973 people; RR 1.03, 95% CI 0.99 to 1.08). [20] [22] It found that venlafaxine significantly increased the proportion of people leaving the study early due to adverse effects (19 RCTs, 3984 people; RR 1.34, 95% CI 1.12 to 1.61).

Comment: See comment on prescription antidepressant drugs versus placebo, p 4 .

Clinical guide:
A retrospective observational analysis of the General Practice Research Database (GPRD) found that people prescribed venlafaxine were more likely to attempt or complete suicide compared with people prescribed citalopram, fluoxetine, and dosulepin (dothiepin). [59] However, adjustment for several possible confounders substantially reduced the excess risk. In the UK, guidelines currently recommend that venlafaxine treatment should only be initiated by or managed under the supervision of specialist mental health medical practitioners, [20] although the MHRA has relaxed this guidance to apply only to those severely depressed or hospitalised patients who require doses of 300 mg daily. [60] Observational evidence indicates that, in suicidal people who had ever used antidepressants, the current use of any antidepressant was associated with a markedly increased risk of attempted suicide, and with a markedly decreased risk of completed suicide and death. [61] In this analysis, venlafaxine was associated with the highest risk of suicide. Finally, warnings have been issued by the FDA, by the MHRA, and by the drug manufacturer of venlafaxine about the potential risk of cardiotoxicity and toxicity in overdose associated with venlafaxine use. [62] Overall, there is a consistent, albeit unexplained, risk signal with venlafaxine. Despite the evidence for marginally greater efficacy compared with other antidepressants, [44] the current evidence suggests that venlafaxine should not be considered a routine first-line treatment for people with major depression. [63]

OPTION ELECTROCONVULSIVE THERAPY

Contributed by Andrea Cipriani, Rob Butler,and John Geddes

Symptom severity
Electroconvulsive therapy compared with simulated electroconvulsive therapy Electroconvulsive therapy seems more effective than simulated electroconvulsive therapy at improving symptoms at the end of 1 to 6 weeks of treatment in adults with severe depression who are primarily inpatients (moderate-quality evidence).

Electroconvulsive therapy compared with prescription antidepressant drugs Electroconvulsive therapy seems more effective than prescription antidepressant drugs (tricyclic antidepressants, monoamine oxidase inhibitors, SSRIs, phenelzine, tryptophan) at improving symptoms over 3 to 12 weeks in adults with severe depression who are primarily inpatients (moderate-quality evidence).

Bilateral compared with unilateral electroconvulsive therapy Bilateral electroconvulsive therapy seems more effective than unilateral electroconvulsive therapy at improving symptoms in adults with severe depression who are primarily inpatients (moderate-quality evidence).

Different types of electroconvulsive therapy compared with each other in older adults We don't know whether real electroconvulsive therapy is more effective than simulated electroconvulsive therapy, or whether unilateral electroconvulsive therapy is more effective than bilateral electroconvulsive therapy in older people, as we found insufficient evidence (very low-quality evidence).

Note
Because electroconvulsive therapy may be unacceptable to some people, and because it is a short-term treatment, there is consensus that it should normally be reserved for people who cannot tolerate or have not responded to antidepressant drug treatment, when a rapid response is required.

For GRADE evaluation of interventions for depression in adults: drug and physical treatments, see table, p 38 .

Benefits: We found two systematic reviews [64] [65] and three subsequent RCTs. [66] [67] [68]

The first, most comprehensive, systematic review (search date 2001) assessed the efficacy and safety of electroconvulsive therapy (ECT) in younger and older adults with severe depression, who were primarily inpatients. [64] The review used change in symptoms on a continuous scale as the primary outcome measure (see comment below). The second review [65] included the results from the first review; [64] we have therefore reported the first review in detail.

Electroconvulsive therapy versus simulated electroconvulsive therapy:
The first review found that ECT significantly improved symptoms compared with simulated ECT at the end of 1 to 6 weeks' treatment (6 RCTs, 256 people; mean difference in Hamilton Depression Rating Scale [HAM-D] score 9.7, 95% CI 5.7 to 13.5 with ECT *v* simulated ECT). [64]

Electroconvulsive therapy versus prescription antidepressant drugs:
The first review found that ECT significantly improved symptoms compared with antidepressant drugs (tricyclic antidepressants, monoamine oxidase inhibitors, SSRIs, phenelzine, and trytophan) over 3 to 12 weeks (18 RCTs, 1144 people; mean difference in HAM-D score 5.2, 95% CI 1.4 to 8.9). [64]

Bilateral versus unilateral electroconvulsive therapy:
The first review found that bilateral ECT significantly improved symptoms compared with unilateral ECT (22 RCTs, 1408 people; mean difference in HAM-D score 3.6, 95% CI 2.2 to 5.2). [64] High-dose ECT also significantly improved symptoms compared with low-dose ECT (7 RCTs, 342 people; mean difference in HAM-D score 4.1, 95% CI 2.4 to 5.9). The review found no significant difference in outcomes between twice weekly and three times weekly treatment, or between brief pulse waveform and sine wave.

The first subsequent RCT (90 depressed people, HRSD score 18 or greater) compared right unilateral ECT at 6 times seizure threshold versus bilateral ECT at 2.5 times seizure threshold, and in a factorial design, people were further randomised to either a traditional brief pulse (1.5 milliseconds) or an ultrabrief pulse (0.3 milliseconds). [66] Remission was defined as an HRSD score of 10 or less, and there were 22 to 23 people in each of the 4 groups. The RCT found that remission rates were significantly different between groups at 1 week post ECT and varied by the length of pulse given (remission: 73% with right unilateral and ultrabrief pulse *v* 35% with bilateral and ultrabrief pulse *v* 59% with right unilateral and brief pulse *v* 65% with bilateral and brief pulse; bilateral ultrabrief *v* right unilateral ultrabrief; P = 0.09; bilateral ultrabrief *v* bilateral brief; P = 0.02; bilateral ultrabrief *v* both right unilateral groups; P = 0.048, all P values after covariate adjustment).

The second subsequent RCT (92 patients diagnosed with treatment-resistant major depression, minimal HAM-D 21-item version score 15) compared 6 right unilateral ECT treatments (2.5 times stimulus intensity of titrated threshold) versus 6 bifrontal ECT (1.5 times threshold) treatments over a 3-week period. [67] Concomitant psychotropic medications were allowed. Eight people did not complete the course of the study because of minor adverse effects or withdrawal of consent. The RCT found no significant difference between groups in the proportion of people who responded (response defined as reduction of >50% in the initial HAM-D score: 12/46 [26%] with unilateral *v* 12/46 [26%] with bilateral; OR 1.0, 95% CI 0.35 to 2.8). [67]

The third subsequent RCT (45 people referred for ECT, Hamilton Depression Rating Scale [HDRS] 4-item score >16) compared bifrontal, moderate dose (50% above seizure threshold; 15 people) ECT; bitemporal, low-dose (just above seizure threshold; 15 people) ECT; and right unilateral, high-dose (400% above the seizure threshold; 15 people) ECT. [68] Thirty-nine people completed the course of treatment. The RCT found no significant difference among groups in effectiveness measured by HDRS (results presented graphically; P >0.05). [68]

Older adults:
We found one systematic review (search date 2006). [69] It included one RCT (35 people), which compared real ECT versus simulated ECT. The review reported that this was a post-hoc analysis of data in older people who had participated in a larger RCT. It reported that an analysis of completers performed by the RCT had found that the mean Montgomery–Asberg Depression Rating Scale (MADRS) scores were significantly better in the real ECT groups (unilateral and bilateral) than in the simulated groups (P <0.05). However, the review noted that this was not an intention-to-treat analysis (12 people were withdrawn before completing treatment), and since this was a post-hoc analysis, these findings should be interpreted with caution. The review was unable to perform its own analysis because of lack of data. It also included one RCT (29 people) that compared unilateral versus bilateral ECT. It found no significant difference between groups in outcome measured by HDRS (mean difference 6.06, 95% CI –5.20 to +17.32). [69]

Harms:

The first review could not perform a meta-analysis assessing effects on cognitive function because cognitive function was inconsistently assessed. [64]

Electroconvulsive therapy versus simulated electroconvulsive therapy:
One RCT identified by the review suggested that ECT was more likely to impair cognitive functioning immediately after treatment than was simulated ECT, but found no significant difference in cognitive functioning at 6 months. [64]

Electroconvulsive therapy versus prescription antidepressant drugs:
One RCT identified by the review found that ECT was more likely to impair cognitive functioning immediately after treatment than was antidepressant drug treatment, and another RCT found no significant difference in cognitive function. [64] The RCTs are likely to have been underpowered to detect a clinically important difference. The review found that significantly more people taking antidepressant drugs withdrew from treatment compared with ECT (OR 0.41, 95% CI 0.12 to 0.88).

