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Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2000 British Association for Psychopharmacology guidelines

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On Behalf of the Consensus Meeting; endorsed by the British Association for Psychopharmacology

Abstract

A revision of the 2000 British Association for Psychopharmacology evidence-based guidelines for treating depressive disorders with antidepressants was undertaken to incorporate new evidence and to update the recommendations where appropriate. A consensus meeting involving experts in depressive disorders and their management was held in May 2006. Key areas in treating depression were reviewed, and the strength of evidence and clinical implications were considered. The guidelines were drawn up after extensive feedback from participants and interested parties. A literature review is provided, which identifies the quality of evidence to inform the recommendations, the strength of which are based on the level of evidence. These guidelines cover the nature and detection of depressive disorders, acute treatment with antidepressant drugs, choice of drug versus alternative treatment, practical issues in prescribing and management, next-step treatment, relapse prevention, treatment of relapse, and stopping treatment.

Key words

antidepressants; depressive disorder; evidence-based guidelines; treatment

Other members of the consensus meeting: Dr David Baldwin, Prof Thomas Barnes, Dr David Coghill, Dr Christian de Bodinat, Mr Rodney Elgie, Dr Paul Gandhi, Prof Guy Goodwin, Dr Peter Haddad, Prof Tony Hale, Prof John Henry, Mr Andy Hockey, Dr Alan Lenox-Smith, Prof Brian Leonard, Dr Chris Manning, Dr David Perahia, Dr Stephen Pilling, Prof Ian Reid, Prof Barbara Sahakian, Dr Shaw Sorooshian, Dr Clare Stanford, Dr Guy Yeoman.

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Introduction

The British Association for Psychopharmacology (BAP) aims to advance education and research in the science of psychopharmacology, by arranging scientific meetings, fostering research and teaching, encouraging publication of research results and providing guidance and information to the public and professions on matters relevant to psychopharmacology. As an important part of this process the BAP has published a series of evidence-based guidelines for the use of drugs in psychiatric disorders, with the emphasis on producing comprehensive but concise and useable guidelines based on a review of the evidence (see www.bap.org.uk).

This revision of the British Association for Psychopharmacology (BAP) guidelines for treating depressive disorders with antidepressants (Anderson, *et al.*, 2000) was undertaken to update the guidelines in the light of new evidence. Every effort was taken to make recommendations explicitly evidence based.

Methodology

A consensus meeting was held under the auspices of the BAP in May 2006 involving experts in the field of depression and antidepressant treatment, user representatives and medical and scientific staff from pharmaceutical companies. Presentations on key areas with an emphasis on systematic reviews and randomised-controlled trials (RCTs) were followed by discussion about the quality of evidence and its implications. Subsequently, a literature review together with recommendations and their strength based on the level of evidence were circulated to participants, user groups and other interested parties for feedback, which was incorporated into the final version of these guidelines.

Identification of relevant evidence

The breadth of information covered in these guidelines did not allow for a systematic review of all possible data from primary sources. Major systematic reviews and RCTs were identified from MEDLINE and EMBASE searches, and from the Cochrane Database as well as from previous guidelines (e.g. American Psychiatric Association, 2000a; National Institute for Clinical Excellence, 2004; Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Depression, 2004; Bauer, *et al.*, 2007), cross referencing and identification by experts in the field.

Presentation of data, levels of evidence and strength of recommendations

We have tried, where possible, to present effect sizes or numbers needed to treat or harm (NNT or NNH) to aid interpretation of the magnitude of effect seen. As a rough guide it has been suggested that effect sizes of 0.2, 0.5 and 0.8 reflect small, medium and large effects, respectively (Cohen, 1988). NNTs of five or fewer are likely to be clinically important, and those above 10 unlikely to be so in initial phases of treatment. Larger NNTs may, however, be clinically relevant in the context of more severe and/or treatment-resistant depression. Therefore the assessment of clinical significance depends on context and this needs to be judged in individual situations. In addition, the outcome measures used are ratings of depressive symptoms, which only capture a part the clinical condition. A further problem is that patients entered into clinical trials are not representative of patients seen in routine practice (Zimmerman, *et al.*, 2002; Zimmerman, *et al.*, 2005). This reminds us that the effect size estimates from RCTs have limitations in their generalisability and their interpretation requires caution. Statistical significance is taken as $p<0.05$; for simplicity and space considerations we do not give 95% confidence intervals.

Categories of evidence for causal relationships and strength of recommendations are provided in Table 1. They have been developed from Shekelle, *et al.* (1999) and have been modified slightly from previous BAP guidelines to reflect uncertainties around results from small and non-replicated RCTs. There are no generally agreed categories for non-causal evidence and we have not routinely graded this evidence but, if appropriate, we have done so as outlined in Table 1. We have also included a category for standard of care (S) relating to good clinical practice.

It is very important to emphasise that the strength of a recommendation reflects the quality of the evidence on which it is based, not upon its clinical importance, and weaker levels of recommendation often cover vital practical issues. The principal recommendations apply to the management of 'typical' patients, and therefore can be expected to apply much of the time; for this reason we use expressions such as 'should consider…' in the recommendations. We accept that, for many patients and for many clinical decisions, unthinking adherence to treatment recommendations may be potentially harmful. In situations where the evidence is weaker we use phrases such as 'could consider…' or 'options include…' as implementation will depend upon clinician experience, patient clinical features and preference, and local circumstance (Haynes, *et al.*, 2002). Standards of clinical care are intended always to be applied.

Scope and target of the guidelines

These guidelines are primarily concerned with the use of antidepressant drugs to treat the most common (unipolar) depressive disorders in adults and do not cover depression occurring in bipolar affective (manic-depressive) disorder, which are covered by another BAP guideline (Goodwin, 2003). We consider the place of antidepressants within the range of treatments available for depression. We also consider how the guidelines apply in special situations, such as depression in children, adolescents and the elderly, in the context of medical illness, pregnancy and the postnatal period and when accompanied by psy-

Table 1 Categories of evidence and strength of recommendation[a]

Categories of evidence for causal relationships and treatment

I: Evidence from meta-analysis of randomised controlled trials*, at least one large, good quality, randomised controlled trial* or replicated, smaller, randomised controlled trials*
II: Evidence from small, non-replicated, randomised controlled trials*, at least one controlled study without randomisation or evidence from at least one other type of quasi-experimental study
III: Evidence from non-experimental descriptive studies, such as uncontrolled, comparative, correlation and case-control studies
IV: Evidence from expert committee reports or opinions and/or clinical experience of respected authorities

Proposed categories of evidence for non-causal relationships

I: Evidence from large representative population samples
II: Evidence from small, well designed, but not necessarily representative samples
III: Evidence from non-representative surveys, case reports
IV: Evidence from expert committee reports or opinions and/or clinical experience of respected authorities

Strength of recommendation

A Directly based on category I evidence
B Directly based on category II evidence or extrapolated# recommendation from category I evidence
C Directly based on category III evidence or extrapolated# recommendation from category I or II evidence
D Directly based on category IV evidence or extrapolated# recommendation from category I, II or III evidence
S Standard of good practice

[a]Developed from Shekelle, *et al.*, 1999

*Randomised controlled trials must have an appropriate control treatment arm; for primary efficacy this should include a placebo condition.

#Extrapolation may be necessary because of evidence that is only indirectly related, covers only a part or the area of practice under consideration, has methodological problems or is contradictory.

chotic symptoms, but these are not comprehensive guidelines for these situations.

The content of these guidelines is relevant for all doctors seeing and treating patients with depressive disorders; in most cases these will be doctors who are not specialists in psychiatry, usually general practitioners (primary care physicians). We recognise that the detail required in reviewing evidence and producing specific recommendations can result in advice of complexity and length that is not useful in everyday practice. Therefore, we present the recommendations separately from the evidence as a stand-alone resource.

Guidelines

1. Diagnosis, detection and service delivery

- All clinicians should have a working knowledge of the criteria for major depression (DSM-IV; equivalent to ICD-10 moderate or severe depressive episode, i.e. 5 or more depressive symptoms) (S) and routinely determine the severity and duration of depressive symptoms (A). For the purposes of this guideline four grades of severity are used:
  - subthreshold depression – significant depressive symptoms below the threshold for DSM-IV major depression, including ICD-10 mild depressive episode with only four symptoms;
  - mild major depression – symptoms barely meet the minimum criteria and mild functional impairment;
  - moderate major depression – more than minimum number of symptoms and moderate functional impairment;
  - severe major depression – most symptoms are present and marked or greater functional impairment.
- Non-targeted screening for depression using single-stage screening questions or questionnaires should not be used in primary care (A). However, consider targeted screening in groups at high risk of depression (D).
- Routinely check for a history of hypomania or mania in patients diagnosed with depression (S).
- Treatment of major depression with antidepressants in primary care should be in the context of case management to improve outcomes (A). At the minimum this should include:
  - scheduled follow up (A),

- a strategy to enhance adherence to medication (B).
- Referral to psychiatric services should occur if there:
  - is a significant perceived risk of suicide, of harm to others or of severe self-neglect (S),
  - are psychotic symptoms (S),
  - is a history of, or likelihood of, bipolar affective disorder (S).
- Consultation with, or referral to, a psychiatrist (or a specialist in the treatment of affective disorders), is appropriate:
  - when the general practitioner feels insufficiently experienced to assess or manage a patient's condition (S),
  - if two or more attempts to treat a patient's depressive disorder with medication have failed, or resulted in insufficient response (S).
- Treatment of depression in specialist psychiatric care should use a systematic approach implementing evidence-based guidelines with standardised assessments and critical decision points to improve outcomes (B).

2. Acute treatment

2.1 Indications for antidepressants

- Determine the duration and severity of depression to guide treatment choice (A).
- Antidepressants are a first line treatment for:
  - moderate and severe major depression in adults irrespective of environmental factors and depression type (A),
  - subthreshold depression that has persisted for 2 years or more (A).
- Antidepressants are a treatment option in short duration mild major depression in adults (B) and should be considered if there is a prior history of moderate to severe recurrent depression (D) or the depression persists for more than 2–3 months (D).
- Antidepressants are not a first line treatment for:
  - short duration subthreshold depression in adults (A) but should be considered if the depression persists for more than 2–3 months (C), or there is a prior history of moderate to severe recurrent depression (D),
  - major depression in children and adolescents (B) but should be considered when other treatment has failed (A) or there is a history of moderate to severe recurrent depression (D).
- When antidepressants are not used as first line treatment the minimum management should include structured follow-up and active monitoring of symptoms (S).

2.2 Alternatives to antidepressants for acute treatment

- Choice between drug and non-drug treatments for depression should be informed by the evidence base, individual patient characteristics and choice, and treatment availability, (S).

Psychological and behavioural treatments

- Psychological and behavioural treatments should be administered by appropriately trained practitioners with fidelity to techniques showing evidence-based efficacy (S).
- For major depression of mild to moderate severity:
  - cognitive behaviour therapy (CBT) (A), behaviour therapy/activity scheduling (BT/AS) (A) and interpersonal psychotherapy (IPT) (A) are alternatives to antidepressants in acute treatment,
  - CBT is recommended if psychological treatment is used as monotherapy for recurrent depression (B).
- For severe major depression:
  - psychological or behavioural treatment is not recommended as sole therapy (B) but routinely consider adding CBT (A) or BT/AS (B) to antidepressant treatment,
  - therapists using psychological and behavioural techniques should be experienced in treating depression (B).
- For major depression in children and adolescents:
  - consider CBT for those not responding to initial structured supportive treatment (B),
  - the choice between CBT and an SSRI in adolescents should be based on individual assessment and availability of treatments (D),
  - combining CBT with an SSRI is not recommended routinely as first line treatment for adolescents (B).
- Guided self-help treatments:
  - computerised CBT and guided bibliotherapy based on CBT principles are not recommended as routine primary treatments for major depression in clinical populations (B),
  - they could be considered for self-motivated individuals with mild to moderate major depression (B) or as an adjunct to antidepressant treatment (D).
- Supervised high intensity exercise:
  - is not a first line alternative to antidepressant treatment for major depression (D),
  - could be considered as an adjunct to other antidepressive treatments (C).

Physical treatments

- Electroconvulsive therapy (ECT):
  - should be considered as a first line treatment for severe major depression in the emergency situation (e.g. not eating or drinking, depressive stupor, extreme distress, suicidality) (B). Bilateral ECT is the treatment of choice in such circumstances (B),
  - is not recommended as a first line treatment for depression in non-urgent circumstances (B),
  - should be considered for treating major depression where first line treatments are not possible or feasible (A) after considering the risk-benefit balance, taking into account depression severity (including psychotic

features) and degree of disability. Consider unilateral ECT initially to minimise adverse cognitive effects (B),
    - should be followed by effective prophylaxis to prevent depressive relapse (A); consider an antidepressant either as monotherapy or combined with lithium (B).
- Repetitive transcranial magnetic stimulation (rTMS):
    - is not recommended as a first line treatment for major depression (D),
    - could be considered for situations where first line treatments are not possible or feasible (B); it should only be administered by an experienced centre as part of a clinical trial or with structured outcome evaluation (S).
    - should be followed by effective prophylaxis to prevent depressive relapse (D).
- Vagus nerve stimulation (VNS) is not recommended as a first line treatment for depression (D) since available data only relate to treatment-resistant, mostly chronic, major depression.
- Light therapy:
    - is a first line treatment for the acute treatment of seasonal autumn/winter major depression (seasonal affective disorder) (A) but effective prophylaxis against relapse is then needed, including consideration of an antidepressant (B).
    - is not a first line alternative to antidepressants for non-seasonal major depression (D) but could be considered if first line treatments are not feasible or tolerated (C).
    - routinely combining light therapy with antidepressants is not recommended (A).

Complementary and other treatments

- Hypericum extracts (St John's Wort):
    - are not recommended as a first line treatment for depression (D) given only preliminary medium-term data and lack of longer-term and relapse-prevention data,
    - could be considered for mild and moderate major depression where first line treatments are not possible or not tolerated (A) provided a recognised standardised preparation is used.
- Omega-3 fatty acids are not recommended as a monotherapy treatment for major depression (B).

2.3 Choice of antidepressant drug

- Match choice of antidepressant drug to individual patient requirements as far as possible, taking into account likely short-term and long-term effects (S) (Table 5).
- In the absence of special factors, choose antidepressants that are better tolerated and safer in overdose (S). There is most evidence for selective serotonin reuptake inhibitors (SSRIs), which, together with other newer antidepressants, are first line choices (D).
- Older tricyclic antidepressants (TCAs) should be reserved for situations when first line drug treatment has failed (D) as should older monoamine oxidase inhibitors (MAOIs) (D). MAOIs should only be initiated by practitioners with expertise in treating mood disorders (D).
- In more severely ill patients, and in other situations where maximising efficacy is of overriding importance, consider an older TCA, venlafaxine (≥ 150 mg) or escitalopram (20 mg) in preference to another SSRI (C) or MAOI (C).
- In psychotic depression combine an antidepressant with an antipsychotic initially in preference to treating with an antidepressant alone (D); do not use an antipsychotic alone (A).
- Factors to consider in choosing an antidepressant include:
    - patient preference (B),
    - associated psychiatric disorder that may specifically respond to a particular class of antidepressant (e.g. obsessive compulsive disorder and serotonin reuptake inhibitors) (B),
    - previous treatment response to a particular drug (D),
    - tolerability and adverse effects of a previously given drug (D),
    - likely side effect profile (e.g. sedation, sexual side effects, weight gain) (C),
    - low lethality in overdose if history or likelihood of overdose (D),
    - concurrent medical illness or condition that may make the antidepressant more noxious or less well tolerated (C),
    - concurrent medication that may interact with the antidepressant drug (C),
    - a family history of differential antidepressant response if choosing between a TCA and MAOI (C).