Bilateral versus unilateral electroconvulsive therapy:
The first review reported that bilateral ECT and high-dose ECT were more likely to result in short-term cognitive impairment than were unilateral ECT and low-dose ECT. Data on long-term cognitive functioning were limited. [64] The first subsequent RCT reported that the ultrabrief right unilateral group had less severe cognitive adverse effects than the other three groups in virtually all primary outcome measures assessed in the acute postictal period, and during and immediately following therapy. [66] It found that people rated their memory deficits as less severe following ultrabrief right unilateral ECT compared with each of the other three interventions (P <0.001). [66] The second subsequent RCT found no significant difference between unilateral and bilateral groups in outcome assessment using the modified Mini-Mental State Examination (3MS: 92 people; difference 1.8, 95% CI –0.2 to +3.5). [67] The third subsequent RCT found that the moderate-dose bifrontal group had significantly less cognitive effects measured by the MMSE than did the low-dose bitemporal and high-dose unilateral groups (bifrontal *v* bitemporal, P = 0.002; bifrontal *v* right unilateral, P = 0.011; results presented graphically). [68]

Older adults:
We found one further systematic review (search date 2008), which examined the impact of ECT on cognitive functioning (27 studies) in depressed older people. [70] The systematic review found mixed results and methodological weaknesses, so no firm conclusions could be drawn.

Comment:

To aid interpretation of results, the first review calculated standardised weighted mean differences and translated them into mean differences in symptoms on the Hamilton Depression Rating Scale (HAM-D). [64] Many of the RCTs included in the systematic review were small and old. There was substantial clinical heterogeneity among participants (diagnostic criteria used, severity of depression, inpatients and outpatients, previous treatments) and the modes of treatment compared (electrode placement, dose, waveform, frequency of administration, duration of treatment), but the review did not formally assess statistical heterogeneity.

Clinical guide:
Because electroconvulsive therapy may be unacceptable to some people, and because it is a short-term treatment, there is consensus that it should normally be reserved for people who cannot tolerate or have not responded to antidepressant drug treatment, when a rapid response is required.

OPTION ST JOHN'S WORT (HYPERICUM PERFORATUM)

Contributed by Andrea Cipriani, Corrado Barbui, and John Geddes

Symptom severity
Compared with placebo St John's wort may be more effective than placebo at improving symptoms in adults with mainly mild to moderate depression (very low-quality evidence).

Compared with tricyclic antidepressants (TCAs) We don't know whether St John's wort is more effective than TCAs at improving symptoms in adults with mainly mild to moderate depression (very low-quality evidence).

Compared with SSRIs We don't know whether St John's wort is more effective than SSRIs at improving symptoms in adults with mainly mild to moderate depression (very low-quality evidence).

Note
St John's wort may interact with antidepressant drugs and other drugs, which may potentially reduce or enhance plasma levels or efficacy of various conventional drugs. Preparations of St John's wort may vary.

For GRADE evaluation of interventions for depression in adults: drug and physical treatments, see table, p 38 .

Benefits:

We found one systematic review (search date 2008, 29 RCTs, 5489 people; see comment), which included double-blind RCTs in adults with major depression (meeting DSM-IV or ICD-10 criteria). It included RCTs of hypericum (St John's wort) and excluded trials investigating combinations of St John's wort with other herbs. [41] The primary outcome reported was the proportion of responders (as measured by HAM-D, or other responder measures such as CGI). Because of the clinical diversity of the studied populations, the diverse extracts used, and drugs compared, the review reported a random effects analysis for all results. Of the 29 included RCTs, the severity of depression was described as mild to moderate in 19 RCTs, moderate to severe in 9 RCTs, and the remaining RCT did not classify severity. [41]

St John's wort versus placebo:

The review found that St John's wort significantly increased the proportion of people who responded compared with placebo (18 RCTs; 877/1635 [54%] with St John's wort *v* 518/1429 [36%] with placebo; RR 1.48, 95% CI 1.23 to 1.77). [41] However, there was significant heterogeneity among RCTs (P <0.00001, I^2 = 75%). In a sensitivity analysis, the review found that effects in favour of St John's wort were smaller in more precise RCTs than in less precise RCTs (precision of CI: more precise trials, 9 RCTs, 2044 people; RR 1.28, 95% CI 1.10 to 1.49; less precise trials, 9 RCTs, 1020 people; RR 1.87, 95% CI 1.22 to 2.87). There was significant heterogeneity among RCTs in both analyses (more precise, P = 0.01, I^2 = 61%; less precise, P <0.00001, I^2 = 79%). In a prespecified subgroup sensitivity analysis, the review found that trials from German-speaking countries reported larger effects with St John's wort compared with placebo than did trials from other countries (trials from German-speaking countries: 11 RCTs, 1770 people; RR 1.78, 95% CI 1.42 to 2.25 [significant heterogeneity, P = 0.0002]; trials from other countries: 7 RCTs, 1294 people; RR 1.07, 95% CI 0.88 to 1.31). The review found that St John's wort significantly increased the proportion of people in remission compared with placebo (HAM-D score <8 or <7: 6 RCTs; 193/696 [28%] with St John's wort *v* 61/540 [11%] with placebo; RR 2.77, 95% CI 1.80 to 4.26). Analyses based on mean HAM-D values yielded similar findings. At the completion of treatment, the review found that mean HAM-D score points were significantly lower with St John's wort compared with placebo (17 RCTs, 2871 people; mean difference –3.04 points, 95% CI –4.29 points to –1.78 points). There was significant heterogeneity among RCTs (P <0.00001; I^2 = 86%). Trials from German-speaking countries reported much larger effects in favour of St John's wort compared with placebo than did studies from other countries (trials from German-speaking countries: 11 RCTs, 1720 people; mean difference –4.29 points, 95% CI –5.61 points to –2.97 points; studies from other countries: 6 RCTs, 1151 people; mean difference –0.77 points, 95% CI –1.74 points to +0.20 points). [41] In a univariable meta-regression analysis of responders, country of origin (studies from German-speaking countries showing larger effects sizes, P = 0.002), precision (more precise studies showing smaller effects, P = 0.032), and higher HAM-D baseline values (higher values associated with smaller effect sizes, P = 0.048) were significantly associated with effect sizes. In multiple analysis, the association remained significant for country of origin (P = 0.035) and precision (P = 0.017) but not for HAM-D baseline values. [41]

St John's wort versus tricyclic antidepressants:

The review compared St John's wort versus older antidepressants, which were largely tricyclic antidepressants (5 RCTs in total, of which 3 RCTs used imipramine, 1 RCT used amitriptyline, and 1 RCT used maprotiline). [41] The review found no significant difference between groups in the proportion of people responding (measured by HAM-D score: 5 RCTs; 247/508 [48.6%] with St John's wort *v* 248/508 [48.8%] with older antidepressants; RR 1.02, 95% CI 0.90 to 1.15). [41]

St John's wort versus SSRIs:

The review compared St John's wort versus SSRIs. [41] The review found no significant difference between groups in the proportion of people responding (measured by HAM-D score: 12 RCTs; 471/905 [52%] with St John's wort *v* 462/889 [52%] with SSRIs; RR 1.00, 95% CI 0.90 to 1.12).

Older adults:

We found no systematic review or RCTs specifically in older adults.

Harms:

Two reviews, which included case reports and data from the Adverse Drug Events database of the World Health Organization Collaborating Centre for International Drug Monitoring (administered by the Uppsala Monitoring Centre) and from the MHRA, found evidence of significant interactions of St John's wort with antidepressant drugs and other drugs that may potentially reduce or enhance plasma levels or efficacy of various conventional drugs. [71] [72] The clinical importance of drug interaction with St John's wort depends on several factors associated with co-administered drugs (dose, dosing regimen, administration route, pharmacokinetic and therapeutic range), herb (dose,

dosing regimen, administration route), and patients (genetic polymorphism, age, gender, and pathological conditions). [73]

St John's wort versus placebo:
The review found no significant difference between St John's wort and placebo in the proportion of people withdrawing because of adverse effects (16 RCTs, 2784 people; OR 0.92, 95% CI 0.45 to 1.88). [41] The review found no significant difference between groups in the proportion of people dropping out of the trial (16 RCTs, 2784 people; OR 0.87, 95% CI 0.67 to 1.12) or in the proportion of people reporting adverse effects (14 RCTs, 2496 people; OR 0.98, 95% CI 0.78 to 1.23). [41]

St John's wort versus tricyclic antidepressants:
The review found that, compared with older antidepressants (3 RCTs, imipramine; 1 RCT, amitriptyline; 1 RCT, maprotiline), significantly fewer participants withdrew for any reason with St John's wort (5 RCTs, 1016 people; OR 0.67, 95% CI 0.47 to 0.95), significantly fewer participants withdrew because of adverse events (5 RCTs, 1016 people; OR 0.24, 95% CI 0.13 to 0.46), and significantly fewer reported adverse effects (5 RCTs, 1016 people; OR 0.39, 95% CI 0.30 to 0.50). [41]

St John's wort versus SSRIs:
The review found that significantly fewer people withdrew because of adverse effects with St John's wort compared with SSRIs (11 RCTs, 1769 people; OR 0.53, 95% CI 0.34 to 0.83), with no significant difference between groups in the reporting of adverse effects, although the result was of borderline significance (9 RCTs, 1641 people; OR 0.70, 95% CI 0.49 to 1.00; P = 0.048). [41] The review found no significant difference between groups in overall withdrawal rates (11 RCTs, 1769 people; RR 0.83, 95% CI 0.63 to 1.08). [41]

Comment:

The review reported that there were two issues that complicated the interpretation of its findings. [41] First, results from more precise trials showed smaller effects over placebo than did less precise trials. Second, results of trials from German-language speaking countries were considerably more favourable for St John's wort than were trials from other countries. [41]

Questions have been raised regarding the methodological quality of available studies, which have examined heterogeneous patient populations and inconsistently used standardised symptom rating instruments. [71] The results of the systematic reviews must be interpreted with caution because the preparations and doses of St John's wort and types and doses of antidepressant drugs varied widely. [41] RCTs that use standardised preparations of St John's wort are needed. The interactions of St John's wort may be partly explained by the induction of hepatic and intestinal systems involved in drug metabolism. [73] Because these systems metabolise >50% of all therapeutic drugs, St John's wort is likely to interact with many more drugs than has been previously reported.

Clinical guide:
Even though most available comparisons between St John's wort and synthetic standard antidepressant drugs suggest similar effects, current best evidence from placebo comparisons showed only minor benefits of St John's wort in people with major depression, and perhaps no benefit in people with prolonged duration of depression. There is no robust evidence about effectiveness in severe depression.

OPTION EXERCISE

Contributed by Rob Butler and Simon Hatcher

Symptom severity
Exercise compared with control or different forms of exercise or other treatments We don't know whether exercise is more effective than control or drug treatment (sertraline) at improving symptoms in adults with depression, or whether one form of exercise is more effective than any other, as we found insufficient evidence (very low-quality evidence).

Exercise compared with control or different forms of exercise or other treatments in older adults We don't know whether exercise is more effective than control or drug treatment (sertraline) at improving symptoms in older adults with depression, or whether one form of exercise is more effective than any other, as we found insufficient evidence (very low-quality evidence).

For GRADE evaluation of interventions for depression in adults: drug and physical treatments, see table, p 38 .

Benefits:

Exercise versus control or different forms of exercise or other treatments:
We found one systematic review on all forms of exercise (search date 2007), [74] one systematic review on yoga (search date 2008), [75] and three subsequent RCTs. [76] [77] [78]

The review on all forms of exercise identified 28 RCTs. [74] Of these, 19 were peer-reviewed papers, 6 were doctoral dissertations, and three were published in abstract form only. In total, 21 RCTs recruited from non-clinical populations, while 6 RCTs recruited participants from hospital inpatients or outpatients, and one RCT recruited from both. The review reported that the majority of the RCTs had methodological weaknesses. Allocation concealment was adequate in 8 RCTs, 7 RCTs performed an intention-to-treat (ITT) analysis, and 7 RCTs had blinding of outcome assessor. The review found that exercise significantly reduced depression symptoms post treatment compared with no intervention or placebo (23 RCTs, 907 people; SMD –0.82, 95% CI –1.12 to –0.54). However, there was significant heterogeneity among RCTs (P <0.0001; I^2 = 77%). The review undertook a sensitivity analysis including RCTs that had adequate allocation concealment, ITT analysis, and blinded outcome assessment. The review found no significant difference between exercise and control in reduction of symptoms post treatment (3 RCTs, 216 people; SMD –0.42, 95% CI –0.88 to +0.03). [74] The review included two RCTs (age range 61–88 years; mean age 52 years) that compared exercise (walking or jogging; aerobic exercise) versus drug therapy (sertraline in both RCTs). It found no significant difference between groups in reduction of depression scores post treatment (2 RCTs, 203 people; SMD –0.04, 95% CI –0.31 to +0.24). [74]

The review of yoga was narrative in character and did not pool results. [75] It identified previous reviews, RCTs, and observational data in people with depression. Overall, the review of yoga found the intervention potentially beneficial as a monotherapy or augmentation to medication in mild to moderate depression. However, the included RCTs used different types of yoga, different comparison groups, and the methodological quality of the studies was poor.

The first subsequent RCT (80 people with moderate depression, HRSD score of 12 or more) compared 4 aerobic treatment groups that varied total energy expenditure over 12 weeks. [76] The RCT found that 41% to 44% of the group assigned to the highest energy expenditure exercise responded to treatment (50% or greater reduction in HRSD score) compared with 23% of non-aerobic exercise controls (P <0.05).

The second subsequent RCT (54 women with Beck Depression Inventory [BDI]-II score of 14–28) found no significant difference between high exercise intensity, low exercise intensity, and stretching in reducing depression scores measured by BDI-II at 10 weeks (P = 0.064). [77]

The third subsequent RCT (23 people with clinical depression) found no significant difference between aerobic exercise and stretching after 12 weeks (measured by BDI-II, P = 0.27; measured by Montgomery–Asberg Depression Rating Scale [MADRS], P = 0.33). [78]

Older adults:
We found one systematic review (search date 2006, 5 RCTs), which compared exercise treatments versus placebo or other treatments in older adults. [79] The review did not pool data because of clinical heterogeneity between RCTs. One RCT identified by the review included 14 people, which is below the minimum criteria for this *Clinical Evidence* review; we have therefore not reported it further. The first RCT (30 people, mean age 72 years, moderately depressed [BDI score 12–24], volunteers), which compared aerobic exercise, social control (student home visits), and waiting list control, found that somatic symptoms were significantly reduced in the exercise group only (P <0.05, between-group analysis not reported). The second RCT (156 people, mean age 57 years) found no significant difference between aerobic exercise, sertraline, and exercise plus medication (P value not reported). The third RCT (32 people, mean age 71 years, BDI score >12, volunteers) found that symptoms were significantly improved with aerobic exercise compared with a health education control (BDI, P = 0.002; HRSD, P = 0.008). The fourth RCT (86 people, mean age 64 years) found that aerobic exercise significantly increased response compared with a social control (health education talks; P = 0.05). However, the review reported that only one RCT adequately described both allocation concealment and blinding, an ITT analysis was described in only one RCT, and two RCTs were in volunteers. It concluded that no firm conclusions could be drawn because of the heterogeneity of the trials and lack of good-quality research. [79]

Harms:

Exercise versus control or different forms of exercise or other treatments:
The two reviews [74] [75] and subsequent RCTs [76] [77] [78] did not report on adverse effects.