2.4 Practical issues in acute management

- Initially review patients every one to two weeks following commencement of antidepressant treatment and thereafter according to clinical situation and patient need (S). Telephone consultation and the use of suitably trained non-medical staff may appropriately take the place of some medical consultations (B).
- Educate patients about the nature of depressive disorders, the possibility of worsening or emerging suicidal thoughts, possible side effects and benefits of medication, likely duration of treatment, problems associated with stopping medication (S).
- At each review assess response, adherance to drug treatment, side effects and suicidal risk (S). The use of simple, standardised, rating scales is recommended (B). Be aware that lack of significant improvement after 2–4 weeks treatment substantially reduces the probability of eventual sustained response (A).
- Consider limiting the total amount of antidepressant drug available to the patient (especially if from a more toxic class) to reduce the risk of death/medical complications if taken in overdose (D).
- When prescribing an older TCA, or a drug requiring dose titration, increase the dose every 3–7 days to allow adjustment to side effects (C).

- Aim for a target dose for which there is established efficacy taking into account age and medical comorbidity (S). The target dose of TCAs is an imipramine dose-equivalence of ≥ 125 mg if tolerated (D).
- If a patient has responded to a lower than target dose of an antidepressant still increase the dose to one of established efficacy, if possible, to reduce the likelihood of relapse in continuation treatment (C). Where this is not possible continue the drug at the same dose and monitor the patient for relapse (D).
- Therapeutic drug monitoring is mainly relevant to TCAs and should be considered where there is the potential for antidepressant toxicity (B); it is also an option for assessing treatment adherence and lack of efficacy at apparently adequate doses (B).
- Manage side effects that are likely to be transient (e.g. SSRI-induced nausea) by explanation, reassurance and, if necessary, dose reduction and retitration (C).
- For persistent, severe or distressing side effects the options are:
  - dose reduction (B) and retitration if possible (D),
  - switching to an antidepressant with a lower propensity to cause that side effect (B),
  - non-drug management of the side-effect (e.g. diet and exercise for weight gain) (D),
  - symptomatic treatment with a second drug (e.g. benzodiazepines for agitation/anxiety/insomnia early in treatment (B), sidenafil for erectile dysfunction in men (A), modafinil for persisting sleepiness) (B).

3. Next-step treatments following inadequate treatment response to an antidepressant

3.1 Treatment failure and treatment resistance

- Assess the efficacy and risks of each alternative next-step treatment option against the severity and risks associated with the individual's depression, the degree of treatment resistance and past treatments that have been tried (S).
- Check the adequacy of treatment including dose and non-adherence (S); increase dose to recommended therapeutic dose if only a low or marginal dose has been achieved (D).
- Review diagnosis including the possibility of other medical or psychiatric diagnoses, which should be treated in addition (S).
- Consider social factors maintaining the depression and, if present, help the patient address them if possible (S).
- Continue adequately dosed antidepressants for at least 4 weeks before changing treatment for lack of efficacy (B).
- Assessment after 4 weeks adequate treatment:
  - if there is at least some improvement continue treatment with the same antidepressant for another 2–4 weeks (B),
  - if there is no trajectory of improvement undertake a next-step treatment (B); however in patients who have failed a number of treatments consider longer trials before changing treatment (D).
- Assessment after 6–8 weeks adequate treatment:
  - if there is moderate or greater improvement continue the same treatment,
  - if there is minimal improvement undertake a next-step treatment (B); however in patients who have failed a number of treatments consider longer trials before changing treatment (D).

3.2 Next-step drug treatment options

- Dose increase (C).
  - consider especially if:
    - there are minimal side effects (D) and/or,
    - there has been some improvement on the antidepressant (D) and/or,
    - the current antidepressant has a possible dose-response (there is modest evidence for venlafaxine, escitalopram, TCAs) (C).
- Switching antidepressants (A).
  - consider especially if:
    - there are troublesome or dose-limiting side effects (D) and/or,
    - there has been no improvement (D)
  - switching abruptly is generally preferable unless there is a potential drug interaction (D) in which case follow the recommended taper/washout period (S)
  - options include switching either within- or between-antidepressant class initially (B)
  - consider a different antidepressant class after more than one failure with a specific class (D); consider venlafaxine after more than one SSRI failure (B)
- Augmentation/combination treatment (A).
  - consider adding a second agent especially if:
    - there is partial/insufficient response on the current antidepressant (D) and,
    - there is good tolerability of current antidepressant (D),
    - switching antidepressant has been unsuccessful (D).
  - establish the safety of the proposed combination (S).
  - choose the combinations with the best evidence-base first (S).
  - consider adding lithium (A), olanzapine (A), quetiapine (B), risperidone (B), aripiprazole (B), tri-iodothyronine (B) or mirtazapine (B) being aware that the evidence mainly supports lithium and tri-iodothyronine added to TCAs and the other drugs added to SSRIs.
  - other additions that could be considered in specialist centres with careful monitoring (S) are lamotrigine (C), tryptophan (C), modafinil (C), stimulants (C), oestrogen in perimenopausal women (C) and antiglucocorticoids (C).

3.3 Next-step psychological treatment options

- Consider adding CBT to ongoing antidepressant treatment (B).
- Consider adding other psychological or behavioural treatments that have established acute treatment efficacy (D).

3.4 Next-step physical treatment options

- ECT should be considered (A), especially in more severely ill patients in whom two or more treatments have failed (C). Unilateral electrode placement should be considered initially in non-urgent situations (B).
- rTMS could be considered (C) but should only be given in centres with expertise in treating treatment-resistant patients as part of a clinical trial or with structured service outcome evaluation (S).
- VNS could be considered for patients with chronic treatment-resistant depression (C) but should only be given in specialist centres with expertise in treating treatment-resistant patients as part of a clinical trial or with structured service outcome evaluation (S).
- Ablative neurosurgery could be considered for patients refractory to pharmacological and psychological treatment (D) but only in highly specialised centres with multidisciplinary teams who have experience in the assessment and management of such patients and where procedures are performed as part of a clinical trial or a clinical programme subject to independent external review (S).

3.5 Next-step other treatment options

- Consider adding omega-3 fatty acids (B), folate (C) or supervised physical exercise (C).

4. Relapse prevention, treatment of relapse and stopping treatment

4.1 Relapse prevention

- Be aware that there is a high risk of relapse after a depressive episode, especially in the first 6 months, and that this risk declines with time in remission (S).
- Assess patients for risk factors for relapse (S). The most important are presence of residual symptoms, number of previous episodes, severity, duration and degree of treatment resistance of the most recent episode.
- Medication-responsive patients should have their medication continued at the acute treatment dose after remission with the duration determined by risk of relapse (A).
  - in patients at lower risk of relapse (e.g. first episode patients without other risk factors) the duration should be at least 6-9 months after full remission (A),
  - duration in other cases should be tailored to the individual relapse risk; consider a duration of at least 1 year after full remission in patients with any increased risk of relapse (D). In higher risk patients (e.g. more than 5 lifetime episodes and/or 2 episodes in the last few years) at least 2 years should be advised (A) and for most long-term treatment should be considered (C).
- Lithium:
  - continue lithium in patients who needed lithium augmentation of antidepressants in acute treatment (B),
  - consider adding lithium to antidepressants in patients at high risk of relapse (B) or suicide (A),
  - do not routinely use lithium as monotherapy for relapse prevention but consider as a second-line alternative to antidepressants (B).
- CBT added to medication should be considered for patients with residual symptoms (A) or at high risk of relapse (A).
- In responders to acute phase CBT, continuation medication is not routinely recommended (A); in unstable or partial remitters consider continuation CBT (B) or antidepressants (D).
- IPT is not recommended as a sole continuation treatment for relapse prevention (A) unless acute response was to IPT monotherapy (C). Consider continuation IPT as an adjunct to antidepressants in patients with recurrent depression responding to acute phase IPT combined with antidepressants (C).
- In responders to acute phase ECT prophylactic medication should be continued/initiated (A); consider continuation ECT in patients with frequent relapses who have been refractory to prophylactic medication (C).

4.2 Treatment of relapse while on continuation therapy

- Check the adequacy of treatment including dose and adherence (S).
- Review diagnosis including the possibility of additional medical or psychiatric diagnoses which should be treated in addition (S).
- Consider social factors and, where present, help the patient address them if possible (S).
- Be aware that relapses may be self-limiting (S) and be cautious about frequent or too-early treatment changes (D).
- Treatment options:
  - if antidepressants have been stopped re-start the patient on an antidepressant at adequate dose (B); if the dose had been lowered re-establish the previous dose (B),
  - in a patient on an adequate dose of medication with a recent-onset relapse initially consider providing support and monitoring without changing the medication dose (B),
  - consider increasing the dose of antidepressant (B),
  - consider other next-step treatments as in Section 3 (D).

4.3 Stopping treatment

- Be aware of the characteristic symptoms of a discontinuation reaction and its possibility in any patient who stops antidepressant drug treatment (S).
- Warn patients that a discontinuation reaction may occur if treatment is abruptly stopped after more than a few weeks treatment (S).
- When stopping antidepressant treatment after a period of prophylaxis, match the timing to both risk and consequences of relapse (D) and warn the patient that the highest period of risk is in the 6 months after stopping (S).
- Take into account the clinical situation to determine the rate of taper (S); Serious adverse events may warrant rapid discontinuation; otherwise a minimum period of 4 weeks taper is advised after longer-term treatment (D) and a period of some months may be appropriate for planned treatment withdrawal after long-term prophylaxis (D).
- If a discontinuation reaction does occur:
  - explanation and reassurance are often all that is required (C).
  - if this is not sufficient, and for more severe reactions, the antidepressant should be restarted and tapered more slowly (C); for SSRIs and SNRIs consider switching to fluoxetine which can then be stopped after discontinuation symptoms have fully subsided (D).

5. Special considerations

5.1 Age

- Be aware of age-related factors that may influence treatment with antidepressants (S) including:
  - increased incidence of deliberate self harm in adolescents and young adults.
  - smaller antidepressant-placebo difference when treating depression in children and adolescents compared with adults.
  - decreased tolerability of the elderly to antidepressants.
  - high risk of depressive relapse in the elderly with comorbid medical illness.

5.2 Comorbid medical illness

- Be aware that increasing severity of comorbid medical illness and painful conditions are associated with poorer response to antidepressants and a greater risk of depressive relapse (S).
- Be aware of potential drug-drug interactions and routinely choose antidepressants with a lower risk of interaction in patients on multiple medications (S).
- Consider the potential interaction between the medical illness and adverse-effects of the drug when choosing an antidepressant (S).
- Where possible avoid TCAs in patients at high risk of cardiovascular disease, arrhythmias and cardiac failure (C).
- In acute coronary syndromes choose drugs which do not increase the risk of subsequent cardiac events (S): there is best evidence for SSRIs, mirtazapine and bupropion.
- In patients with bleeding disorders choose antidepressants that are not serotonin reuptake inhibitors (SRI) in preference to those that are (e.g. SSRIs, SNRIs) (B).
- In patients on aspirin/non-steroidal anti-inflammatory drugs requiring an antidepressant choose a non-SRI antidepressant (A) or combine an SRI with an ulcer-protective drug (B).

5.3 Pregnancy and breastfeeding

- Be aware that untreated depression may lead to adverse outcomes for mother and baby (S).
- Inform women taking prophylactic antidepressants who are pregnant, or planning to get pregnant, about the risk of relapse if they are stopped and about potential risks to the baby (including the neonatal behavioural syndrome) (S).
- In women needing treatment for depression while pregnant choose alternatives to antidepressants where possible (S) but,
- Consider recommending treatment with an antidepressant when there is a favourable risk-benefit balance (S):
  - choose antidepressants for which there is most evidence for a lack of adverse outcomes (S), these include most SSRIs and TCAs,
  - avoid the use of paroxetine (B).
- If mothers wish to breastfeed while taking antidepressants, where possible choose drugs which do not accumulate in the baby (S): sertraline and nortriptyline have undetectable levels while fluoxetine and citalopram may lead to significant levels in the infant. Breastfeeding while taking lithium should be avoided where possible (D).

Evidence

1. Depressive disorders: diagnosis, epidemiology, detection and service delivery

1.1 The diagnosis of depressive disorders

Summary

Determination of the severity and duration of depression guide treatment choice (II). DSM-IV major depression is a useful marker for the severity above which antidepressants provide sig-

nificant benefit in acute depressive episodes (II) with poorer evidence for a minimum duration 'threshold'. Individual illness history needs to be taken in to account in deciding treatment (IV).

The dilemma for clinicians (and guidelines) is that categories help to guide decision making, but in reality most illnesses exist along continua (Rose and Barker, 1978). There is now more emphasis on thinking of depression along a continuum of severity between normal sadness and severe illness (Paykel and Priest, 1992; Lewinsohn, *et al.*, 2000). Community surveys illustrate that the key symptoms of depression are common in the community and exist across the whole range of severity (Jenkins, *et al.*, 1997). A greater number of depressive symptoms are associated with greater morbidity and impact as measured by number of prior episodes, episode duration, family history, functioning, co-morbidity and heritability (Kessing, 2007). When depression severity is considered as a dimension, general practitioners appear better able to detect significant levels of depression than categorical studies have suggested (Thompson, *et al.*, 2001). Different symptom profiles (such as melancholia, atypical features, presence of psychosis) do not form distinct categories (e.g. Kendell, 1968; Angst, *et al.*, 2007) and on current evidence do not significantly influence antidepressant choice (see Evidence section 2.3). A similar argument about continua is applicable to the duration of depressive symptoms. Dysthymia refers to depressive symptoms that are subthreshold for, and not a consequence of, a major depressive episode and that last for 2 years or more. The diagnosis of dysthymia is difficult to make and its validity and impact on treatment choice are unclear.

We have taken as a starting point that an episode of depression can usefully be considered along three main dimensions – severity, chronicity and risk of relapse. We believe this conceptual basis is helpful in informing the decision about when, and for how long, to use antidepressants. Nevertheless, because prescribing decisions are categorical, thresholds for treatment still need to be determined for individual patients and these broadly map on to the first two dimensions (Figure 1) although there is more uncertainty about thresholds for duration than severity.

There is now an international consensus over the diagnostic criteria for depression. Both of the current major diagnostic manuals, the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV; American Psychiatric Association, 2000b) and the 10th Revision of the International Classification of Diseases (ICD-10; World Health Organization, 1992)] have virtually the same diagnostic features for what is considered a 'clinically significant' severity of depression, termed a major depressive episode in DSM-IV or a depressive episode in ICD-10. Nevertheless their respective thresholds differ in that DSM-IV requires a minimum of five symptoms and ICD-10 only four so that DSM-IV identifies more severe depression than ICD-10 (Wittchen, *et al.*, 2001). We use DSM-IV criteria in preference to ICD-10 in these guidelines (Tables 2, 3) given its predominance in treatment studies of depressive disorders and because it is a better guide to the threshold for treatment with antidepressants (see Evidence section 2.1). Of note, the criteria for major depression

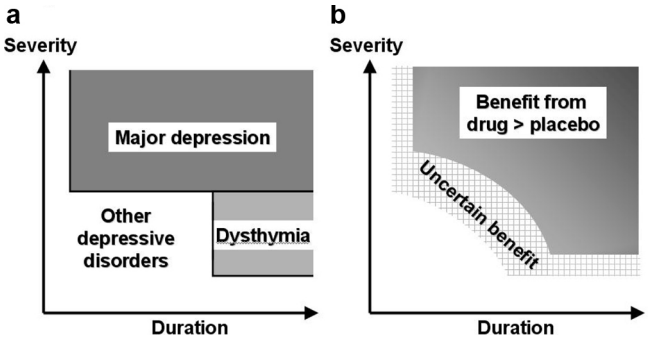

Figure 1 A dimensional approach to depressive disorders and response to treatment. a) Relationship between dimensions and categories of depressive disorder (see Table 2 for criteria for a major depressive episode). b) Benefit from antidepressant drug treatment over placebo increases with severity and duration. There are 'threshold zones' where benefit is uncertain.

can be met even if a person only complains of loss of interest rather than low mood. The criteria also allow for hypersomnia and increased appetite as well as the more conventional syndrome in which there is reduced sleep and appetite.

The duration of depression symptoms affects treatment response to antidepressants and to placebo as discussed in Evidence section 2.1. The most important impact appears to be on response to placebo and the 2-year cut-off required for dysthymia does not have a good evidence base so that in this guideline we do not give it special status but consider it with subthreshold depression (Table 2).

Identification of the severity and duration of depressive symptoms helps in the decision as to whether to prescribe antidepressants (for discussion see Evidence section 2.1). It must, however, be recognised that the severity of depression commonly varies over time within individuals (Judd, *et al.*, 1998a) so that decisions about prescribing antidepressants needs also to take into account individual history (see also Evidence section 4.1).