Older adults:
The review did not report on harms. [79]

Comment: There is a need for a well-designed RCT of the effects of exercise in people with all grades of depression recruited from clinical populations, assessing clinical outcomes over an adequate time period.

Clinical guide:
There is currently little evidence that exercise is an effective treatment for depression on its own. However, exercise is beneficial for many other reasons, and is often part of activity scheduling in cognitive behavioural therapy. The judicious use of exercise in combination with other effective treatments would seem to make sense in the treatment of depression.

QUESTION What are the effects of interventions in treatment-resistant depression?

OPTION AUGMENTING PRESCRIPTION ANTIDEPRESSANT DRUG TREATMENT WITH LITHIUM

Contributed by Rob Butler

Symptom severity
Compared with placebo augmentation Augmentation with lithium may be more effective than augmentation with placebo at improving response in people who had not responded to antidepressant treatment. However, evidence was weak and there was a wide variation between RCTs in populations included and the treatments used (very low-quality evidence).

For GRADE evaluation of interventions for depression in adults: drug and physical treatments, see table, p 38 .

Benefits: We found two systematic reviews, which had slightly different inclusion criteria, [80] [81] and one subsequent RCT. [82]

The first review (search date 2000, 2 RCTs, 50 people aged 18–75 years with major depression who had not responded to a minimum of 4 weeks of imipramine or equivalent at a recommended dose) compared lithium augmentation versus placebo augmentation. [80] RCTs that included people with bipolar depression were excluded, as the review noted that it might be difficult to generalise results from people with bipolar depression to those with unipolar depression, especially in relation to lithium use. It found that lithium augmentation significantly increased the proportion of people who responded over 2 weeks compared with placebo (11/26 [42%] with lithium *v* 4/24 [17%] with placebo; absolute risk difference 25%, 95% CI 2% to 49%; RR not reported). [80] The review concluded that there was some evidence of benefit for lithium augmentation, but the evidence was very weak.

The second systematic review (search date 2003) compared augmentation with lithium versus placebo in people with major depression with no or partial response to acute-phase treatment. [81] It did not specify exclusion criteria, or the length of time people had been on antidepressant treatment. The review found 9 acute-phase RCTs (234 people in total; 159 [68%] people with unipolar depression, 14 [6%] people with bipolar depression, 61 [26%] people not reported) published between 1983 and 1996, which were included in an earlier meta-analysis. It included two RCTs identified by the first review and 7 RCTs not included in the first review. Trial size ranged from 7 to 61 people (4 RCTs of 17 people or less), and lithium dosages varied widely, as did the duration of augmentation therapy (2–42 days). The antidepressants used included various tricyclic antidepressants, monoamine oxidase inhibitors, tetracyclics, and SSRIs, and dosages were not reported in all RCTs. The review reported in a combined analysis of all 9 RCTs that lithium augmentation significantly improved response rate compared with placebo (responder [not further defined]: 45% with lithium *v* 18% with placebo; P <0.001; results presented graphically; absolute results not reported). The review reported that there was heterogeneity in the design and outcome of the trials, and all had some limitation in quality (quality score as percentage of achievable score according to Quality Assessment Scale: range 39–93%). [81] The review reported that the response rate varied between 18% and 62% in the lithium arm and between 0% and 25% in the placebo arm between the individual RCTs.

The subsequent RCT compared lithium augmentation versus placebo augmentation. [82] It found no significant difference between lithium augmentation and placebo in the proportion of people who responded over 6 weeks (35 people with major depression who had failed to respond to at least 1 earlier trial of antidepressant drugs during the current episode of depression or to 6 weeks' treatment with nortriptyline; response defined as a 50% or greater reduction in HAM-D-17 scores: 2/18 [11%] with lithium *v* 3/17 [18%] with placebo; reported as not significant; CI not reported).

Harms: The systematic reviews [80] [81] and subsequent RCT [82] did not report on adverse effects. For further details about the harms of lithium, see review on Bipolar disorder.

Comment: **Clinical guide:**
Lithium is sometimes prescribed to augment prescription antidepressant medications. Sometimes a prescription antidepressant medication (e.g., an SSRI) may have led to a clinical improvement and it is felt that adding lithium will boost the antidepressant effects.

OPTION AUGMENTING PRESCRIPTION ANTIDEPRESSANT DRUG TREATMENT WITH PINDOLOL

Contributed by Rob Butler

Symptom severity
Compared with placebo We don't know whether augmentation with pindolol is more effective than augmentation with placebo at increasing response in people with depression who had not responded to antidepressant treatment (low-quality evidence).

For GRADE evaluation of interventions for depression in adults: drug and physical treatments, see table, p 38 .

Benefits: We found one systematic review [80] and one subsequent RCT. [83]

The systematic review (search date 2000, 3 RCTs, 106 people aged 18–75 years with major depression who had not responded to a minimum of 4 weeks of imipramine or equivalent) compared pindolol augmentation versus placebo augmentation. [80] It found no significant difference in the proportion of people who responded over 1 to 8 weeks between pindolol augmentation and placebo (responders: 10/53 [19%] with pindolol augmentation *v* 6/53 [11%] with placebo; absolute risk difference +8%, 95% CI –6% to +21%; RR not reported). The meta-analysis is likely to have been underpowered to detect a clinically important difference between interventions.

The subsequent RCT (42 people with major depressive disorder who had had an insufficient response to an adequate trial of an SSRI) compared pindolol 7.5 mg versus sham augmentation. The RCT found no significant difference in outcome (results presented graphically). [83]

Harms: The review [80] and subsequent RCT [83] gave no information on adverse effects.

Comment: **Clinical guide:**
Pindolol is sometimes prescribed to augment prescription antidepressant medications. If a prescription antidepressant medication (e.g., an SSRI) has led to a clinical improvement, it may be felt that adding pindolol will boost the antidepressant effects. A rationale for this treatment is that beta-blockers control some of the symptoms of anxiety (e.g., tachycardia) that can accompany depression. However, beta-blockers are not licensed for the treatment of depression.

QUESTION Which interventions reduce relapse rates?

OPTION CONTINUING PRESCRIPTION ANTIDEPRESSANT DRUG TREATMENT

Contributed by Andrea Cipriani, Rob Butler, and John Geddes

Relapse rates
Compared with placebo Continuing prescription antidepressant drug treatment after recovery seems more effective than placebo at reducing relapse in people with depression who had responded to antidepressants (moderate-quality evidence).

Compared with placebo in older adults Continuing prescription antidepressant drug treatment after recovery may be more effective than placebo at reducing relapse in older people with depression who had responded to antidepressants (low-quality evidence).

For GRADE evaluation of interventions for depression in adults: drug and physical treatments, see table, p 38 .

Benefits: We identified 5 systematic reviews. [84] [85] [86] [87] [42]

The first review compared continuation treatment with prescription antidepressant drugs versus placebo over 12 months in people who had responded to antidepressant treatment over the previous 1 month to 3 years. [84] It found that, overall, continuing antidepressant drugs in people who had

responded to them significantly reduced the proportion of people who relapsed compared with placebo (search date 2000, 31 RCTs, 4410 people with first episode or recurrent depression; numbers relapsing: 465/2527 [18%] with continuing antidepressants *v* 1031/2505 [41%] with placebo; OR 0.30, 95% CI 0.22 to 0.38). [84] The review found that, in people who had responded to antidepressants after 2 months' treatment, the number needed to treat by continuing antidepressants to prevent one additional relapse over 6 months was 6 (95% CI 5 to 8), to prevent relapse over 12 months was 5 (95% CI 4 to 6), and over 18 to 36 months was 4 (95% CI 3 to 7). In people who had responded to antidepressant drugs and received 4 to 6 months' treatment, the number needed to treat by continuing antidepressants to prevent one additional relapse over 12 months was 7 (95% CI 5 to 8), and over 18 to 36 months was 3 (95% CI 3 to 4). [84] The review found that relapse was most likely to occur in the first 12 months after discontinuation of antidepressants (relapse in first 12 months: 19% with continuing antidepressants *v* 60% with placebo), but the benefits of continuing were apparent for up to 36 months (first relapse over 12 to 36 months: 10% with continuing antidepressants *v* 29% with placebo). [84]

The second review (search date 2007) examined long-term therapy with SSRI versus placebo. [85] It included 6 RCTs of 6 to 8 months' duration, which included 1299 people aged 18 to 89 years with moderate to severe depression who received an SSRI. Three RCTs included people with depression after MI, CVA, or alcohol dependence, which are outside the scope of this review. We have therefore reported the subgroup analysis that included the three RCTs in people without comorbidity. These three RCTs examined the effects of paroxetine, sertraline, and citalopram. The review reported on efficacy (response to treatment defined as a 50% improvement in depression score relative to baseline), remission (a score of 7 or below on the Hamilton Rating Scale for Depression), and total withdrawals (as a proxy measure of treatment acceptability). The review found that, compared with placebo, SSRIs significantly increased response to treatment at 6 to 8 months (3 RCTs; 240/406 [59%] with SSRIs *v* 134/316 [42%] with placebo; OR 2.13, 95% CI 1.11 to 4.08) and remission (2 RCTs; 117/295 [40%] with SSRIs *v* 50/200 [25%] with placebo; OR 2.06, 95% CI 1.41 to 3.01), but the review found no significant difference between groups in acceptability (withdrawals: 3 RCTs; 242/406 [60%] with SSRIs *v* 199/316 [63%] with placebo; OR 0.72, 95% CI 0.44 to 1.17). The completion rate in the three RCTs was 23%, 34%, and 78%, and all reported the last observation carried forward. No RCT reported data beyond 12 months, and two RCTs had unclear sequence generation and allocation concealment. [85]

The third systematic review (search date 2007) examined the efficacy of continuation or maintenance treatment of major depressive disorder with either SSRIs or tricyclic antidepressants (TCAs), and included people entering a continuation or maintenance phase after achieving remission from the acute phase. [86] The review found that SSRIs and TCAs significantly reduced the risk of relapse in the maintenance phase compared with placebo over 1 year's follow-up of maintenance treatment (SSRIs: OR 0.24, 95% CI 0.20 to 0.29; P <0.001; TCAs: OR 0.29, 95% CI 0.23 to 0.38; P <0.001; results presented graphically; absolute numbers not reported). The review reported that the prophylactic effect seemed to be constant over the length of the continuation phase. In subgroup analysis, the review found that people with recurrent episodes experienced less protection from antidepressants compared with placebo over the maintenance phase (OR 0.37, 95% CI 0.31 to 0.44; P <0.001; regression analysis) than did people with single episodes (OR 0.12, 95% CI 0.06 to 0.26; P <0.001; regression analysis). [86] The review reported that definitions of relapse and remission varied between RCTs, some did not define the antidepressant used, and the trials were heterogeneous with respect to diagnostic criteria, withdrawal rates, power at the start of the trial, and outcome criteria.

The fourth systematic review (search date 2007) examined the efficacy and effectiveness of second-generation antidepressants for preventing major depression relapse and recurrence during both continuation and maintenance phases of treatment. [87] The primary outcome was loss of response or remission (continuation phase relapse or maintenance phase relapse). It included 23 RCTs. In 12 RCTs, the follow-up was <1 year, and these trials were deemed to represent relapse prevention during continuation phase treatment. In 11 RCTs, follow-up was >1 year and these were deemed to represent recurrence prevention during maintenance phase treatment. The review found that second-generation antidepressants significantly reduced the risk of relapse compared with placebo in trials with follow-up of <1 year (12 RCTs; RR 0.54, 95% CI 0.46 to 0.62; results presented graphically; absolute numbers not reported). Drugs included in the analysis included bupropion, citalopram, escitalopram, fluoxetine, mirtazapine, nefazodone, sertraline, and venlafaxine. The review found that second-generation antidepressants significantly reduced the risk of recurrence compared with placebo in trials with a follow-up of 1 year or more (11 RCTs; RR 0.56, 95% CI 0.48 to 0.66; results presented graphically; absolute numbers not reported). Drugs included in the analysis included citalopram, escitalopram, fluoxetine, nefazodone, paroxetine, sertraline, and venlafaxine. [87]

The fifth systematic review (search date 2007) included RCTs of venlafaxine versus placebo in the prevention of relapse or recurrence after a major depressive episode. [42] It included three RCTs (765 people), of which one RCT (258 people) was unpublished (data supplied by the manufacturer). The review reported two different statistical analyses. The review found that venlafaxine significantly reduced relapse compared with placebo when calculated by the conditional maximum likelihood method (OR 0.37, 95% CI 0.27 to 0.51), but not when calculated by random effects analysis (OR 0.36, 95% CI 0.03 to 3.48; absolute numbers not reported). [42]

Older adults:
We found 4 RCTs that compared continuing antidepressant drugs versus placebo in older people treated for depression. [88] [89] [90] [91]

The first RCT compared dosulepin (dothiepin) versus placebo. [88] It found that dosulepin significantly reduced the risk of relapse after recovery compared with placebo after 2 years (69 people aged >60 years, with mild to moderate or severe depression who had recovered sufficiently and consented to enter a 2-year trial of continuation treatment; relapse: RR 0.45, 95% CI 0.22 to 0.96). [88] The second RCT compared citalopram versus placebo for 48 weeks or more. [89] It found that citalopram significantly reduced the proportion of people who relapsed after recovery compared with placebo after 48 weeks (121 people aged >64 years with major depression who had responded to citalopram 20–40 mg for 8 weeks and who continued to receive the dose they had responded to for a further 16 weeks; proportion who relapsed: 19/60 [32%] with citalopram *v* 41/61 [67%] with placebo; HR 0.32, 95% CI 0.19 to 0.56). [89] The third RCT compared sertraline versus placebo for a further 2 years. It found no significant difference between sertraline and placebo in the proportion of people who did not relapse after 2 years (113 people aged 65 years or older, HAM-D >17, who had responded to sertraline 50–200 mg/day for 8 weeks; proportion of people not relapsing: 39% with sertraline *v* 31% with placebo; ARI +8%, 95% CI –12% to +28%). [90] The fourth RCT (116 people, 70 years and older with major depression, with no relapse during a 16-week open continuation treatment with paroxetine) compared paroxetine versus placebo over a 12-month period in a randomly assigned two (paroxetine *v* placebo) by two (monthly interpersonal therapy versus clinical management) double-blind maintenance trial. [91] It found that, after controlling for the effects of psychotherapy, paroxetine was significantly superior to placebo in preserving overall well-being (measured by health-related quality of life; P = 0.04; results presented graphically; absolute numbers not reported). [91]

Harms:

Two reviews reported data about discontinuation and adverse effects. [84] [87] In the first review, adverse effects seemed to be similar to those reported in trials of acute treatment. [84] The review found that significantly more people continuing prescription antidepressant drugs withdrew from the trials compared with people taking placebo (18% with antidepressants *v* 15% with placebo; OR 1.30, 95% CI 1.07 to 1.59). Six people continuing antidepressant drugs committed suicide (5/767 [0.7%] with maprotiline and 1/185 [0.5%] with sertraline) compared with one person taking placebo (OR 5.96, 95% CI 0.72 to 49.47). [84] The other review found no significant difference between active treatment and placebo in loss to follow-up because of adverse effects (18 RCTs; RR 1.42, 95% CI 0.92 to 2.20; absolute numbers not reported). [87]

Older adults:
The first RCT gave no information on adverse effects. [88] However, a case-control study found that, after adjustment for confounding factors and the use of other antidepressants, people who had taken dosulepin were significantly more likely to develop ischaemic heart disease than those who had not (OR 1.67, 95% CI 1.17 to 2.36). [92] The second RCT found that, compared with placebo, continuing citalopram significantly increased sweating, tremor, and fatigue (sweating: 4/60 [7%] with citalopram *v* 3/61 [5%] with placebo; tremor: 3/60 [5%] with citalopram *v* 0/61 [0%] with placebo; fatigue: 10/60 [17%] with citalopram *v* 6/61 [10%] with placebo; reported as significant for all outcomes; CI not reported). [89] The third and fourth RCTs did not report on adverse events. [90] [91]

Comment:

A substantial number of people who respond to antidepressants experience a relapse despite ongoing pharmacotherapy. The return of symptoms has been interpreted as a loss of the effectiveness of antidepressant activity. A systematic review (search date 2005) tried to estimate the proportion of relapse attributable to the loss of true drug response versus a loss of placebo response. [93] Authors reviewed continuation studies of new-generation antidepressants that began as placebo-controlled acute-phase studies. Four studies were reviewed, and the review estimated the proportion of relapse attributable to the loss of true drug response versus the loss of response attributable to the non-specific effects of treatment. The relapse rate in placebo responders was 24.1%, whereas the relapse rate in antidepressant responders was 7.4%. The review reported that the different methods of estimating relapse suggested that the majority of relapses in patients taking antidepressants during continuation treatment could be attributed to relapses occurring in patients who were not true drug responders. [93]

GLOSSARY

Augmentation involves adding a medication to enhance the effects of another.