1.2 Descriptive epidemiology: the size and nature of the problem

Summary

Depression is a common, recurrent disorder, about twice as common in women as men (I). It is one of the major causes of morbidity world-side and is associated with increased mortality (I). Depression is commonly associated with other psychiatric disorders and increased rates are seen in medical illness (I).

Depression is a relatively common condition that is seen in all societies. The prevalence of major depression shows significant variation between countries, but some of this variation can be explained by differences in the way depression is assessed, the threshold used to define depression and cultural variation in response to the assessments (Weissman, *et al.*, 1996; Ballenger, *et al.*, 2001; Simon, *et al.*, 2002b). In a meta-

Table 2 Classification of depressive states

Classification used in Guideline	DSM-IV[a] (code)	ICD-10[b] (code)
Major depression	Major depressive episode, single episode or recurrent (296)	Depressive episode, severe (F32.2), moderate (F32.1) or mild with at least five symptoms[c] (F32.0) Recurrent depressive disorder current episode severe (F33.2), moderate (F33.1) or mild with at least five symptoms[c] (F33.0)
Subthreshold depression (includes 'minor' depression)	Depressive disorder not otherwise specified (311) Adjustment disorder with depressed mood/mixed anxiety and depressed mood (309)	Depressive episode, mild with four symptoms[c] (F32.0) Recurrent depressive disorder current episode mild with four symptoms[c] (F33.0) Mixed anxiety and depressive disorder (F41.2) Adjustment disorder – depressive reaction/ mixed anxiety and depressive reaction (F43.2) Other mood [affective] disorders (F38)
	Dysthymia (300.4)	Dysthymia (F34.1)

[a]4th Revision of the American Psychiatric Association's Diagnostic and Statistics Manual (American Psychiatric Association, 2000b).

[b]10th Revision of the International Classification of Diseases (World Health Organization, 1992).

[c]For list of symptoms see Table 3. Must include at least two of (i) depressed mood, (ii) loss of interest or pleasure, (iii) decreased energy or increased fatiguability.

analysis of 23 prevalence and incidence studies (Waraich, *et al.*, 2004) the best-estimate pooled rates for 1-year and lifetime prevalence of major depression were found to be 4.1% and 6.7%, respectively. The 1-year and lifetime prevalence rates for dysthymic disorder were 2.0% and 3.6%, respectively. Prevalence was fairly similar across the age range 18–64 years with women having 1.5–2.5 times higher prevalence than men. It should be noted that this meta-analysis, which pooled similarly conducted high quality studies, gives about half the rates of those commonly quoted (e.g. Kessler, *et al.*, 2003). This may be partly due to regional differences but, for lifetime risk there is also the problem of recall bias and period of risk; the standardised measure that is used also appears to affect prevalence estimates. Modelling based on prospective studies has suggested that the lifetime risk of major depression could be as high as high as 40% in women (Andrews, *et al.*, 2005).

Major depression is a predominantly recurrent disorder with approximately 80% of people who have received psychiatric care for an episode of major depression having at least one more episode and a median of four episodes in a lifetime. The median duration of an episode is around 16–23 weeks. Recovery from prolonged episodes continues to occur over time but about 12% of patients have a chronic unremitting course (Judd, 1997; Kessler, *et al.*, 2003; Posternak, *et al.*, 2006a). In a 12-year follow up study of psychiatric patients varying degrees of depressive symptoms were present for 59% of the time with

Table 3 Abridged DSM-IV-TR criteria for major depressive episode[a]

A Over the past 2 weeks, five of the following features should be present most of the day, or nearly every day (must include 1 or 2):
1. Depressed mood
2. Loss of interest or pleasure in almost all activities
3. Significant weight loss or gain (more than 5% change in 1 month) or an increase or decrease in appetite nearly every day
4. Insomnia or hypersomnia
5. Psychomotor agitation or retardation (observable by others)
6. Fatigue or loss of energy
7. Feelings of worthlessness or excessive or inappropriate guilt (not merely self reproach about being sick)
8. Diminished ability to think or concentrate, or indecisiveness (either by subjective account or observation of others)
9. Recurrent thoughts of death (not just fear of dying), or suicidal ideation, or a suicide attempt, or a specific plan for committing suicide.

B The symptoms cause clinically significant distress or impairment in functioning.

C The symptoms are not due to a medical/organic factor or illness
The symptoms are not better explained by bereavement (although this can be complicated by major depression).

Episodes are classified as mild (symptoms barely meet minimum criteria, mild functional impairment), moderate (more than minimum symptoms and functional impairment between mild and severe), severe (most symptoms present, marked or greater functional impairment).

[a]Adapted from American Psychiatric Association, 2000b.

15% of the time spent in major depression (Judd, *et al.*, 1998b). Of patients with a diagnosis of major depression about 7–12% subsequently experience hypomanic/manic episodes, the former occurring approximately twice as often as the latter (Angst, 1985; Akiskal, *et al.*, 1995). Patients with early onset depression in adolescence appear to have an even greater risk eventual bipolar disorder (Kovacs, 1996).

The elderly have more medical comorbidity and more previous depressive episodes, both of which adversely affect outcome, and relapse rates appear higher than in younger subjects (Mitchell and Subramaniam, 2005). The overall outcome of major depression in the elderly is poor with a meta-analysis of 12 studies of elderly community patients showing that 21% of patients had died and almost half of those remaining alive were still depressed after 2 years (Cole, *et al.*, 1999).

The true extent of the disability from depressive disorders is often not recognised and the Global Burden of Disease study has estimated that the disability resulting from depression will be second only to heart disease, worldwide, by the year 2020 (Murray and Lopez, 1997) and it causes a greater decrement in health state than angina, arthritis, asthma, and diabetes (Moussavi, *et al.*, 2007). Prolonged depression has major consequences for psychosocial function, both because of the symptoms of depression, and because it is associated with impaired cognitive function (O'Brien, *et al.*, 2004; DeBattista, 2005). Depressive disorders are also associated with increased mortality. In a meta-analysis of 36 studies the lifetime prevalence of suicide has been reported to be 4% in hospitalised depressed patients, rising to 8.6% if hospitalised for suicidality. In mixed inpatient/outpatients populations the lifetime prevalence is 2.2% compared with less than 0.5% in the non-affectively ill population (Bostwick and Pankratz, 2000). A meta-analysis of 54 observational studies found that depressive disorders are associated with an 80% increased risk both of coronary heart disease and of subsequent mortality; however it concluded that potential confounders meant that the role of depression as an independent risk factor has yet to be established (Nicholson, *et al.*, 2006).

In attenders in general practice studies have reported that 4–10% of consecutive patients have a major depression with a similar percentage having depression of lower severity (Blacker and Clare, 1988; Barrett, *et al.*, 1988; Tiemens, *et al.*, 1999; Wittchen, *et al.*, 2001).

Depressive disorders are frequently associated with other psychiatric disorders, most commonly with an anxiety disorder but also with substance misuse, impulse control disorders and eating disorders in women (Weissman, *et al.*, 1996; Kessler, *et al.*, 2003). Medical illness is also associated with increased rates of major depression (Wells, *et al.*, 1988; Sutor, *et al.*, 1998; Moussavi, *et al.*, 2007).

1.3 Detection and outcome

Summary

Enhanced education of clinicians is not, on its own, sufficient to make a substantial impact on increasing the detection or outcome of depressive disorders (I–II). Non-targeted, single stage, screening/case finding questionnaires have minimal impact on the detection, management and outcome of depressive disorders in primary care although two-stage screening may increase detection and improve management, but not outcome (I). There is a lack of evidence about whether screening patients at high risk is effective.

Thirty to fifty percent of cases of depression in primary care and medical settings are not detected (Freeling, *et al.*, 1985; Ronalds, *et al.*, 1997; Rost, *et al.*, 1998). Depressive disorders are missed for a variety of reasons include somatic (physical symptom) presentation, patients' and doctors' beliefs about depression and its treatment, the patient not telling the doctor because of stigma or non-recognition and lack of skills or time by the doctor (Tylee, *et al.*, 1995; Priest, *et al.*, 1996; Davidson and Meltzer-Brody, 1999). However undetected patients have less severe disorders and are functioning better than detected patients (Schwenk, *et al.*, 1996; Ronalds, *et al.*, 1997; Simon, *et al.*, 1999a) and it has been argued that detection is simply an indicator of severity (Dowrick and Buchan, 1995). A large international naturalistic study in 15 cities around found that about 50% of undetected cases still met criteria for caseness 1 year later (Goldberg, *et al.*, 1998). A small longitudinal study (Kessler, *et al.*, 2002) found that the majority of undetected individuals either recovered or were diagnosed during the follow-up period; nevertheless, nearly 20% of the identified cases in this study remained undetected and unwell after 3 years.

The time-limited benefit on depression management and suicide rates from an educational programme for doctors in Gotland (Rutz, *et al.*, 1992) appears to have been related to improvements in already diagnosed patients (Rutz, 1999) and, although there is some inconsistency, the best evidence indicates that education alone does not improve doctors' identification of depression (Hannaford, *et al.*, 1996; Thompson, *et al.*, 2000; Lin, *et al.*, 2001).

Screening questions and self-report scales for the detection of depressive disorders are generally fairly sensitive but vary in specificity (Wilkinson and Barczak, 1988; Goldberg, *et al.*, 1988; Whooley, *et al.*, 1997; Arroll, *et al.*, 2003; Gilbody, *et al.*, 2007b). Three are described in Table 4. A meta-analysis of 12 RCTs, mostly in primary care, found only a small, statistically heterogeneous, impact on the recognition of depression when clinicians were fed back scores on depression screening/case finding instruments (Gilbody, *et al.*, 2005). This appeared to be accounted for by three, two-stage, screening studies in which only high scorers were included (high risk feedback). Similar findings were found for active management and the prescription of antidepressants with significant impact only apparent in the 2 'high-risk feedback' studies. From limited data, case identification on its own did not improve outcome. These findings suggest limited benefit from screening and are consistent with non-randomised prospective studies in which detection alone has not been shown to be associated with adequate treatment (Simon, *et al.*, 2004) or improved medium to longer-term outcome (Tiemens, *et al.*, 1996; Ronalds, *et al.*,

Table 4 Screening for depressive disorders

Questions
A Two question test[a,b]
During the past month, have you often been bothered by feeling down, depressed or hopeless?
2 During the past month, have you often been bothered by little interest or pleasure in doing things?
Yes to both gives 96–97% sensitivity at picking up depression but only 57–67% specificity.
Questionnaires
Hospital Anxiety and Depression (HAD) Scale[c]
A 14-item self-rating scale for severity of depression and anxiety symptoms. It was developed for general medical patients and lacks questions relating to fatigue, sleep, appetite and weight loss, which might be caused by medical illness. In general practice it has a 90% sensitivity at detecting depression with 86% specificity[d].
Patient Health Questionnaire-9 (PHQ-9)[f]
A nine-item self-rating scale for the proportion of the time in the past 2 weeks that depressive symptoms have been present. It has an 80% sensitivity at detecting depression and a 92% specificity[g].

[a]Whooley, *et al.*, 1997
[b]Arroll, *et al.*, 2003
[c]Zigmond and Snaith, 1983
[d]Wilkinson and Barczak, 1988
[f]Kroenke, *et al.*, 2001
[g]Gilbody *et al.*, 2007b

1997; Simon, *et al.*, 1999a; Thompson, *et al.*, 2000) although it may be associated with modest greater short-term improvement (Simon, *et al.*, 1999a). Screening may be useful in situations when a depressive disorder is suspected and in high-risk populations; however evidence is lacking.

1.4 Service delivery

Summary

In primary care, broadly defined collaborative care for depressive symptoms improves outcome in primary care but the size of effect is small (I) and it is expensive on average (I). Case management in patients with major depression appears more clinically effective (I) and can be delivered more cheaply (I). Improved antidepressant treatment adherence is associated with better outcomes in collaborative care and case management studies (I). Structured follow-up itself appears to be an important aspect of improved outcome (I). In secondary (specialist psychiatric) care there does not appear to be any benefit from telephone case-management in treating major depression (II) but guideline/algorithm-driven treatment combined with structured assessment and management of improves outcome over treatment as usual (I).

The elements of a 'system level approach' to chronic illness management can be grouped into four main components: (i) a multi-professional approach; (ii) application of a structured management plan; (iii) scheduled patient follow-up; and (iv) enhanced inter-professional communication (Gunn, *et al.*, 2006). Depression studies have focussed on primary care and the principal models have been case management (Von Korff and Goldberg, 2001) and collaborative management of care (Katon, *et al.*, 1997) but there is considerable overlap and variation in the interventions used.

A meta-analysis of 27 studies of collaborative care in primary care patients with depression (Gilbody, *et al.*, 2006a) found a small significant effect size of 0.25, maintained up to 5 years (effect size 0.15) with increased medication adherence related to improved outcome. The studies included had a broad range of depression severity and interventions (defined as structured care involving as greater use of non-medical specialists to augment treatment). A meta-analysis of 13 RCTs of case management (continuity of care with at least systematic monitoring of symptoms) in patients with major depression (Gensichen, *et al.*, 2006) showed a larger significant effect size of 0.40 in favour of case management after 6–12 months with an NNT of five to achieve response. The intervention groups showed enhanced medication adherence of 66% compared with 50% in the control groups (NNT 6–7); no difference was found between complex and simple case management (defined as number of elements involved). The key elements necessary to improve outcome are not clear but systematic identification of patients, scheduled follow-up, a structured management approach, enhanced medication adherence and case-manager quality appear important (Gensichen, *et al.*, 2006; Bower, *et al.*, 2006; Gilbody, *et al.*, 2006a). Systematic follow-up itself appears to have a significant effect. A systematic review of placebo-controlled antidepressant RCTs with different num-

bers of scheduled assessments up to 6 weeks found that decreases in depressive symptoms were considerably greater for both antidepressant and placebo groups if there were more scheduled follow-up assessments, although this was not able to be statistically tested (Posternak and Zimmerman, 2007a). A primary care study found that systematic follow-up was as effective as a more intensive depression care programme (Vergouwen, *et al.*, 2005).

Collaborative care costs on average about £10/$20 per additional depression-free day (Gilbody, *et al.*, 2006b). This appears high and, although the most cost effective approach is not known, it is possible that low complexity case management interventions may be the most cost-effective. For example, telephone case management at a cost of about £40/$80 per patient resulted in significantly better response rates at 6 months than usual care (response 56% *versus* 40%) (Simon, *et al.*, 2000)

There is less evidence in secondary care. Telephone case management did not improve outcomes in one study (Simon, *et al.*, 2006a) but RCTs implementing a systematic treatment approach using standardised assessments and outcome definitions, and critical decision points for interventions based on evidence-based guidelines or algorithms (Trivedi, *et al.*, 2004; Adli, *et al.*, 2006), did show improved outcomes over treatment as usual, persisting at least to 1 year.

1.5 Psychiatric/specialist referral

Summary

Criteria for psychiatric/specialist referral are based on risk and requirement for specialist expertise (IV)

Certain conditions, such as high suicide risk, psychotic major depression and major depression in bipolar patients, have specific treatment implications (Goodwin, 2003; National Institute for Clinical Excellence, 2004) generally regarded as requiring specialist expertise. There are no controlled data related to indications for referral.