Continuation treatment Continuation of treatment after successful resolution of a depressive episode to prevent relapse.

Dysthymic disorder Characterised by at least 2 years of depressed mood for more days than not, accompanied by additional symptoms that do not reach the criteria for major depressive disorder.

Effect size This expresses the degree of overlap between the range of scores in the control and experimental groups. The effect size can be used to estimate the proportion of people in the control group who had a poorer outcome than the average person in the experimental group; a proportion of 50% or less indicates that the treatment has no effect.

Mild to moderate depression Characterised by depressive symptoms and some functional impairment.

Severe depression Characterised by agitation or psychomotor retardation in addition to depressive symptoms and functional impairment with marked somatic symptoms. Treatments are considered to have been assessed in severe depression if the RCT included inpatients.

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Major depressive disorder Characterised by one or more major depressive episodes (i.e., at least 2 weeks of depressed mood or loss of interest accompanied by at least 4 additional symptoms of depression).

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Augmenting prescription antidepressant drug treatment with lithium in treatment-resistant depression New evidence added. [81] Categorisation unchanged (Unknown effectiveness), as there remains insufficient evidence to judge the effects of this intervention.

Continuing prescription antidepressant drug treatment to reduce relapse rates New evidence added. [42] [85] [86] [87] [91] [93] Categorisation unchanged (Beneficial).

Electroconvulsive therapy in mild to moderate or severe depression New evidence added. [65] [66] [68] [67] [69] [70] Categorisation unchanged (Beneficial).

Exercise in mild to moderate or severe depression New evidence added. [74] [75] [77] [78] [79] Categorisation unchanged (Unknown effectiveness), as there remains insufficient evidence to judge the effects of this intervention.

Monoamine oxidase inhibitors versus other prescription antidepressant drugs (tricyclic antidepressant drugs, SSRIs, or venlafaxine) in atypical depressive disorders New evidence added. [20] [22] Categorisation unchanged (Beneficial).

Prescription antidepressant drugs (tricyclic antidepressants [including low-dose tricyclic antidepressants], SSRIs, monoamine oxidase inhibitors, or venlafaxine) versus placebo in mild to moderate or severe depression New evidence added. [12] [13] [20] [22] [24] [25] [26] [29] [30] [31] [32] [33] [34] [35] [36] [37] Categorisation unchanged (Beneficial).

SSRIs versus each other and other prescription antidepressant drugs (tricyclic antidepressants, monoamine oxidase inhibitors, or venlafaxine) in mild to moderate or severe depression New evidence added. [20] [22] [38] [41] [42] [43] [51] [52] [55] [56] [57] Categorisation unchanged (Beneficial).

St John's wort (*Hypericum perforatum*) in mild to moderate or severe depression Search updated for an already included systematic review. [41] New evidence added. Categorisation unchanged (Likely to be beneficial).

Tricyclic antidepressants versus each other and other prescription antidepressant drugs (SSRIs, monoamine oxidase inhibitors, or venlafaxine) in mild to moderate or severe depression New evidence added. [20] [22] [38] [40] [41] [42] Categorisation unchanged (Beneficial).

Venlafaxine versus other prescription antidepressant drugs (tricyclic antidepressant drugs, SSRIs, or monoamine oxidase inhibitors) in mild to moderate or severe depression New evidence added. [20] [22] [42] [43] Categorisation unchanged (Beneficial).

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Disclaimer

TABLE 1 **Summary estimates of OR for efficacy (response rate) and acceptability (withdrawal rate) in meta-analyses of direct comparisons between SSRIs and venlafaxine and multiple-treatments meta-analysis (MTM) between SSRIs and venlafaxine (see note below).** [43]

				Efficacy (ORs >1 favour the first antidepressant)			Acceptability (ORs <1 favour the first antidepressant)		
				Direct comparisons		MTM (direct and indirect comparison)	Direct comparisons		MTM (direct and indirect comparison)
Comparisons		Number of studies included	Number of people randomised	Response rate (responders / total randomised)	OR (95% CI)	OR (95% CrI)	Withdrawal rate (withdrawals / total randomised)	OR (95% CI)	OR (95% CrI)
Citalopram *v*	Escitalopram	5	1604	319/622 *v* 426/725	**0.68 (0.53 to 0.87)**	0.84 (0.70 to 1.01)	127/750 *v* 141/854	1.17 (0.83 to 1.64)	1.07 (0.86 to 1.31)
	Fluoxetine	3	740	216/364 *v* 219/376	1.05 (0.77 to 1.43)	1.10 (0.93 to 1.31)	75/364 *v* 68/376	1.17 (0.80 to 1.70)	0.90 (0.73 to 1.09)
	Fluvoxamine	1	217	33/108 *v* 31/109	1.11 (0.62 to 1.98)	1.13 (0.86 to 1.47)	22/108 *v* 29/109	0.71 (0.37 to 1.33)	**0.73 (0.54 to 0.99)**
	Paroxetine	1	406	77/199 *v* 102/207	**1.54 (1.04 to 2.28)**	1.08 (0.90 to 1.30)	43/207 *v* 41/199	1.01 (0.62 to 1.63)	0.81 (0.65 to 1.01)
	Sertraline	2	615	139/200 *v* 136/200	0.93 (0.61 to 1.42)	0.88 (0.72 to 1.07)	60/307 *v* 82/308	**0.67 (0.46 to 0.98)**	1.02 (0.81 to 1.28)
	Venlafaxine	1	151	50/75 *v* 49/76	1.10 (0.56 to 2.16)	0.86 (0.71 to 1.05)	–	–	0.84 (0.67 to 1.06)
Escitalopram *v*	Citalopram	5	1604	426/725 *v* 319/622	**1.47 (1.15 to 1.90)**	1.19 (0.99 to 1.43)	141/854 *v* 127/750	0.86 (0.61 to 1.20)	0.93 (0.76 to 1.16)
	Fluoxetine	2	543	143/276 *v* 126/267	1.23 (0.87 to 1.74)	**1.32 (1.12 to 1.55)**	66/276 *v* 68/267	0.98 (0.37 to 2.56)	0.84 (0.70 to 1.01)
	Fluvoxamine	–	–	–	–	**1.35 (1.02 to 1.76)**	–	–	**0.69 (0.50 to 0.94)**
	Paroxetine	2	784	274/398 *v* 255/386	1.12 (0.76 to 1.65)	**1.30 (1.10 to 1.53)**	40/398 *v* 50/386	0.75 (0.48 to 1.17)	**0.76 (0.62 to 0.93)**
	Sertraline	2	489	144/243 *v* 152/246	0.90 (0.62 to 1.30)	1.06 (0.88 to 1.27)	47/243 *v* 40/246	1.24 (0.77 to 1.97)	0.95 (0.77 to 1.19)
	Venlafaxine	2	495	172/249 *v* 160/246	1.21 (0.69 to 2.11)	1.03 (0.86 to 1.24)	52/249 *v* 56/246	0.90 (0.58 to 1.39)	**0.78 (0.64 to 0.97)**
Fluoxetine *v*	Citalopram	3	740	219/376 *v* 216/364	0.95 (0.70 to 1.29)	0.91 (0.76 to 1.08)	68/376 *v* 75/364	0.86 (0.59 to 1.25)	1.11 (0.92 to 1.37)
	Escitalopram	2	543	126/267 *v* 143/276	0.81 (0.57 to 1.15)	**0.76 (0.65 to 0.89)**	68/267 *v* 66/276	1.02 (0.39 to 2.67)	1.19 (0.99 to 1.43)
	Fluvoxamine	2	284	83/143 *v* 83/141	0.97 (0.60 to 1.55)	1.02 (0.81 to 1.30)	28/143 *v* 31/141	0.85 (0.48 to 1.52)	0.82 (0.62 to 1.07)
	Paroxetine	13	2806	771/1287 *v* 740/1277	1.01 (0.82 to 1.24)	0.98 (0.86 to 1.12)	447/1406 *v* 468/1400	0.93 (0.79 to 1.09)	0.91 (0.79 to 1.05)
	Sertraline	8	1352	344/666 *v* 406/686	**0.70 (0.56 to 0.88)**	**0.80 (0.69 to 0.93)**	151/546 *v* 135/568	1.25 (0.88 to 1.77)	1.14 (0.96 to 1.36)
	Venlafaxine	12	2446	607/1126 *v* 679/1116	**0.74 (0.62 to 0.88)**	**0.78 (0.68 to 0.90)**	290/1226 *v* 302/1220	0.94 (0.78 to 1.13)	0.94 (0.81 to 1.09)
Fluvoxamine *v*	Citalopram	1	217	31/109 *v* 33/108	0.90 (0.50 to 1.62)	0.88 (0.68 to 1.16)	29/109 *v* 22/108	1.42 (0.75 to 2.66)	**1.37 (1.01 to 1.85)**
	Escitalopram	–	–	–	–	**0.74 (0.57 to 0.98)**	–	–	**1.45 (1.06 to 2.00)**
	Fluoxetine	2	284	83/141 *v* 83/143	1.03 (0.64 to 1.66)	0.98 (0.77 to 1.23)	31/141 *v* 28/143	1.17 (0.66 to 2.09)	1.22 (0.93 to 1.61)
	Paroxetine	3	281	72/143 *v* 77/138	0.83 (0.51 to 1.34)	0.96 (0.76 to 1.23)	42/143 *v* 38/138	1.08 (0.62 to 1.85)	1.10 (0.84 to 1.47)
	Sertraline	2	185	48/89 *v* 49/96	1.21 (0.53 to 2.75)	0.79 (0.61 to 1.01)	22/89 *v* 12/96	1.47 (0.19 to 11.11)	**1.38 (1.03 to 1.89)**
	Venlafaxine	1	111	14/34 *v* 48/77	**0.42 (0.19 to 0.96)**	**0.77 (0.59 to 0.99)**	13/34 *v* 18/77	2.03 (0.85 to 4.84)	1.14 (0.86 to 1.54)
Paroxetine *v*	Citalopram	1	406	77/199 *v* 102/207	**0.65 (0.44 to 0.96)**	0.93 (0.77 to 1.11)	41/199 *v* 43/207	0.99 (0.61 to 1.60)	1.23 (0.99 to 1.54)

Comparisons		Number of studies included	Number of people randomised	Efficacy (ORs >1 favour the first antidepressant) Direct comparisons Response rate (responders / total randomised)	OR (95% CI)	MTM (direct and indirect comparison) OR (95% CrI)	Acceptability (ORs <1 favour the first antidepressant) Direct comparisons Withdrawal rate (withdrawals / total randomised)	OR (95% CI)	MTM (direct and indirect comparison) OR (95% CrI)
	Escitalopram	2	784	255/386 *v* 274/398	0.89 (0.61 to 1.32)	**0.77 (0.65 to 0.91)**	50/386 *v* 40/398	1.33 (0.85 to 2.07)	**1.32 (1.08 to 1.61)**
	Fluoxetine	13	2806	740/1277 *v* 771/1287	0.99 (0.85 to 1.22)	1.02 (0.89 to 1.16)	468/1400 *v* 447/1406	1.08 (0.92 to 1.26)	1.10 (0.95 to 1.27)
	Fluvoxamine	3	281	77/138 *v* 72/143	1.20 (0.74 to 1.96)	1.04 (0.81 to 1.32)	38/138 *v* 42/143	0.93 (0.54 to 1.60)	0.91 (0.68 to 1.19)
	Sertraline	4	664	204/325 *v* 241/339	0.57 (0.30 to 1.07)	**0.82 (0.69 to 0.96)**	75/325 *v* 69/339	1.47 (0.65 to 3.33)	**1.25 (1.04 to 1.52)**
	Venlafaxine	1	361	105/178 *v* 113/183	0.89 (0.58 to 1.36)	**0.79 (0.67 to 0.94)**	52/178 *v* 47/183	1.19 (0.75 to 1.90)	1.03 (0.86 to 1.24)
Sertraline *v*	Citalopram	2	615	139/200 *v* 136/200	1.07 (0.70 to 1.64)	1.14 (0.93 to 1.39)	82/308 *v* 60/307	**1.49 (1.02 to 2.18)**	0.98 (0.78 to 1.23)
	Escitalopram	2	489	152/246 *v* 144/243	1.12 (0.77 to 1.61)	0.94 (0.79 to 1.14)	40/246 *v* 47/243	0.81 (0.51 to 1.29)	1.05 (0.84 to 1.30)
	Fluoxetine	8	1352	406/686 *v* 344/666	**1.42 (1.13 to 1.78)**	**1.25 (1.08 to 1.45)**	135/568 *v* 151/546	0.80 (0.56 to 1.14)	0.88 (0.74 to 1.04)
	Fluvoxamine	2	185	49/96 *v* 48/89	0.83 (0.36 to 1.88)	1.27 (0.99 to 1.64)	12/96 *v* 22/89	0.68 (0.09 to 5.15)	**0.72 (0.53 to 0.97)**
	Paroxetine	4	664	241/339 *v* 204/325	1.76 (0.93 to 3.32)	**1.22 (1.04 to 1.45)**	69/339 *v* 75/325	0.68 (0.30 to 1.54)	**0.80 (0.66 to 0.96)**
	Venlafaxine	5	611	177/303 *v* 190/308	0.87 (0.59 to 1.29)	0.98 (0.82 to 1.16)	49/303 *v* 70/308	0.56 (0.24 to 1.33)	**0.82 (0.67 to 1.00)**
Venlafaxine *v*	Citalopram	1	151	49/76 *v* 50/75	0.91 (0.46 to 1.78)	1.16 (0.95 to 1.41)	–	–	1.19 (0.94 to 1.49)
	Escitalopram	2	495	160/246 *v* 172/249	0.82 (0.47 to 1.44)	0.97 (0.81 to 1.16)	56/246 *v* 52/249	1.12 (0.72 to 1.73)	**1.28 (1.03 to 1.56)**
	Fluoxetine	11	2446	679/1116 *v* 607/1126	**1.36 (1.14 to 1.62)**	**1.28 (1.11 to 1.47)**	302/1220 *v* 290/1226	1.07 (0.88 to 1.29)	1.06 (0.92 to 1.23)
	Fluvoxamine	1	111	48/77 *v* 14/34	**2.36 (1.04 to 5.38)**	**1.30 (1.01 to 1.69)**	18/77 *v* 13/34	0.49 (0.21 to 1.18)	0.88 (0.65 to 1.16)
	Paroxetine	1	361	113/183 *v* 105/178	1.12 (0.74 to 1.71)	**1.27 (1.06 to 1.49)**	47/183 *v* 52/178	0.84 (0.53 to 1.33)	0.97 (0.81 to 1.16)
	Sertraline	5	611	190/308 *v* 177/303	1.15 (0.78 to 1.69)	1.02 (0.86 to 1.22)	70/308 *v* 49/303	1.78 (0.75 to 4.18)	**1.22 (1.00 to 1.49)**

Statistically significant results for direct and indirect comparisons are in bold: for efficacy analysis, ORs >1 favour the first antidepressant; for acceptability, ORs <1 favour the first antidepressant. Note: although we have just presented results for SSRIs and venlafaxine in this table, it should be noted that bupropion, duloxetine, milnacipran, mirtazapine, and reboxetine were also included in the multiple-treatments meta-analysis (MTM) and will have contributed to the effect size reported in the MTM analysis. In the analysis of comparative efficacy for the MTM analysis, fluoxetine was selected as the reference drug. For the MTM analysis, to obtain ORs for comparisons in the opposite directions, the reciprocals have been taken (e.g., the OR for citalopram compared with fluoxetine is 1.10; the OR for fluoxetine compared with citalopram is 1/1.10 = 0.91).
CrI, credibility interval.