2. Acute treatment

2.1 Acute efficacy of antidepressant drugs

Summary

Antidepressants are effective in the acute treatment of major depression of moderate and greater severity in adults (response rates of about 50% compared with 30% on placebo, NNT 5) (I). Nevertheless 55–65% of depressed patients treated with antidepressants have significant continuing symptoms (I). Smaller drug-placebo differences (principally due to greater responses to placebo) are seen in primary care patients versus *psychiatric outpatients (II), children and adolescents* versus *adults (II) and to a lesser degree elderly* versus *working age adults (I). In children <13 years the drug-placebo difference is small and not statistically significant (I). Antidepressants are effective for major depression associated with medical illness (I) but the response is poorer with active medical illness (II). The benefit for antidepressants over placebo appear to increase with the severity of depression (II) and with duration (II). Clear thresholds for clinically significant benefit are not known and likely to differ between individuals. Most consistently associated with efficacy (compared with placebo) are major depression that is clearly above the threshold for diagnosis in both number and severity of individual symptoms (I) and a duration of at least 2–3 months (III). Response to antidepressants in major depression does not appear to be greatly influenced by depression type or prior life events (II). Response to placebo appears lower in more severe depression and melancholia and higher in less severe, shorter duration episodes preceded by life events, and in children and adolescents (I–III).*

The National Institute for Clinical Excellence (NICE) depression guidelines (National Institute for Clinical Excellence, 2004) outlined a 'rule of thumb' requiring a Hamilton Depression Rating Scale (HDRS) or Beck Depression Inventory weighted-mean difference of three points (two points for treatment-resistant depression), an effect size of 0.5 or a relative risk of 0.8 *versus* placebo for clinical efficacy. This guideline takes the view that statistical separation between drug and placebo in RCTs is informative about whether a treatment is effective but that pragmatism and clinical judgment are needed to decide clinical usefulness based on the risk-benefit balance in specific situations rather than an arbitrary cut-off. This requires taking into account an individual's history and the availability of alternative evidence-based treatments, remembering that placebo treatment is not 'no' treatment and that systematic follow up itself may have substantial benefit (see Evidence section 2.4).

There is strongest evidence for the efficacy of treating major depression of at least moderate severity [e.g. typically an HDRS >17 or Montgomery Asberg Depression Rating Scale (MADRS) >20], the entry criterion for most randomised controlled studies (RCTs) with a placebo condition. Antidepressants have been shown to improve response (usually defined as a 50% reduction in HDRS/MADRS scores or marked improvement or better on Clinical Global Impression) and remission (commonly defined as HDRS <8 or MADRS <11–13 and absence of significant symptoms) compared with placebo. In a meta-analysis of 75 short-term RCTs, intention-to-treat response rates were about 50% on antidepressants compared with 30% on placebo (NNT 5) (Walsh, *et al.*, 2002), but with wide variation and evidence that responses rates, especially to placebo, have been increasing over time. A meta-analysis of 15 antidepressant RCTs in depressed patients (mostly major depression) recruited from primary care (Arroll, *et al.*, 2005) found a significant advantage to antidepressants over placebo (response 58% *versus* 44%, NNT 7 recalculated from the paper). This suggests generally higher response rates to antidepressant and placebo with less difference between them than in RCTs predominantly carried out in psychiatric outpatients.

It is important to note that placebo is likely to have an effect above spontaneous improvement but data are scarce. A meta-analysis of waiting list controls in 19 studies of major depression found rating scale score decreases of 12–16% over 2–20 weeks and up to 20% of patients showed 50% or greater improvement (Posternak and Miller, 2001). This compares with an average 30% response rate on placebo (Walsh, *et al.*, 2002) (ie NNT of ~10). A meta-analysis found a similar sized, but non-significant, benefit to placebo over no treatment in depression (effect size 0.27) from four very atypical studies (Hrobjartsson and Gotzsche, 2004).

Recently emphasis has been on remission as a goal of treatment as responders may still have significant residual symptoms, even if subthreshold for major depression. This is estimated to occur in about 30% of patients at the end of acute treatment and is associated with greater functional disability, suicide risk, and risk of relapse (Kennedy and Foy, 2005). There are fewer studies reporting remission rates and these typically find 35–50% remission with antidepressants and 25–35% with placebo in short-term studies (Thase, *et al.*, 2001; Smith, *et al.*, 2002; Dawson, *et al.*, 2004) indicating that over half of depressed patients have significant continuing symptoms after acute treatment with antidepressants.

A meta-analysis of 17 RCTs in the elderly found a benefit for antidepressants over placebo with NNTs ranging from 4 to 8 for different classes of drugs (Wilson, *et al.*, 2001). In an elderly (≥60 years) subgroup of six studies from the meta-analysis by (Walsh, *et al.*, 2002) the antidepressant-placebo difference was significantly smaller than in studies with younger adults (NNT 7–8 *versus* 5) (Walsh and Sysko, 2005). The use of antidepressants in children and adolescents has been the subject of much controversy with regard to risk-benefit balance and the relative difference between individual drugs. Simple pooling of all antidepressants shows a significant overall benefit for antidepressants in 18 RCTs (odds ratio 1.52) (Papanikolaou, *et al.*, 2006). A statistical advantage for tricyclic antidepressants (TCAs) over placebo in 13 studies was found only for continuous measures but not in a responder analysis (Hazell, *et al.*, 2002; Papanikolaou, *et al.*, 2006) whereas selective serotonin reutake inhibitors (SSRIs) as a group were effective (five studies, odds ratio 1.84) (Papanikolaou, *et al.*, 2006). In a meta-analysis including unpublished studies, which combined SSRIs (11 studies) with nefazodone, mirtazapine and venlafaxine (15 studies altogether) the response rates were 61% on antidepressants compared with 50% on placebo (NNT 10) (Bridge, *et al.*, 2007). The significance for individual antidepressants depends to some extent on method of analysis. Effect sizes for continuous data (reduction in depressive symptoms) were significant for fluoxetine (0.43), citalopram (0.34), sertaline (0.28) and venlafaxine (0.29) but not for paroxetine (0.07) in another meta-analysis (Whittington, *et al.*, 2004). Analysis of SSRI and other newer antidepressant studies in adolescents and younger children (aged 5–12 years) separately show a significant benefit in the former (10 studies, 62% *versus* 49% response, NNT 7–8) with a lack of statistically significant benefit found in the latter (five studies, 65% *versus* 58% response, NNT 14) (Bridge, *et al.*, 2007); however studies of fluoxetine did show similar significant benefit in both age groups (NNT 5). The real issues about antidepressants in the treatment of children and adolescents are whether the benefits outweigh adverse events as first-line treatment and what is their place in the overall management (see Evidence section 2.3)

A systematic review of 18 studies of antidepressant treatment in depressive disorders associated with medical illness reported similar response rates to those seen in the primary depression studies but the nature and degree of medical illness varied widely and it is difficult to draw conclusions about efficacy in specific conditions or the effect of current severity on outcome (Gill and Hatcher, 1999). A review of studies comparing depressed patients with and without medical illness found that the response to antidepressants is poorer in those with a significant current severity of comorbid medical illness (Iosifescu, *et al.*, 2004a) as also found in the recent large STAR*D trial (Trivedi, *et al.*, 2006b).

Reliable assessment of the severity of depression is problematic. NICE (National Institute for Clinical Excellence, 2004), following ICD-10 criteria, proposed that moderate depression is defined as 5–6 symptoms and severe depression as 7 or more, while recognising that symptom counting alone is insufficient to determine severity. Definitions related to rating scale scores are also problematic because of variation in instruments and assessment practices as well as lack of clinical utility. In this guideline we have adopted the DSM-IV definition of severity, which includes both number of symptoms and degree of functional impairment (Table 3).

From limited evidence, the threshold of diagnosis of (DSM-IV) major depression may be a rough marker for benefit from antidepressants over placebo. In *post-hoc* analyses, two studies (Stewart, *et al.*, 1983; Paykel, *et al.*, 1988) showed that patients with depression below the threshold for major depression (subthreshold or minor depression) showed no advantage for a tricyclic over placebo whereas there was an advantage for those with major depression. Similarly, two RCTs in primary care of enhanced treatment resulting in improved medication adherence showed benefits for the intervention compared with treatment as usual in those with major depression but not those with minor (subthreshold) depression (Katon, *et al.*, 1996; Peveler, *et al.*, 1999).

Two RCTs with patients with minor depression have shown little or no benefit for antidepressants over placebo (Williams, *et al.*, 2000; Barrett, *et al.*, 2001). One minor depression study with a prospective 4 week single blind placebo run-in period had a low placebo remission rate and found a significant advantage for fluoxetine (Judd, *et al.*, 2004). The reason for the lack of separation of antidepressants from placebo seen in the other trials is the high remission rate on placebo (49–66%) (Williams, *et al.*, 2000; Barrett, *et al.*, 2001); in one of the studies milder depression severity predicted response to placebo but not to paroxetine (Sullivan, *et al.*, 2003).

In patients with dysthymia a meta-analysis of 15 RCTs showed that 55% of patients responded on antidepressant drug treatment compared with 30% on placebo (NNT 4)

(Lima and Moncrieff, 2000). This is supported in more recent studies (Williams, *et al.*, 2000; Barrett, *et al.*, 2001) although in elderly patients the effect was of marginal clinical significance (46% *versus* 40% remission, NNT 17).

Although the belief that the separation in effect between antidepressants and placebo increases with severity of depression has been questioned (Moncrieff and Kirsch, 2005), such evidence as we have supports this (Ottevanger, 1991; Angst, *et al.*, 1993; Kirsch, *et al.*, 2002; Khan, *et al.*, 2005a). HDRS scores above 24 provide the most consistent and clinically significant separation between drug and placebo and this can be considered to be at the borderline between moderate and severe major depression (Muller, *et al.*, 2003; Khan, *et al.*, 2005a).

Benefit (statistical and clinical) from an antidepressant over placebo in depression is likely to vary widely depending on patient characteristics rather than there being a clear threshold. Major depression of moderate severity is approximately where benefit can be detected in group analyses and there is increasing likelihood of benefit as severity increases further. Greater duration of depressive episode (over time scales of 1–2 years) is associated with a poorer response to placebo (Stewart, *et al.*, 1989; Khan, *et al.*, 1991; Stewart, *et al.*, 1993), with less effect on response to antidepressants (Khan, *et al.*, 1991; Joyce, *et al.*, 2002; Trivedi, *et al.*, 2006b) suggesting increasing drug-placebo difference with increasing duration. Two studies with lower than expected placebo improvement rates, one in subthreshold depression (24% defined as 'not depressed' on placebo at the end of the study, Judd, *et al.*, 2004) and one in adolescents (35% response rate, March, *et al.*, 2004) required a minimum duration of stable depressed mood prospectively for 4 weeks or retrospectively for 6 weeks, respectively, and found significant advantage for an antidepressant. A naturalistic follow-up study of recurrent major depressive episodes found a high natural recovery rate without taking antidepressants for many patients experiencing a relapse in the first 3 months (Posternak, *et al.*, 2006b). This suggests placebo response/spontaneous remission rates are high in the initial 2–3 months and that benefit for antidepressant treatment over placebo may become more apparent after this time.

Given the continuum of depression a major problem is in distinguishing between depressive states that are relatively transient and those that are precursors of more severe, recurrent or chronic conditions where antidepressants are likely to be helpful (Kessing, 2007). Overall the clinical presentation of depression and whether there was a preceding life-event affects response to antidepressants relatively little (e.g. Vallejo, *et al.*, 1991; Angst, *et al.*, 1993; Tomaszewska, *et al.*, 1996; Fava, *et al.*, 1997; Ezquiaga, *et al.*, 1998; Brown, 2007) but greater severity (see above) and melancholia (Brown, 2007) are associated with a poorer response to placebo, and hence potentially greater benefit from antidepressant treatment. Although poorly researched, response to placebo may be greater if there has been a precipitating life-event and short duration of depression (Browne, *et al.*, 1992), lesser severity (Sullivan, *et al.*, 2003; Stein, *et al.*, 2006) and in children and adolescents (Bridge, *et al.*, 2007) and in these situations short-term benefit from antidepressants may be less clear. However these findings are not strong enough to allow confident prediction on an individual basis

The decision about when to use an antidepressant in an individual case, particularly in recent onset mild major depression, remains uncertain, since the average behaviour observed in trials may not reflect the need for early treatment in particular individuals. At present there is no firm evidence on which to base rules about 'watchful waiting', or indeed how it should be carried out.

2.2 Alternatives to antidepressants for acute treatment

Psychological and behavioural treatments

Summary

Assessment of the efficacy of psychological treatments attributable to the specific technique used is made difficult by the broad definition of depression and the lack of adequate control groups in many studies. Non-specific psychological treatment (ie psychological placebo) appears to be moderately effective against waiting list/no treatment (II). In major depression there is evidence for efficacy attributable to the specific technique for cognitive behaviour therapy (CBT) (I), behaviour therapy/activity scheduling (BT/AS) (I), interpersonal psychotherapy (IPT) (I) and high intensity supervised exercise (I/II); only CBT has evidence for reducing subsequent relapse (I). Specific benefit has not been demonstrated for problem solving therapy (PST) (I), marital therapy (II), brief psychodynamic psychotherapy (II), counselling (I) and self-help techniques such as computerised CBT and guided self-help (I/II). Efficacy attributable to the specific technique is not clear in subthreshold and mild major depression or severe major depression in adults and there is only limited evidence for CBT in children and adolescents with depressive symptoms (I). Experienced therapists are needed for treating moderate to severe major depression if psychological therapies are employed (II).

CBT, BT/AS and IPT are as effective as antidepressants in the acute treatment of mild to moderate major depression in adults (I) but whether they are as effective in severe major depression and in adolescents is not clear. In primary care following patient preference for psychological or antidepressant treatment does not influence overall outcome (II).

Combination psychological and antidepressant treatment appears no more effective than psychotherapy alone in the acute treatment of adults with mild to moderate major depression (I) but it may be in moderate to severe major depression (II). Combination treatment is more effective than antidepressant monotherapy in major depression (I), probably accounted for by depression of moderate or greater severity (II). In depression in adolescents most studies find that combining an SSRI and CBT is no more effective than an SSRI alone (I).

It is important to recognise that studies of psychological therapies in depression often do not have adequate placebo control, many are small and the mood disorder may be broadly defined. This makes them vulnerable to bias and confounding

with non-specific effects. In addition the high placebo response/spontaneous improvement seen in antidepressant drug trials in patients with shorter, less severe illness is relevant to non-drug alternatives. Elaborate or expensive non-drug treatments require comparable evaluation to that required for antidepressants. It is outside the remit of this review of evidence to consider the different varieties or variations of specific psychological techniques.

Recent reviews/meta-analyses have concluded that in adults with depressive symptoms there is evidence of acute efficacy for cognitive behaviour therapy (CBT) *versus* waiting list/drug placebo (20 studies, effect size 0.82) (Haby, *et al.*, 2006), behaviour therapy (BT) *versus* waiting list/drug placebo/relaxation/treatment as usual (12 studies, effect size 0.70) (Ekers, *et al.*, 2007), activity scheduling (AS, overlapping with BT) *versus* waiting list/ placebo/treatment as usual (10 studies, effect size 0.87) (Cuijpers, *et al.*, 2007b), interpersonal psychotherapy (IPT) *versus* waiting list/drug placebo/usual treatment (nine studies, risk ratio 0.72) (de Mello, *et al.*, 2005) and problem solving therapy (PST) *versus* control treatment/placebo/waiting list (13 studies, effect size 0.34–0.83 depending on method of analysis) (Cuijpers, *et al.*, 2007c). There is only preliminary/modest evidence against waiting list/usual care/no treatment for marital therapy (two studies, effect size 1.28) (Barbato and D'Avanzo, 2006), brief psychodymamic therapy (two studies) (Leichsenring, *et al.*, 2004) and counselling (six studies, effect size 0.28) (Bower, *et al.*, 2003).

The size of the effect seen with specific psychological treatments is reduced if non-specific effects are taken into account. A recent meta-regression analysis (Haby, *et al.*, 2006) of 33 CBT studies in depression and anxiety disorders found that taking into account the effect of attentional placebo (i.e. an active control condition) significantly reduced the effect size by 0.52 compared with those against waiting list. Similarly (Wampold, *et al.*, 2002) found only a modest benefit for CBT over 'non-*bona fide*' (ie placebo) therapies in depression (11 studies, effect size 0.49) and with PST the effect size against usual care and placebo was much smaller than against waiting list (effect sizes 0.05 *versus* 0.27 *versus* 1.61, respectively) (Cuijpers, *et al.*, 2007c).

The evidence for specific psychological therapies in subthreshold depression is limited to comparison with treatment as usual/waiting list and is predominantly CBT-based. A meta-analysis of seven studies found a significant moderate effect size (0.42) after treatment, which was small and not significant at 6- and 12-month follow-up (effect size 0.16–0.17) (Cuijpers, *et al.*, 2007a). This could be accounted for by non-specific effects of the interventions (see above).