TABLE 2 **Adverse events (% of people) with SSRIs versus tricyclic antidepressant drugs (see text, p 11).** [46]

Adverse effects	SSRI event rates (%)	TCA event rates (%)
Dry mouth	21	55
Constipation	10	22
Dizziness	13	23
Nausea	22	12
Diarrhoea	13	5
Anxiety	13	7
Agitation	14	8
Insomnia	12	7
Nervousness	15	11
Headache	17	14

TCA, tricyclic antidepressants.

TABLE **GRADE evaluation of interventions for depression in adults: drug and physical treatments**

Important outcomes	**Symptom severity, relapse rates, adverse effects**								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of drug and physical treatments in mild to moderate or severe depression?									
At least 150 (at least 16,000) [14] [15] [16] [17] [18] [19] [20]	Symptom severity	Prescription antidepressant drugs *v* placebo	4	0	0	–1	0	Moderate	Directness point deducted for issues affecting generalisability of trial results to clinical practice (placebo issue, sponsorship, publication bias)
At least 24 (at least 2115) [23] [24] [25] [26]	Symptom severity	Prescription antidepressant drugs *v* placebo in older adults	4	–1	0	–2	0	Very low	Quality point deducted for incomplete reporting of results. Directness point deducted for diverse populations included and short-term RCTs
1 (unclear) [27]	Symptom severity	Prescription antidepressant drugs *v* placebo in psychotic depression	4	–1	0	–2	0	Very low	Quality point deducted for incomplete reporting of results. Directness points deducted for imprecision of result (CI 0.5 to 147) and small number of comparators (amitriptyline only)
4 (250) [28]	Symptom severity	Prescription antidepressant drugs *v* placebo in atypical depression	4	0	0	–1	0	Moderate	Directness point deducted for 1 RCT with extreme result compared with other RCTs, which may affect robustness of overall result
84 (5376) [38]	Symptom severity	Tricyclic antidepressants *v* each other	4	0	–1	–1	0	Low	Consistency point deducted for significant heterogeneity among RCTs. Directness point deducted for inclusion of treatments other than tricyclic antidepressants in analysis
6 (551) [15]	Symptom severity	Low-dose tricyclic antidepressants *v* standard-dose tricyclic antidepressants	4	0	0	–2	0	Low	Directness points deducted for short-term results and unclear clinical relevance of results
Unclear (unclear) [39]	Symptom severity	Tricyclic antidepressants plus benzodiazepines *v* tricyclic antidepressants alone	4	–1	0	–2	0	Very low	Quality point deducted for incomplete reporting of results. Directness points deducted for inclusion of treatments other than tricyclic antidepressants in analysis and unclear clinical relevance (improvement at 1 week, not apparent at 6 weeks)
1 (unclear) [27]	Symptom severity	Tricyclic antidepressants in people with psychotic depression	4	–1	0	–2	+1	Low	Quality point deducted for incomplete reporting of results. Directness points deducted for small number of comparators (imipramine and fluvoxamine only) and unclear outcome. Effect-size point added for RR >2
117 (25,928) [43]	Symptom severity	SSRIs *v* each other	4	0	0	–1	0	Moderate	Directness point deducted for generalisability issues (applies to acute phase treatment only, differences between direct and multiple treatments meta-analysis analysis)
At least 49 (at least 4073) [20] [38] [44]	Symptom severity	SSRIs *v* tricyclic antidepressants	4	0	0	0	0	High	
At least 8 (at least 597) [20] [28]	Symptom severity	SSRIs *v* monoamine oxidase inhibitors	4	0	0	0	0	High	

Important outcomes	Symptom severity, relapse rates, adverse effects								
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
1 (50) [45]	Symptom severity	SSRIs plus benzodiazepines *v* SSRIs alone	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for small number of comparators
3 (102) [27]	Symptom severity	SSRIs *v* each other or other antidepressants in people with psychotic depression	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for unclear generalisability (small trials, widely different response rates between RCTs [response to fluvoxamine 30% in 1 RCT, 82% in another])
At least 13 (at least 2153) [20] [22] [28]	Symptom severity	Monoamine oxidase inhibitors *v* tricyclic antidepressants	4	0	–1	0	0	Moderate	Consistency point deducted for inconsistent results between RCTs depending on analysis
At least 15 (at least 773) [20] [22] [42]	Symptom severity	Venlafaxine *v* tricyclic antidepressants	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results in 1 review
At least 29 (at least 3692 people) [20] [22] [42] [43]	Symptom severity	Venlafaxine *v* SSRIs	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results in 1 review
6 (256) [64]	Symptom severity	Electroconvulsive therapy *v* simulated electroconvulsive therapy	4	0	0	–1	0	Moderate	Directness point deducted for clinical heterogeneity
18 (1144) [64]	Symptom severity	Electroconvulsive therapy *v* prescription antidepressant drugs	4	0	0	–1	0	Moderate	Directness point deducted for clinical heterogeneity
25 (1635) [64] [66] [67] [68]	Symptom severity	Bilateral *v* unilateral electroconvulsive therapy	4	0	0	–1	0	Moderate	Directness point deducted for clinical heterogeneity
1 (64) [69]	Symptom severity	Different types of electroconvulsive therapy *v* each other in older adults	4	–3	0	0	0	Very low	Quality points deducted for sparse data, post-hoc analysis, and no intention-to-treat analysis
18 (3064) [41]	Symptom severity	St John's wort *v* placebo	4	–1	–1	–2	0	Very low	Quality point deducted for weak methods. Consistency point deducted for statistical heterogeneity. Directness points deducted for variation in preparations used and variation in results depending on location of trial
5 (1016) [41]	Symptom severity	St John's wort *v* tricyclic antidepressants	4	–1	0	–2	0	Very low	Quality point deducted for weak methods. Directness points deducted for variation in preparations used and variation in results depending on location of trial
12 (1794) [41]	Symptom severity	St John's wort *v* SSRIs	4	–1	0	–2	0	Very low	Quality point deducted for weak methods. Directness points deducted for variation in preparations used and variation in results depending on location of trial
At least 28 (at least 1267) [74] [75] [76] [77] [78]	Symptom severity	Exercise *v* control or different forms of exercise or other treatments	4	–2	–1	–1	0	Very low	Quality points deducted for weak methods and incomplete reporting of results. Consistency point deducted for statistical heterogeneity. Directness point deducted for inclusion of non-clinical populations
4 (298) [79]	Symptom severity	Exercise *v* control or different forms of exercise or other treatments in older adults	4	–2	0	–1	0	Very low	Quality points deducted for weak methods and incomplete reporting of results. Directness point deducted for heterogeneity among RCTs
What are the effects of interventions in treatment-resistant depression?									

Important outcomes	**Symptom severity, relapse rates, adverse effects**								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
At least 10 (at least 269) [80] [82] [81]	Symptom severity	Lithium augmentation *v* placebo augmentation	4	–2	0	–1	0	Very low	Quality points deducted for incomplete reporting of results and weak methods. Directness point deducted for clinical heterogeneity between RCTs
4 (148) [80] [83]	Symptom severity	Augmentation with pindolol *v* placebo augmentation	4	–2	0	0	0	Low	Quality points deducted for sparse data and for incomplete reporting of results
Which interventions reduce relapse rates?									
At least 31 (at least 4410) [85] [86] [87] [42] [84]	Relapse rates	Continuing prescription antidepressant drug *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
4 (419) [88] [89] [90] [91]	Relapse rates	Continuing prescription antidepressant drug *v* placebo in older adults	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results

Type of evidence: 4 = RCT. Consistency: similarity of results across studies.
Directness: generalisability of population or outcomes.
Effect size: based on relative risk or odds ratio.