The evidence for the efficacy of specific psychological therapies against placebo control in well-defined major depression is more limited. As discussed below there is some evidence for CBT, BT and IPT in major depression but a meta-analysis of PST studies found only a small (although statistically significant) effect size when studies of major depression were analysed separately (six studies, effect size 0.15) (Cuijpers, *et al.*, 2007c).

A meta-analysis found modest positive effects for CBT in children and adolescents in small studies against active control/waiting list (six studies, effect size 0.41) (Haby, *et al.*, 2004) but doubts have been raised about its efficacy by a recent large negative study against drug placebo (March, *et al.*, 2004) in which CBT was also less effective than fluoxetine. A subsequent small study found CBT to be more effective than sertraline acutely with combined treatment intermediate (Melvin, *et al.*, 2006). There are only preliminary results for IPT in this age group which suggest it is more effective than waiting list/clinical monitoring (Mufson and Sills, 2006). A non-quantitative review of psychological treatments for major depression in the elderly reported efficacy for CBT (five studies) and PST (one study) against waiting list (Frazer, *et al.*, 2005).

The specific psychotherapy with strongest evidence for significant reduction of subsequent relapse is CBT (see Evidence section 4.1).

In comparative studies of broadly defined depression there appears little difference in efficacy between CBT and other '*bona-fide*' psychotherapies (11 studies, non-significant effect size 0.16 in favour of CBT) (Wampold, *et al.*, 2002), CBT and BT (12 studies, non-significant effect size 0.08 in favour of CBT) (Ekers, *et al.*, 2007) or CBT and AS (10 studies, non-significant effect size 0.01 in favour of AS) (Cuijpers, *et al.*, 2007b). A placebo-controlled RCT found no difference between CBT, BT and antidepressants in mild to moderate major depression but an advantage to antidepressants and BT over CBT in the moderately to severely depressed (Dimidjian, *et al.*, 2006). A recent RCT comparing CBT and IPT found no overall difference but an advantage to CBT in patients with more severe major depression (MADRS >29) (Luty, *et al.*, 2007). BT was found to be more effective than brief dynamic or interpersonal psychotherapy (three studies, effect size 0.56) and supportive therapy (two studies, effect size 0.75) in treating depressive symptoms (Ekers, *et al.*, 2007).

In comparing specific psychotherapies and antidepressants the influential NIMH study (Elkin, *et al.*, 1989) found no significant difference over all between imipramine, CBT and IPT although imipramine was numerically superior. A meta-analysis of six RCTs of well-defined mild to moderate major depression with control treatment arms found equal remission rates for antidepressants and psychotherapy (primarily CBT and IPT) (46% for both), which were both more effective than the control condition (26%) (Casacalenda, *et al.*, 2002). A secondary analysis of CBT compared with antidepressants in patients with at least moderate major depression (17-item HDRS scores >19) from four RCTs (Derubeis, *et al.*, 1999) found overall equal efficacy to antidepressants but two subsequent placebo-controlled RCTs have had mixed results. One found no significant difference in comparative efficacy with both superior to placebo (Derubeis, *et al.*, 2005) but a numerical advantage to antidepressants over CBT (8 week response 50% *versus* 43%), significant in one treatment centre attributed to lower therapist expertise (Derubeis, *et al.*, 2005). The other RCT found improvement over placebo for antidepressants but not CBT over 8 weeks but final response rates were similar at

16 weeks (Dimidjian, *et al.*, 2006). A large study using the cognitive behavioural-analysis system of psychotherapy (CBASP), which includes cognitive, behavioural and interpersonal techniques, in patients with major depression and at least 2 years of depressive symptoms found equal efficacy for CBASP compared with nefazodone (Keller, *et al.*, 2000).

There continues to be a debate about whether specific psychotherapies are effective, or as effective as antidepressants in severe major depression, particularly given the cognitive deficits which might be expected to impair engagement, concentration and memory (Tavares, *et al.*, 2003). In the NIMH study superior treatment response was found in depressed patients to IPT if they had lower social dysfunction pre-treatment, to CBT (and imipramine) if they had lower cognitive dysfunction pre-treatment, to imipramine and IPT with high depression severity and to imipramine with high work dysfunction (Sotsky, *et al.*, 1991). By contrast, a recent study found IPT to be less effective than CBT in more severely ill patients (Luty, *et al.*, 2007). In the study by Dimidjian, *et al.* (2006) CBT was less effective than BT in more severely depressed patients seemingly due to a subset of CBT subjects who had a particularly poor response. A difficulty in interpretation is the definition of 'severe' major depression in the psychotherapy studies. In studies purporting to examine this (Derubeis, *et al.*, 1999; Derubeis, *et al.*, 2005; Dimidjian, *et al.*, 2006; Luty, *et al.*, 2007) the mean 17-item HDRS scores was 23–25 across studies. Although there is no agreed definition of severe major depression, in drug studies a minimum score of 25 or greater has been used (Angst, *et al.*, 1995; Khan, *et al.*, 2005a) which is supported by the HDRS cut-off corresponding to severe depression on the clinical global impression scale (Muller, *et al.*, 2003). Therefore the scores in these CBT studies are better viewed as indicative of moderate/marked rather than severe major depression and the efficacy of psychotherapies in the latter remains unclear. Although therapist expertise has been little studied, there is evidence for CBT that experienced therapists are required to achieve good outcomes in moderate to severe major depression (Scott, 1996; Shaw, *et al.*, 1999; Derubeis, *et al.*, 2005).

Thase, *et al.* (1997) in a mega-analysis (combined individual data) of six studies found equal efficacy for combined drug and psychotherapy compared with IPT or CBT in patients with mild to moderate major depression (HDRS <20) but a poorer response to psychotherapy alone in those with moderate to severe major depression with recurrent illness. A large study of chronic subthreshold depression (dysthymia) in primary care found that sertraline and IPT combined with sertraline were more effective than IPT alone (Browne, *et al.*, 2002). A meta-analysis of 89 studies in the elderly found similar effect sizes for antidepressant and psychological treatments in major depression and a possible greater effect size for psychological treatment than antidepressants in subthreshold depression (Pinquart, *et al.*, 2006). However, the drug and psychological treatment were not from comparative studies nor were the studies directly comparable in terms of blinded assessment or adequate placebo condition, making interpretation insecure.

A meta-analysis of 16 studies of major depression and dysthymia in adults found a 12.6% advantage (NNT 8) for combined treatment over antidepressant drug alone, with greater benefit and decreased dropout in studies longer than 12 weeks (Pampallona, *et al.*, 2004); the authors reported not being able to examine the effect of severity. The two largest studies (accounting for 28% of the weight) in the meta-analysis were one with patients of at least moderately severe major depression with chronic depressive symptoms in which combined nefazodone and CBASP was found more effective than either treatment alone (Keller, *et al.*, 2000) and a study of dysthymia in which no advantage was found for combined IPT and sertraline over setraline (Browne, *et al.*, 2002). More recently an RCT of depressed in-patients (mean HDRS 23.5) reported greater efficacy for IPT combined with antidepressants compared with antidepressants and clinical management (response 70% *versus* 51%) (Schramm, *et al.*, 2007). In recent studies in adolescents greater efficacy for combined CBT and fluoxetine compared with either treatment alone (CBT not separating from placebo) was reported in one study (March, *et al.*, 2004) but three subsequent studies have found no benefit from combined treatment over an SSRI alone (Clarke, *et al.*, 2005; Melvin, *et al.*, 2006; Goodyer, *et al.*, 2007).

Primary care studies have found that patients generally prefer psychotherapy to antidepressants (van Schaik, *et al.*, 2004) but allocation by patient preference has not found any difference in outcomes between the two although there may be a more rapid improvement if treatment is matched to treatment preference (van Schaik, *et al.*, 2004; Lin, *et al.*, 2005). One naturalistic study found antidepressants to be the most cost-effective strategy for the majority of patients (Miller, *et al.*, 2003).

In summary the evidence suggests similar efficacy for antidepressants, some specific therapies (CBT, BT and IPT) and the combination in mild to moderate depression in adults and the elderly with greater efficacy of combination treatment in moderate to severe depression but a lack of evidence for very severe depression. In adolescents CBT is probably effective but may be inferior to fluoxetine and most studies find no benefit for combined treatment over an SSRI alone.

Assessing self-help therapies is difficult because of the wide range of potential approaches, the patient populations involved and a lack of a consistent methodology for its application including the degree of guidance and treatment in control arms. A recent review of computerised CBT (Kaltenthaler, *et al.*, 2006) found some evidence for its efficacy in depression compared with treatment as usual but a lack of data on relative efficacy versus therapist-led CBT or other treatments. There are, however, concerns about the quality and generalisability of evidence and uncertainties about organisational issues in purchasing these products. A meta-analysis of internet-based CBT, mostly against waiting list/treatment as usual/attention (ie active) placebo found only a small significant effect for studies of subjects with depressive symptoms (five studies, effect size 0.27) compared with a large effect for those with anxiety symptoms (six studies, effect size 0.96) but this may have partly

been accounted for by the degree of support by monitoring with or without feedback (Spek, *et al.*, 2007). Bibliotherapy based on CBT principles was evaluated in a recent meta-analysis, which identified 11 studies (Anderson, *et al.*, 2005). There was a significant benefit against treatment as usual/waiting list (eight studies, effect size 1.28) but most of the effect was due to six US studies using *Feeling Good* (Burns, 1999) involving small groups of self-selected subjects and weekly contact by research workers familiar with the intervention. Two recent moderate sized RCTs in primary care clinical populations comparing guided self-help against waiting list controls (Mead, *et al.*, 2005) or added to standard antidepressant treatment (Salkovskis, *et al.*, 2006) failed to find benefit although a previous study found some evidence of an advantage at 1 month but not 3 months when added to treatment as usual (Richards, *et al.*, 2003).

A meta-analysis of 10 RCTs of exercise for depression found an effect size of 1.1 against no treatment with no significant difference from CBT (three studies, effect size 0.3 in favour of exercise) or sertraline (1 study) (Lawlor and Hopker, 2001). However, most studies were in non-clinical populations with a poorly defined diagnosis of depression and methodological limitations. Considering RCTs published since that meta-analysis, a small RCT of supervised exercise in major depression in adults found that 12 weeks high intensity exercise was significantly more effective than low-intensity exercise and stretching exercise in mild severity depression (Dunn, *et al.*, 2005) and that 10 days of endurance training was more effective than stretching exercises as an adjunct to antidepressants in moderately to severely depressed inpatients (Knubben, *et al.*, 2007). Two RCTs of 8–10 weeks supervised weight training in mixed minor (subthreshold) and major depression in elderly patients found benefit against education control (which continued to 10 weeks unsupervised follow-up) (Singh, *et al.*, 2001) and against low-intensity exercise and usual care (Singh, *et al.*, 2005). In minor/mild severity depression in older subjects there was possible benefit for 10–16 weeks exercise on its own (Brenes, *et al.*, 2007) or as an adjunct in those poorly responsive to antidepressants (Mather, *et al.*, 2002). Most studies involved volunteers following advertisement.

Physical treatments

Summary

Electroconvulsive therapy (ECT) is highly effective in the short term treatment of depression (I), acts quickly (II) and is more effective than antidepressants (I), but relapse rates without continuation treatment are very high (I). Repetitive transcranial magnetic stimulation (rTMS) may be effective in acute treatment but optimal treatment parameters are not clear (I) and there is a lack of efficacy data extending beyond the acute period of treatment. Vagus nerve stimulation (VNS) appears to be more effective than usual treatment in the medium term for chronic refractory depression of at least moderate severity (II) with good stability of response over 2 years (III). Light therapy (especially given in the morning) appears to be effective in the short-term treatment of seasonal affective disorder and non-seasonal depression (I) but there is no benefit in combining it with antidepressants (I). There is a lack of data on sustained benefit, but relapse after effective light therapy in seasonal affective disorder may be reduced by an antidepressant or CBT (II). Sleep deprivation is associated with temporary improvement in depressive symptoms but there is no evidence of persistent benefit in the treatment of depressive episodes (II-III).

A systematic review (UK ECT Review Group, 2003) found that ECT is significantly more effective in acute treatment than sham treatment (six studies, effect size 0.91) and drug treatment (mostly TCAs and MAOIs, 18 studies, effect size 0.80) although the latter rarely had a sham ECT condition. Bilateral ECT is a little more effective than unilateral ECT (22 studies, effect size 0.32) and high stimulus dose moderately more effective than low dose (seven studies, effect size 0.58). A subsequent meta-analysis looking at categorical outcomes (Pagnin, *et al.*, 2004) found superiority of ECT to TCAs and MAOIs considered separately. Significant benefit occurs early with 54% of patients responding after three treatments in one study (Husain, *et al.*, 2004a). There are more limited longer-term follow-up data. In placebo-controlled relapse prevention RCTs following ECT there is a 65–84% relapse rate on placebo over 6 months contrasting with 18–60% on a TCA alone, 26% on paroxetine and 39% on nortriptyline + lithium (Lauritzen, *et al.*, 1996; Sackeim, *et al.*, 2001a; van den Broek, *et al.*, 2006). In comparative study arms nortiptyline + lithium was better than nortriptyline alone (39% *versus* 60% relapse) (Sackeim, *et al.*, 2001a) and paroxetine was better than imipramine (26% *versus* 47% relapse) (Lauritzen, *et al.*, 1996). The primary limitation to treatment with ECT is short-term, and probably longer-term, impairments in cognitive functioning, which may have been underestimated by clinicians (Rose, *et al.*, 2003) although the data are heterogeneous and there are difficulties in teasing out treatment effects from those attributable to the course of illness. Bilateral (compared with non-dominant unilateral) ECT and higher stimulus dose are associated with increased short-term cognitive deficits (UK ECT Review Group, 2003). A prospective study found that bilateral and sine wave treatments were significantly associated with adverse cognitive outcomes at 6 months but that persisting depression and patient characteristics were also predictive (Sackeim, *et al.*, 2007b). It is not clear at present whether, and if so to what degree, optimisation is possible to maximise efficacy and minimise side effects. Little is known about prediction of response to ECT, especially compared with alternative treatments and ECT appears effective across the depressive subtypes (Sobin, *et al.*, 1996).

ECT is the most effective antidepressant treatment available with a balance to be struck between short-term benefit and potential longer-term adverse effects. Continuation treatment, usually with medication, is necessary to reduce relapse. Because of its high efficacy and rapid speed of onset of response, ECT may be the treatment of choice for depression in the emergency situation when symptoms are severe including intense and persistent suicidality, psychomotor retardation and/or psychotic symptoms are prominent, and where there is reduced fluid

intake leading to clinically significant dehydration (Scott, 2005). In the non-emergency situation, ECT may be a treatment alternative for more severe depression if there are persuasive reasons to avoid pharmacotherapy but the high risk of relapse if preventative treatment with medication is not possible needs to be taken into account. Strategies to avoid longer-term adverse effects need to be taken where possible, including use of right unilateral electrode placement and individually optimising current dose.

Repetitive transcranial magnetic stimulation (rTMS) involves focal stimulation of the superficial layers of the cerebral cortex using a rapidly changing magnetic field applied using an external coil. A recent meta-analysis of 33 short-term RCTs in depression (Herrmann and Ebmeier, 2006) found a large significant effect size of 0.71 against sham treatment but the studies were small, heterogeneous in methodology and effect size and it was not possible to identify any significant predictors of outcome. Blinding of treatment is problematic and the reported studies are vulnerable to bias. The most common effective methodology was left dorsolateral prefrontal cortex stimulation with frequencies of greater than 5 Hz and 100% or more of motor threshold. There are few RCT data describing efficacy and relapse rates beyond the acute treatment phase, which suggest possible short-term maintenance of effect in patients continuing on antidepressants (Dannon, *et al.*, 2002; Koerselman, *et al.*, 2004; Anderson, *et al.*, 2007). rTMS appears safe when used within published safety parameters.

Stimulation of the left vagus nerve (vagus nerve stimulation, VNS) has been studied in one RCT in patients who had failed to respond to between two and seven adequate treatment trials. Active VNS was no more effective than sham treatment (15% *versus* 10% response after 10 weeks, NNT 20) but it was argued that this was a failed, rather than a negative, trial due to insufficient stimulus titration (Rush, *et al.*, 2005). In a continuation of the same study, after 12 months VNS treatment, more patients had responded compared with a group of comparable treatment-as-usual patients recruited using the same selection criteria (27% *versus* 13%, NNT 7) (George, *et al.*, 2005). In open treatment there appears to be a high maintenance of response over 2 years (60–75%) (Sackeim, *et al.*, 2007a) compared with only 38% of 12 month responders maintaining response at 24 months in a comparable treatment-as-usual patient population (Dunner, *et al.*, 2006).

Evaluation of studies of light therapy is problematic because of wide methodological variation, often very short duration (mostly one week) and lack of long-term data. Golden, *et al.* (2005) identified 20 studies of bright light/dawn simulation against 'placebo' (red light, rapid dawn or no treatment) in major depression. For seasonal affective disorder (usually recurrent autumn/winter depression) both bright light (eight studies, effect size 0.84) and dawn simulation (five studies, effect size 0.73) were effective. In non-seasonal depression bright light used as sole therapy was effective (three studies, effect size 0.53) but not when used as an adjunct to antidepressants (five studies, effect size 0.01). Tuunainen, *et al.* (2004) identified 20 studies of light therapy in non-seasonal depression (17 studies with major depression, 10 studies included bipolar patients); in nine studies it was combined with sleep-deprivation and in 17 it was adjunctive to antidepressants. Results were heterogeneous so only random effect sizes (taking into account differences between studies) are presented here. There was a small non-significant benefit to light therapy (18 studies, effect size 0.22) but larger and significant if confined to morning light therapy (11 studies, effect size 0.43). In two studies without any adjunctive treatment there was a non-significant benefit to light therapy (effect size 0.64) with a smaller non-significant benefit if it was adjunctive to antidepressant medication (14 studies, random effect size 0.24). Sleep deprivation and shorter studies (ie 7 days) tended to be associated with a larger effect of light therapy.

In RCTs subsequent to the meta-analyses, light therapy in seasonal affective disorder was found to have equally efficacy to citalopram in a medium sized 8-week study (Lam, *et al.*, 2006) and to CBT and combined treatment in a very small 6-week study (Rohan, *et al.*, 2004) although CBT had a protective effect against relapse the following winter. In a relapse prevention study citalopram tended to protect against relapse better than placebo over 4 months in responders to 1 week of light therapy (Martiny, *et al.*, 2004) and prophylactic bupropion (amfebutamone) has been shown to prevent relapse the following winter (Modell, *et al.*, 2005). In non-seasonal depression, variable quality small- to medium-sized RCTs have generally favoured light therapy (Martiny, 2004; Epperson, *et al.*, 2004; McEnany and Lee, 2005) but efficacy in the elderly is unclear (Tsai, *et al.*, 2004; Loving, *et al.*, 2005). In one study an advantage of five-weeks adjunctive light therapy was lost after continuing for a further four weeks on sertraline monotherapy (Martiny, *et al.*, 2006); another study found that light therapy hastened response to citalopram over two weeks (Benedetti, *et al.*, 2003).

Taken together, studies suggest short-term benefit for light therapy in seasonal affective disorder (where there is very limited evidence for antidepressant efficacy, see Evidence section 2.3) and as monotherapy, but not added to antidepressants, in non-seasonal depression. Preliminary evidence in seasonal affective disorder suggests that citalopram prevents relapse and bupropion and CBT prevent recurrence the following season.

A review of sleep deprivation studies (Giedke and Schwarzler, 2002) concluded that about 60% of patients significantly had improved the next day but that most relapse after a night's sleep. The effect of sleep deprivation may be prolonged by drug treatment or it may hasten response to antidepressants but the data are limited and the place of sleep deprivation is not established.

Complementary treatments

Summary

Hypericum extracts (St John's Wort) are effective in the acute treatment of mild and moderate major depression and appear comparable in efficacy to antidepressants and well tolerated (I). Apparent efficacy in milder depression probably reflects

methodological problems with older trials. Longer-term efficacy and safety are not established and there is the potential to interact adversely with other medication including antidepressants. Omega-3 fatty acids may be an effective adjunct when added to current treatment in patients with major depression patients not responding to antidepressants (I). There is a lack of evidence for their use as monotherapy for major depression in adults but a small positive trial in young children (II).

Extracts of St John's Wort (Hypericum perforatum) have a long history of being used to treat depression but they are complex mixtures with varying composition depending on the extraction method. A meta-analysis of 26 acute RCTs of hypericum against placebo found an overall benefit but with considerable methodological concerns including publication bias (Linde, *et al.*, 2005); there was only a small effect in better quality studies of major depression (response rate 54% *versus* 46%, NNT 12–13) with a much larger effect in small studies of more poorly defined depression (response rate 50% *versus* 8%, NNT 2–3). However, since then a further five placebo-controlled trials in major depression of moderate severity have been published (Uebelhack, *et al.*, 2004; Bjerkenstedt, *et al.*, 2005; Fava, *et al.*, 2005; Gastpar, *et al.*, 2006; Kasper, *et al.*, 2006). Combining these studies with those from Linde, *et al.* (2005) yields a significant pooled benefit over placebo (17 studies, response rate 53% *versus* 35%, NNT 5–6). Results are heterogenous with possible publication bias but the results are essentially the same when restricted to larger and better quality studies. No difference in efficacy between antidepressants and hypericum is apparent in Linde, *et al.* (2005) (14 studies) or two subsequent studies against SSRIs (Bjerkenstedt, *et al.*, 2005; Gastpar, *et al.*, 2006). However, two further studies found hypericum to be superior to SSRIs, the first against fluoxetine although neither active drug separated from placebo (Fava, *et al.*, 2005) and the second non-inferior and statistically superior to paroxetine in a non-inferiority trial (Szegedi, *et al.*, 2005) with maintained efficacy over a double-blind 4 month extension phase (Anghelescu, *et al.*, 2006). Taken overall these data suggest short- to medium-term efficacy for standardised extracts of hypericum (in doses between 600 mg and 1800 mg) in major depression with at least equal efficacy to antidepressants. Evidence from earlier studies that hypericum may have better efficacy in mild than moderate depression is most likely due to methodological problems. Tolerability of hypericum appears better than with antidepressants and it seems generally safe (Knuppel and Linde, 2004; Linde, *et al.*, 2005) provided its interaction potential with other medication including antidepressants is recognised (Knuppel and Linde, 2004). The drawbacks of hypericum are the availability of non-standardised preparations and a lack of prospective long-term efficacy and safety data.

Omega-3 fatty acids are polyunsaturated fatty acids (PUFAs) that are involved in neuronal, vascular and immune functioning. Eicosapentanoic acid (EPA) and docosahexaenoic acid (DHA) have been studied individually and in combination in treating unipolar and bipolar depression, usually as adjunctive treatment to antidepressants. Two meta-analyses, each of eight RCTs (seven common to both) found a significant benefit *versus* placebo (Freeman, *et al.*, 2006; Appleton, *et al.*, 2006) (effect sizes 0.25 and 0.57, respectively) but the results were heterogeneous with mixed patient populations and varying PUFA compositions making conclusions difficult to draw. In unipolar depression in adults there is a lack of evidence for omega-3 fatty acids as monotherapy and an underpowered negative study for DHA (Marangell, *et al.*, 2003) but a recent study found significant benefit for EPA+DHA in younger children (6–12 years) (Nemets, *et al.*, 2006). There is some evidence for the use of EPA or EPA+DHA/fish oil as adjunctive treatment in three RCTs in major depression not responding to antidepressants (Nemets, *et al.*, 2002; Peet and Horrobin, 2002; Su, *et al.*, 2003). A primary care study of modest dose omega-3 fatty acids supplementation of antidepressants did not find an advantage over placebo supplementation; however, very large improvements were seen in both groups (Silvers, *et al.*, 2005). There are no longer-term data in unipolar depression.

2.3 Choice of antidepressant drug

Choice of drug has to be related to the individual patient and many factors are based on clinical experience and judgement rather than controlled evidence. It is good clinical practice for potential or unknown risks to be minimised, for example, where there is medical illness (e.g. avoiding older TCAs in patients with cardiac disease or those on hypotensive drugs where there might be risk of falls), pregnancy (see Evidence section 5) and previous history of overdose (drugs with lower lethality are to be preferred).

Efficacy considerations

Summary

Antidepressant class: Antidepressant drugs have similar efficacy in first line use for the majority of patients with depression (I). In hospitalised patients amitriptyline may be marginally more effective than other TCAs/ SSRIs, and older monoamine oxidase inhibitors (MAOIs) may be less effective than imipramine (I). Venlafaxine and escitalopram appear to be marginally more effective than other SSRIs (I). For escitalopram at a dose of 20 mg this may be to a clinically significant degree for severely ill patients (II).

In major depression with atypical symptoms, imipramine appears to be less effective than phenelzine (I) but there is limited or lack of evidence for differential efficacy between MAOIs, SSRIs, moclobemide and other TCAs (II). The evidence for antidepressant efficacy in seasonal affective disorder is very limited with the strongest being for SSRIs (II). There is insufficient evidence to choose between antidepressants on the basis of symptom profile, melancholia, comorbidity or psychosis (I–II) except for one study in which sertraline was more effective than desipramine in major depression with comorbid obsessive-compulsive disorder (II).

There is no consistent evidence for a clinically important effect of gender on response to different antidepressants,

although younger women may tolerate TCAs less well than men (I–II). There is a lack of compelling evidence that SNRIs are more effective than SSRIs for painful symptoms associated with depression (II). No clinically useful predictive biological factors have been identifed (II).

Systematic reviews and meta-analyses suggest that the commonly available antidepressants have comparable efficacy in the majority of patients seen in primary care or outpatient psychiatric settings (Anderson, 2001; Macgillivray, *et al.*, 2003). There is, however, a debate about whether some antidepressants may be marginally more effective than others with interpretation of the data complicated by uncertainty about what is a clinically significant difference (see also Evidence section 2.1), by issues of selective analysis and company sponsorship, treatment setting, antidepressant class *versus* individual drug, and lack of power and assay sensitivity in most studies. A meta-regression analysis involving 105 comparative RCTs did not identify a pharmacological predictor of efficacy (Freemantle, *et al.*, 2000) but the classification of drugs was problematic; the largest factor was company sponsorship, although this was not statistically significant.

In a meta-analysis of 100 studies (Guaiana, *et al.*, 2003) amitriptyline had a marginal advantage over other TCAs/SSRIs in inpatients (NNT 24) but not in non-hospitalised patients. Inpatient status may reflect greater severity of depression but other factors (e.g. type of depression, suicidality) could be relevant. A meta-analysis of MAOIs (Thase, *et al.*, 1995) found evidence that phenelzine and isocarboxazid were less effective than imipramine in hospitalised patients (10 studies, response difference 14–20% NNT 5–7) but the quality of studies was variable. A meta-analysis of individual patient data from 12 studies with the reversible inhibitor of monoamine oxide A (RIMA), moclobemide, reported no significant difference in efficacy to imipramine and clomipramine in hospitalised patients, including those with more severe depression or psychosis (Angst, *et al.*, 1995). With regard to newer antidepressants with more specific pharmacology, a focus of interest has been the relative efficacy of dual acting serotonin and noradrenaline reuptake inhibitors (SNRIs) (such as venlafaxine, duloxetine and milnacipran) compared with SSRIs. Two recent meta-analyses of venlafaxine compared with SSRIs with different study inclusion criteria have come to different conclusions about relative efficacy, or at least the size and certainty of any effect. Nemeroff, *et al.* (2007) found a small advantage to venlafaxine (34 studies, remission difference 5.9%, NNT 17), only significant against fluoxetine when SSRIs were considered separately. By contrast, Weinmann, *et al.* (2007) had tighter exclusion criteria and found benefit for venlafaxine in only two of four outcome analyses in 17 studies, non-significant for remission (NNT 34) and final depression score but significant for response (NNT 27) and change in depression score. Neither study found evidence of publication bias. The dose of venlafaxine needs to be considered with limited evidence for a dose response (Rudolph, *et al.*, 1998) and for dual action only at higher doses (above 150 mg) (Debonnel, *et al.*, 2007). A meta-analysis of milnacipran compared with SSRIs found no significant difference in response rates (six studies, 60% *versus* 57.5% response) (Papakostas and Fava, 2007) and neither has duloxetine been shown be more effective than SSRIs (eight studies, 51.6% *versus* 51.4% response) (Papakostas, *et al.*, 2007c) although unpublished secondary analysis of patients with initial HDRS >18 reported an advantage for duloxetine over SSRIs (Thase, *et al.*, 2003). A pooled analysis of two comparative RCTs comparing venlafaxine and duloxetine found no significant difference in efficacy although duloxetine did not meet predefined non-inferiority criteria (Perahia, *et al.*, 2007). It is therefore not possible at present to generalise about relative SNRI, or SNRI *versus* SSRI, efficacy. A recent meta-analysis compared drugs acting on serotonin and noradrenaline with varying pharmacology (SNRIs, mirtazapine, mianserin, moclobemide) against SSRIs and found a small significant benefit for the former (93 studies, 63.6% *versus* 59.3% response, NNT 24) with similar sizes of effect for all drugs except duloxetine which did not show any difference from SSRIs; however the results appeared largely driven by the venlafaxine studies (Papakostas, *et al.*, 2007c). Results for mirtazapine against SSRIs are inconclusive (National Institute for Clinical Excellence, 2004 appendix 19c). Further complicating the picture is the finding that escitalopram is significantly more effective than other SSRIs (eight studies, odds ratio 1.29) (Kennedy, *et al.*, 2006) but not significantly better than venlafaxine although the odds ratio was similar in favour of escitalopram (two studies odds ratio 1.23) (Kennedy, *et al.*, 2006). The difference was, however, small and for all 10 studies together the relative response rates were 66% *versus* 62% (NNT 24) although in secondary analysis in severely depressed patients the difference was greater (68% *versus* 58%, NNT 10). Whether this finding will hold up as further studies are done with escitalopram used as a comparator rather than experimental drug remains to be seen.

Whether different types of depression or symptom profiles might guide choice of antidepressants remains largely unresolved. 'Atypical' depression is currently defined by mood reactivity (i.e. mood improvement in response to environmental stimulation) and at least one associated symptom (from increased appetite/weight gain, increased sleep, severe fatigue/leaden heaviness of limbs, sensitivity to rejection as a personality trait) but historically there have been varying definitions distinguishing it from 'typical' or 'endogenous' depression. Thase, *et al.* (1995) found that the MAOI phenelzine was more effective than TCAs in outpatients with varyingly defined atypical depression (eight studies, 12% response advantage, NNT 8–9) but not non-atypical depression (four studies, <1% response difference). A recent meta-analysis restricted to atypical depression (Henkel, *et al.*, 2006) confirmed a small advantage of phenelzine over imipramine (effect size 0.27) with no difference between phenelzine/moclobemide and SSRIs (three studies, effect size 0.02). Caution is needed in equating moclobemide with phenelzine and in generalising findings with imipramine to other TCAs. There are only a few studies comparing other antidepressants; Joyce, *et al.* (2002) found nortryptyline less effective than fluoxetine in a very small subset of atypically depressed patients whereas a small study found fluoxetine and

reboxetine equally effective (Taner, *et al.*, 2006); there is a lack of evidence for SNRIs or other antidepressant classes.

In seasonal affective disorder (often associated with atypical symptoms) there is very limited evidence for antidepressant efficacy with a positive placebo-controlled study for sertraline (Moscovitch, *et al.*, 2004) and a suggestive study with fluoxetine (Lam, *et al.*, 1995). Comparative (non-placebo-controlled) data and relapse prevention data also suggest efficacy for moclobemide (Partonen and Lonnqvist, 1996) and bupropion (amfebutamone) (Modell, *et al.*, 2005).

There are difficulties in the definition of melancholic/endogenous depression, which overlaps with severity and psychosis, with psychomotor disturbance proposed as a key criterion (Parker, 2000). It has been suggested that TCAs are more effective than SSRIs for major depression with melancholia but the evidence is patchy with studies mostly retrospective, open or using secondary analysis (Angst and Stabl, 1992; Tollefson and Holman, 1993; Heiligenstein, *et al.*, 1994; Parker, *et al.*, 2001; Navarro, *et al.*, 2001; Parker, 2002; Joyce, *et al.*, 2003b) and we conclude it is insufficient to guide first-line choice of antidepressant.

There is limited evidence with regard to the treatment of psychotic depression. A meta-analysis of 10 small RCTs (Wijkstra, *et al.*, 2005) found evidence for a benefit from combined antidepressant-antipsychotic over antipsychotic alone (three studies, response 56% *versus* 30%, NNT 4), a non-significant benefit for antidepressant-antipsychotic over antidepressant alone (two studies, response 54% *versus* 37%, NNT 6) and a lack of efficacy of antipsychotics over placebo (two studies, response 32% *versus* 28%). The place of antiglucocorticoid treatment with mifepristone is unclear as although there have been positive studies (DeBattista, *et al.*, 2006; Flores, *et al.*, 2006) three phase III studies failed to meet primary outcomes (Nihalani and Schwartz, 2007; http://www.corcept.com/press.htm).

In considering symptom profile rather than depression subtype, it has been suggested that improving activation and social behaviour may be preferentially linked to noradrenaline-active drugs and emotional reactivity (including anxiety and impulsivity) to serotonergic drugs (Healy and McMonagle, 1997). While preliminary data were suggestive (Dubini, *et al.*, 1997; Katz, *et al.*, 2004) an analysis of two RCTs of reboxetine against fluoxetine found no reproducible difference in degree of improvement of different symptoms (Nelson, *et al.*, 2005a) or in residual symptom profile (Nelson, *et al.*, 2005b) as measured on the HDRS. This suggests a lack of clinically important differential effects but does not rule out more subtle effects or differences in features not assessed with the HDRS.

Comorbid diagnoses have been little examined in predicting response to different types of antidepressants. Comorbid anxiety disorders are especially common and antidepressants are generally effective in their treatment although there is most evidence for SSRIs (Baldwin, *et al.*, 2005). An exception may be obsessive-compulsive disorder (OCD) where an RCT in patients with comorbid depression found sertraline was more effective than desipramine (NNT 7–8) in treating both depressive and OCD symptoms (Hoehn-Saric, *et al.*, 2000).

The apparently straightforward question as to whether gender influences response to different types of antidepressant is complicated by age, menopausal status and tolerability considerations (e.g. Kornstein, *et al.*, 2000). The literature is not entirely consistent but there are small to medium size studies suggesting that younger women may respond preferentially to SSRIs over noradrenaline reuptake inhibitors (TCAs, maprotiline, reboxetine) with predominantly no difference found for men (Kornstein, *et al.*, 2000; Martenyi, *et al.*, 2001; Joyce, *et al.*, 2002; Baca, *et al.*, 2004; Berlanga and Flores-Ramos, 2006). This appears to be accounted for by poorer tolerability of TCAs in younger women (Kornstein, *et al.*, 2000; Joyce, *et al.*, 2002; Baca, *et al.*, 2004). Significant effects of gender were not seen in aggregated studies comparing SSRIs with clomipramine in inpatients (Hildebrandt, *et al.*, 2003), with the SNRIs venlafaxine (Hildebrandt, *et al.*, 2003) or duloxetine (Kornstein, *et al.*, 2006) nor with bupropion (amfebutamone) (Papakostas, *et al.*, 2007a). Some studies have suggested that women respond better to SSRIs than men (e.g. Kornstein, *et al.*, 2000; Khan, *et al.*, 2005b) but the lack of gender difference seen in a large observational study of sertraline treatment in over 5,000 patients (Thiels, *et al.*, 2005) argues against a clinically relevant effect. Results are inconsistent as to whether men respond better than women to TCAs (Quitkin, *et al.*, 2001). One retrospective analysis in a small group of patients reported that women responded better to MAOIs than men (Quitkin, *et al.*, 2001).

Pain symptoms are common in depression (Ohayon and Schatzberg, 2003) and have been associated with poorer response to treatment (Bair, *et al.*, 2004; Karp, *et al.*, 2005). It has been proposed that SNRIs may be particularly effective, and more effective than SSRIs, in treating pain symptoms because of their dual action (Delgado, 2004). There is however little evidence for a consistent advantage over SSRIs in RCTs (Detke, *et al.*, 2004; Goldstein, *et al.*, 2004; Perahia, *et al.*, 2006; Lee, *et al.*, 2007).

A variety of biological predictors of response to specific antidepressants have been proposed including plasma amino acid concentration (Moller, *et al.*, 1986; Porter, *et al.*, 2005), dexamethasone suppression test status (Rihmer, *et al.*, 1985; Benkelfat, *et al.*, 1987) and cerebrospinal fluid monoamine metabolites (Timmerman, *et al.*, 1987) but these results are not practical or reliable enough to be useful clinically.

Tolerability/safety considerations

Summary

Older TCAs are less well tolerated than SSRIs with little overall difference between newer antidepressants as assessed by treatment discontinuation in RCTs (I). There are significant differences in the pattern of adverse effects between antidepressants (I–II) with the main group differences: (i) TCAs and noradrenaline reuptake inhibitors – antimuscarinic side effects, dizziness and sweating, (ii) SSRIs/SNRIs – gastro-intestinal, stimulatory and sexual side effects, (iii) mirtazapine – sedation and weight gain.

Antidepressant (including SSRI) treatment is not associated with an increased risk of completed suicide (I) and ecological studies find it is associated with decreased suicide rates (II). Antidepressant (including SSRI) treatment does not appear associated with a clinically significant increased risk of suicidal behaviour in adults (I) although individual sensitivity cannot be ruled out. SSRIs may be associated with a small (<1%) increase in non-fatal suicidal ideation/behaviour in adolescents with a benefit-risk ratio of >10 (I). TCAs and MAOIs as a group have greater toxicity and potential to cause death in overdose than SSRIs and most other new antidepressants but there is variation within groups. Lofepramine shows low toxicity and clomipramine and venlafaxine intermediate toxicity (II).

Antidepressants differ in their side-effect profile, their potential to interact with other drugs and in safety in overdose. Selected drugs are displayed in Table 5. In choosing between different drugs the 'overall' side-effect burden or tolerability determined from systematic reviews may be difficult interpret given the different side-effect profiles. A review of antidepressant meta-analyses in which the efficacy and tolerability of antidepressants introduced since 1980 identified 18 informative meta-analyses (Anderson, 2001), mostly of short-term treatment. SSRIs are slightly better tolerated than TCAs overall (NNH for side-effect related dropouts 33). There is a different side-effect profile with significantly more nausea, diarrhoea, anorexia and stimulatory side effects (agitation, insomnia and anxiety) on SSRIs and more antimuscarinic side effects (dry mouth, constipation, blurred vision, urinary disturbance), dizziness and sweating on TCAs. A recent meta-analysis of 29 studies in the elderly found a similar result (Mottram, *et al.*, 2006) and there is a generally increased rate of dropouts in the elderly compared with younger adults (Anderson, *et al.*, 2000). From limited evidence, the newer TCA lofepramine causes fewer side effects (particularly dry mouth, dizziness and sedation) than older TCAs (Anderson, 2001). A meta-analysis of 20 studies comparing SSRIs with other newer antidepressants (venlafaxine, mirtazapine, bupropion) found no difference in overall, or side-effect related, dropouts (Gartlehner, *et al.*, 2005). However, recent meta-analyses have found slightly greater rates of discontinuation due to adverse effects (NNH about 30), but not to all causes, on venlafaxine compared with SSRIs (Weinmann, *et al.*, 2007; Nemeroff, *et al.*, 2007). Data on sexual side effects were not consistently collected in earlier studies; more recent studies have shown a consistent picture of greater sexual side effects on SSRIs and SNRIs than bupropion, reboxetine, mirtazapine, nefazodone and moclobemide (Montejo, *et al.*, 2001; Gregorian, *et al.*, 2002; Clayton, *et al.*, 2003; Thase, *et al.*, 2005; Langworth, *et al.*, 2006). There may be differences between individual SSRIs with fluoxetine possibly causing more agitation and skin rashes, paroxetine more sedation, sexual dysfunction, weight gain and discontinuation reactions, and fluvoxamine more nausea and less sexual dysfunction (Anderson and Edwards, 2001). In short-term studies mirtazapine caused fewer dropouts due to side effects (NNH 25), but not due to all causes, than SSRIs but is associated with sedation and weight gain, the latter clinically significant compared with other newer antidepressants (Leinonen, *et al.*, 1999; Anderson, 2001; Masand and Gupta, 2002; National Institute for Clinical Excellence, 2004 appendix 18c). With regard to the most recent antidepressants, escitalopram appears as well tolerated as other SSRIs (possibly better than paroxetine) and better tolerated than venlafaxine (Baldwin, *et al.*, 2007). Studies with duloxetine have reported both equal and poorer tolerability compared with SSRIs (Hudson, *et al.*, 2005; Perahia, *et al.*, 2006; Khan, *et al.*, 2007; Wade, *et al.*, 2007; Lee, *et al.*, 2007) but fewer sexual side effects than paroxetine (Delgado, *et al.*, 2005). In pooled data from two studies against venlafaxine more patients on duloxetine discontinued overall, and due to side effects, (NNH about 20) (Perahia, *et al.*, 2007)

RCTs are probably not the best way to assess the impact of tolerability in practice. Although data are limited, naturalistic studies have supported a higher rate of switching to another antidepressant with TCAs (including lofepramine) than SSRIs although other reasons apart from tolerability may play a part (Simon, *et al.*, 1999b; Peveler, *et al.*, 2005).

There has been considerable concern as to whether antidepressants, particularly SSRIs may be associated with an increase in suicidal ideation or acts. Two meta-analyses (Gunnell, *et al.*, 2005; Fergusson, *et al.*, 2005) with 702 and 477 studies, respectively, and a large nested case-control study comparing new prescriptions of SSRIs and TCAs (Martinez, *et al.*, 2005) found no evidence of an increase in completed suicide with SSRIs but possible evidence of increased suicidal/self-harm behaviour with SSRIs compared with placebo (NNH 684 and 754 in the two meta-analyses). There was no overall difference between SSRIs and TCAs (Fergusson, *et al.*, 2005; Martinez, *et al.*, 2005) but Martinez, *et al.* (2005) found some evidence for increased self-harm behaviour on SSRIs compared with TCAs in those under 19 years. A meta-analysis of 27 RCTs of SSRIs in children and adolescents with depression, OCD and other anxiety disorders (Bridge, *et al.*, 2007) found no completed suicides but a small significant increase in suicidal ideation/self harm attempts with SSRIs compared with placebo (NNH 143), not significant for each indication separately. However, the inferential and retrospective nature of the ascertainment of 'suicidality' in these studies has been criticised (Klein, 2006).

To assess the risk of suicidal behaviour in clinical practice database linkage methods have been used. The risk of clinically significant suicidal behaviour was found to be highest in the month before starting antidepressants and declined thereafter with significantly higher rates seen in adolescents compared with adults (Jick, *et al.*, 2004; Simon, *et al.*, 2006b). No temporal pattern of completed suicide was evident in the six months after starting an antidepressant (Simon, *et al.*, 2006b) and there was no increase in suicide/suicide attempt seen with SSRIs compared with other antidepressants in adolescents or adults (Jick, *et al.*, 2004; Simon, *et al.*, 2006b). The highest rates of suicidal behaviour were seen in patients treated by psychiatrists but same pattern was also seen with psychological treatments and in primary care (Simon and Savarino, 2007). Ecological data has also failed to find any link between SSRI use and higher completed suicide rates in adults and children/

Table 5 Side-effect profiles and lethality in overdose of commonly used antidepressant drugs

Drug	Action	Anti-cholinergic[a]	Sedation	Insomnia/ agitation	Postural hypotension	Nausea/ gastro intestinal	Sexual dysfunction	Weight gain	Specific adverse effects	Inhibition of hepatic enzymes	Lethality in overdose
Tricyclic antidepressants											
Clomipramine	SRI+NRI	++	+	+	++	+	++	+		–	Moderate
Amitriptyline, dosulepin	NRI>SRI	++	++	–	++	–	+	++		–	High
Imipramine	NRI>SRI	++	+	+	++	–	+	+		–	High
Desipramine, nortriptyline	NRI	+	+	+	+	–	+	–		–	High
Lofepramine	NRI	+	–	+	+	–	?	–	Sweating	–	Low
Selective serotonin reuptake inhibitors											
Citalopram, sertraline	SRI	–	–	+	–	++	++	–		–	Low
Fluoxetine, fluvoxamine, paroxetine	SRI	–	–	+	–	++	++	–		++	Low
Other reuptake inhibitors											
Maprotiline	NRI	++	++	–	–	–	+	++	Increased seizure potential	?	High
Reboxetine	NRI	+	–	+	–	–	+	–		–	Low
Venlafaxine	SRI>NRI	–	–	+	–	++	++	–	Hypertension, sweating	+	Moderate
Duloxetine	SRI+NRI	–	–	+	–	++	++	–		–	?
Bupropion[b]	?DRI+NRI	–	–	+	–	–	–	–	Increased seizure potential	–	?
Receptor antagonists											
Trazodone	5-HT_2 + α_1 > SRI	–	++	–	++	–	–	+	Priapism	?	Low
Nefazodone[b]	5-HT_2 > SRI	+	+	–	+	+	–	++		++	Low
Mianserin	5-HT_2 + α_1+α_2	+	++	–	–	–	–	–	Blood dyscrasia	?	Low
Mirtazapine	5-HT_2 + 5-HT_3 + α_2	–	++	–	–	–	–	++		–	Low
Monoamine oxidase inhibitors											
Phenelzine, tranylcypromine, isocarboxazid	Irreversible	+	+	++	++	+	++	++/–	Hypertensive crisis with sympatheto-mimetics, oedema	?	High
Moclobemide	RIMA	–	–	+	–	+	–	–		–	Low
Other											
Agomelatine[b]	M+5-HT_{2C}	–	–	–	–	–	–	–		?	?

Abbreviations: DRI, dopamine reuptake inhibitor; M, melatonin agonist; NRI, noradrenaline reuptake inhibitor; RIMA; reversible inhibitor of monoamine oxidase-A; SRI, serotonin reuptake inhibitor; 5-HT_2; 5-HT_2 antagonist; 5-HT_3; 5-HT_3 antagonist; $\alpha_1/\alpha_2\alpha_1$ antagonist/α_2 antagonist; ++, relatively common or strong; +, may occur or moderately strong; –, absent or rare/weak; ?, unknown/insufficient information

[a]These refer to symptoms commonly caused by muscarinic receptor blockade including dry mouth, sweating, blurred vision, constipation and urinary retention; however the occurrence of one or more of these symptoms may be caused by other mechanisms and does not necessarily imply that the drug binds to muscarinic receptors.

[b]These are not licensed in the UK but are elsewhere in the world. A licence for agomelatine is being applied for in Europe.

These side-effect profiles are not comprehensive, have been compiled from various sources and are for rough comparison only. Details of drugs used and potential cautions and interactions should be looked up in a reference book such as the British National Formulary (BMJ and RPS, 2007).

adolescents (Gibbons, *et al.*, 2005; Gibbons, *et al.*, 2006; Hall and Lucke, 2006); in fact the association is generally for increased SSRI use to be linked to lower suicide rates and recent data from the Netherlands and United States shows an inverse relationship between decreases in SSRI use and increase in suicide in adolescents since warnings about SSRI use have been issued (Gibbons, *et al.*, 2007). Taken together the evidence indicates a lack of a specific link between antidepressant/SSRI use and suicide/suicidal behaviour in adults. There is some evidence for a small increase in non-fatal suicidal ideation/self harm behaviour in adolescents treated with SSRIs but not for completed suicide; indeed indirect evidence suggests that SSRI use may reduce suicide rates. The risk-benefit analysis therefore needs to take into account the reality that suicidal behaviour is relatively high in depressed adolescents before treatment and that the increased chance of successful treatment following an SSRI (NNT 10) outweighs the increased risk of non-fatal self harm (NNH >100) by more than 10 times.

Antidepressant drugs are involved in 10–20% of drug poisoning deaths in England and Wales (Morgan, *et al.*, 2004; Cheeta, *et al.*, 2004). The relative toxicity of individual drugs in overdose can be investigated using the fatal toxicity index (deaths by poisoning per million prescriptions). This method cannot take into account potential confounds such as dose, frequency of overdose and type of patient. A number of studies have examined the fatal toxicity index in England and Wales between 1993 and 2002 (Buckley and McManus, 2002; Morgan, *et al.*, 2004; Cheeta, *et al.*, 2004). In cases where only antidepressants were mentioned, TCAs and MAOIs had the highest toxicity with about a 10- to 20-fold increase over SSRIs. Within the TCA-related group there was a wide range of toxicity with desipramine (now withdrawn in the UK), amoxapine, dosulepin (dothiepin), amitriptyline and imipramine having the highest and lofepramine among the lowest with clomipramine intermediate. Other newer antidepressants generally had low toxicity apart from venlafaxine, which was intermediate; data are not available for duloxetine. Of the SSRIs citalopram may be associated with a greater tendency for cardiac toxicity than other SSRIs in overdose (Isbister, *et al.*, 2004). A prospective study of 538 self poisonings (Whyte, *et al.*, 2003) found that venlafaxine and dosulepin were pro-convulsant in overdose, TCAs were more likely to cause coma than SSRIs/venlafaxine but less likely to cause serotonin toxicity. SSRIs were less likely than TCAs/venlafaxine to prolong the QRS interval.

Concerns about the reasons for the higher venlafaxine fatal toxicity index led to a review in the UK (Medicines and Healthcare Products Regulatory Authority, 2006), which concluded that it is partly, but not completely, attributable to patient characteristics and possible mechanisms include cardiotoxicity, seizures, serotonin syndrome/muscle toxicity and CNS depression, but that the relative importance of these mechanisms could not be assessed. Caution was recommended in vulnerable patients (e.g. high arrhythmia risk, uncontrolled hypertension) and at doses ≥300 mg daily. TCAs are cardiotoxic, mainly due to cardiac sodium channel blockade leading to conduction defects (Thanacoody and Thomas, 2005) and MAOIs are dangerous in overdose and have interactions with tyramine-containing foodstuffs and a variety of medications; toxic effects including hypertensive crisis, serotonin and noradrenaline toxicity and central nervous system excitation and depression (Bateman, 2003).

This is not a complete review of safety considerations and adverse effects and the prescribing should be done in conjunction with a reference book such as the British National Formulary (BMJ and RPS, 2007); some others are considered in Evidence section 5.

Other factors related to antidepressant choice

Summary

Patient preference in treatment choice does not improve the degree of improvement in depressive symptoms but may lead to earlier improvement and less likelihood of switching antidepressant drug (II). Useful pharmacogenetic predictors of response to different antidepressants are not available. There is very limited evidence for personal and family history predicting differential response to TCAs and MAOIs (III) with a lack of evidence for newer antidepressants.

Patient preference has been relatively little studied. Three studies incorporating a patient preference arm comparing antidepressants (Peveler, *et al.*, 2005) or antidepressants with psychological interventions (Chilvers, *et al.*, 2001; Lin, *et al.*, 2005) have not found that exercising preference improved eventual outcome although there were fewer switches between antidepressants in those receiving their preference in one study (16% *versus* 35%, NNT 6) and patients exercising preference had earlier improvement in another (Lin, *et al.*, 2005).

Cost-effectiveness analyses highlight that drug acquisition costs represent only a minor part of the overall cost of treatment, which change with time as drugs come off patent. A review of cost-effectiveness is outside the scope of this review and most of the evidence is based on modelling; there are few prospective studies comparing antidepressants which have not found consistent differences between different drugs (Simon, *et al.*, 1999b; Peveler, *et al.*, 2005; Serrano-Blanco, *et al.*, 2006).

Pharmacogenetics offers the possibility for predicting antidepressant efficacy based on functional variation in the targets for drugs within the body but findings are not yet at the stage where it is clinically useful. The most commonly studied has been the serotonin transporter promoter gene (5-HTTLPR) and a recent meta-analysis of 15 studies found that among non-Asian subjects those possessing the less active short (S) allelle responded less well to SSRIs than those with the long (L) allele (NNT for S/S + S/L *versus* L/L about 10) (Serretti, *et al.*, 2007); however the largest study so far (STAR*D) was negative (Kraft, *et al.*, 2007) and possessing the S allele did not predict differential response to fluoxetine compared with nortriptyline in another study (Joyce, *et al.*, 2003a). It is possible that genetic effects on tolerability are also important, for example S-allele carriers have been reported to suffer more severe side effects to paroxetine but not mirtazapine (Murphy, *et al.*, 2004). Another use of pharmacogenomics is to identify genetic polymorphisms of drug metabolising enzymes that potentially

could identify individuals at risk of toxicity or lack of response to specific drugs. However, at present there is lack of prospective evidence that testing can improve the risk-benefit ratio of drug therapy (Eichelbaum, *et al.*, 2006).

Previous response to a specific antidepressant might be presumed to be a useful guide to antidepressant choice in a new episode but prospective evidence is lacking. Similarly there is limited evidence as to whether family history of selective response might guide antidepressant choice. A few small studies have suggested that differential response to a TCA or MAOI tends to hold true for subsequent episodes and between family members (Pare and Mack, 1971; O'Reilly, *et al.*, 1994) but there is no good evidence for modern antidepressants. In a study of 45 responders to fluvoxamine 67% of first degree relatives were concordant for response (Franchini, *et al.*, 1998) but it is not clear that this is significantly higher than would occur in a non-selected population.

2.4 Practical issues in acute management

Optimising outcome

In Evidence section 1.4 we considered the method of service delivery; here we focus on individual prescribing practice.

Summary

Structured interventions involving planned follow-up improve treatment adherence and outcome (I). Risk of self-harm during antidepressant treatment is highest in the first month after starting treatment (II) and new suicidal ideation may arise (I). Improved adherence with taking antidepressants can be achieved by interventions that include drug adherence counselling, but not by information leaflets alone (I). Once daily administration of even short half-life antidepressants is as effective as multiple dosing (I) and may be associated with better treatment adherence (II). The minimum effective dose of older TCAs is not established; in acute treatment RCTs doses below 125 mg are as effective as higher doses and better tolerated (I), however more severely depressed patients may benefit from higher does (II). Side effects from antidepressant medication are related to dose (I). Lower initial doses of antidepressants appear appropriate in the elderly because of pharmacodynamic and tolerability considerations (III). In most depressed patients who have a sustained response to antidepressants or placebo there is an onset of improvement within the first two weeks (I). Early, non-persistent, improvement in depressive symptoms appears unlikely to lead to later sustained response (II). Therapeutic drug monitoring has only a limited role in the effective use of antidepressants (II).

Direct evidence for the optimum frequency of monitoring of patients is lacking but structured interventions, including systematic follow-up, improve treatment adherence and outcome (see Evidence section 1.4). A meta-analysis of 41 studies that reported weekly HDRS scores found that the response to placebo was enhanced if there were a greater number of follow up visits (Posternak and Zimmerman, 2007b) and a primary care study found that systematic follow-up was as effective as a more intensive depression care programme (Vergouwen, *et al.*, 2005). The risk of suicide attempts during treatment is highest in the first few weeks (Jick, *et al.*, 2004; Simon, *et al.*, 2006b; Simon and Savarino, 2007) and the need to monitor this risk together with side effects and adherence to treatment indicate that weekly monitoring is advisable in the first phase of treatment. A meta-analysis of 12 short-term studies found that 3% of previously non-suicidal patients developed suicidal ideation during treatment (Beasley, *et al.*, 1991). Whether there is benefit from using standardised symptom ratings as opposed to a clinical impression of depression severity/improvement has not to our knowledge been directly tested but the former have been integral to interventions improving outcome.

Patients report that educational materials are somewhat helpful (Robinson, *et al.*, 1997) but simply providing information about antidepressants or reminders about the need for adherence appears largely ineffective in improving adherence (Hoffman, *et al.*, 2003; Vergouwen, *et al.*, 2003). Adherence counselling involving special educational sessions does improve adherence to antidepressants although most studies have included it as part of collaborative care (Vergouwen, *et al.*, 2003). A favourable attitude to medication and increased confidence in managing side effects predicted antidepressant adherence in a primary care RCT (Lin, *et al.*, 2003). A meta-analysis of 22 studies found no difference in either the efficacy or the number of dropouts when an antidepressant was administered once a day or on multiple occasions, whether or not the antidepressant had a short half-life (<12 hours) (Yyldyz and Sachs, 2001; Yildiz, *et al.*, 2004). A recent database study of over 3000 patients found considerably better treatment adherence with once daily *versus* twice daily bupropion (McLaughlin, *et al.*, 2007). Taken together these data support once daily administration of antidepressants.

The dose formulation of most recent antidepressants means that doses with established efficacy are given from the start. There has long been a debate about effective doses of TCAs with consistent evidence that they are not routinely prescribed at recommended doses (≥125 mg of imipramine/amitriptyline equivalents) in primary care (e.g. Dunn, *et al.*, 1999). However a meta-analysis of TCA studies found that low dose TCAs (≤100 mg) were more effective than placebo (35 studies, NNT 4–6); higher dose studies were no more effective but caused more dropouts (six studies, NNH 11) (Furukawa, *et al.*, 2002). In addition primary care cohort studies comparing depressed patients treated with 'less than recommended' and 'adequate' doses and durations of antidepressant treatment found no difference in clinical outcome between groups although adequate doses may achieve faster improvement (Simon, *et al.*, 1995; Revicki, *et al.*, 1998). The case may be different in more severely ill patient as increased failure to achieve full recovery has been described for 'inadequately' treated depressed hospitalised patients who had inadequate doses and poorer medication adherence (Ramana, *et al.*, 1999). This does not exclude individual patients requiring 'recommended' TCA doses but the debate has largely moved on with the increasing relegation of TCAs to second or third line treatment.

The incidence of side effects increases with dose (Bollini, *et al.*, 1999; Furukawa, *et al.*, 2002). Clinical experience suggests that upward titration of TCAs is advisable because of side effects whereas most new antidepressants can be initiated at doses shown to be therapeutic. Data are lacking about the optimal rate of dose titration with 3–7 days commonly used in practice. The elderly generally have higher plasma concentrations for a given dose (Hammerlein, *et al.*, 1998) and they have a higher rate of side-effect related dropouts in RCTs (Anderson, *et al.*, 2000) so that lower doses of antidepressants are usually recommended (e.g. BMJ and RPS, 2007). If a patient appears to respond to a 'low' dose of an antidepressant there is no controlled evidence about whether or not to continue dose titration; limited evidence from continuation studies (see Evidence section 4.1) suggests that it is best to achieve a dose of proven efficacy if possible, particularly in more severely depressed patients.

The existence of a delay in the onset of antidepressant action has become an accepted belief but does not accord with trial data and is likely to reflect time to appreciable improvement rather than onset. A meta-analysis of 47 studies found that 35% of the eventual rating scale improvement occurred in the first week (Posternak and Zimmerman, 2005b). Significant antidepressant-placebo differences are apparent in the first week (Stassen, *et al.*, 1996; Posternak and Zimmerman, 2005b; Taylor, *et al.*, 2006) and substantial improvement in the first 2 weeks (typically ≥25–30% reduction) strongly predicts final response (Stassen, *et al.*, 1996; Nierenberg, *et al.*, 2000; Aberg-Wistedt, *et al.*, 2000; Szegedi, *et al.*, 2003). Most (Nierenberg, *et al.*, 1995; Szegedi, *et al.*, 2003), but not all (Quitkin, *et al.*, 2003) studies find that only a minority of those with lack of improvement in the first 2 weeks go on to respond. By contrast, it has been suggested, using pattern analysis, that early abrupt improvement (before completion of 2 weeks treatment) in patients on both placebo and antidepressant drug treatment is less likely to be sustained than gradual improvement after 2 weeks, and reflects a placebo response pattern (Quitkin, *et al.*, 1984; Quitkin, *et al.*, 1987). It is difficult to fully reconcile these data, which may reflect separate processes, one triggering a process of improvement occurring more often with antidepressants than placebo and a second variable fluctuation in mood state independent from the resolution of the underlying depression.

Therapeutic drug monitoring is an established procedure for lithium and some anticonvulsants but is rarely used for antidepressants. It potentially has a use in assessing adherence or where there is relatively low therapeutic index and/or a therapeutic window; in practice this applies to TCAs, either when there is a high risk of toxicity or when there is lack of efficacy and side effects despite adequate doses (Baumann, *et al.*, 2005).

Managing specific adverse effects

Summary

Side effects tend to improve over time (I) with some, such as nausea on SSRIs and SNRIs, usually short-lived (I) while others, such as anticholinergic side effects on TCAs, appear not to be (II). Management is primarily based on clinical judgement with a lack of direct evidence. The main strategies are lowering the antidepressant dose, switching drug, symptomatic treatment with another agent or non-drug management of the side-effect. Combining benzodiazepines with antidepressants early in treatment speeds response and reduces dropouts (I) and may be useful for managing early agitation/anxiety and insomnia but needs to be balanced against the risk of long-term use. Beneficial strategies for sexual side effects are switching to an antidepressant with a lower tendency to cause sexual side effects (II) and sidenafil for erectile dysfunction in men (I). Modafinil may improve sleepiness in partial responders to SSRIs with fatigue and sleepiness but its effect on fatigue is unclear (II).

Antidepressants differ in their pattern of adverse effects (Table 5, Evidence section 2.3) and managing side effects is a common clinical necessity. This is complicated by the overlap between symptoms caused by the drug and those related to the depression. Many side effects are most troublesome at the start of treatment and subside over time (Demyttenaere, *et al.*, 2005) presumably due to adaptation and possibly improvement in depression. Nausea associated with SSRIs and SNRIs starts almost immediately and lasts on average for a week before reducing to near placebo levels (Greist, *et al.*, 2004). The relative contribution of drug and condition can be difficult to determine for some short term (e.g. agitation, sleep disturbance) and longer-term (e.g. sexual dysfunction, weight gain, sleep disturbance and somnolence) complaints. Anticholinergic side effects on TCAs have been reported not to diminish with long-term treatment (Bryant, *et al.*, 1987).

There is relatively little good evidence relating to the management of side effects and it is beyond the scope of this review to go into individual adverse effects in detail. Reducing the dose, slower titration, switching antidepressant to a drug with less tendency to cause that side effect, non-drug management and symptomatic treatment with another drug are common clinical strategies. Sleep disturbance and anxiety/agitation early in treatment can be treated with adjunctive benzodiapines. While not testing this indication directly a meta-analyis (Furukawa, *et al.*, 2001) found that combined treatment with antidepressants and benzodiapines in major depression resulted in more rapid symptom resolution than antidepressants alone (nine studies, response at 4 weeks 63% *versus* 38%, no difference at 6 and 8 weeks) with a lower dropout rate. The risk is that benzodiazepine use will continue into the long-term as has been noted in surveys of psychotropic drug use (e.g. Valenstein, *et al.*, 2004). A systematic review of the treatment of sexual side effects caused by antidepressant medication identified 15 RCTs (Taylor, *et al.*, 2005b); sidenafil use improved sexual functioning in men with erectile dysfunction (two studies) and single studies found that switching from sertraline to nefazodone was better than restarting sertraline and adding bupropion improved desire frequency. A subsequent study found no benefit from adding bupropion for SSRI-induced sexual dysfunction (DeBattista, *et al.*, 2005). A study combining data from two RCTs of modafinil augmentation in patients with partial response to SSRIs with persisiting fatigue and sleepiness found an improvement of depression and sleepiness over placebo with

separation from week one but early benefit for fatigue did not separate from placebo at endpoint (Fava, *et al.*, 2007). We could find no controlled evidence for managing weight gain.

3. Next-step treatments

3.1 Next-step treatments following inadequate treatment response to an antidepressant

Summary

The chance of responding to a subsequent treatment declines with each failed treatment trial (II). The likelihood of eventual response decreases if there has been no improvement by 4 weeks treatment (II) with only around 20% chance of remission at 12 weeks if there has been no improvement by 6–8 weeks (II). Lack of a continuing trajectory of improvement beyond 3–4 weeks is associated with lack of response by 12 weeks (II). There is no clinically significant difference between younger adults and elderly patients in the rate of improvement (II).

In clinical practice patients are encountered at different stages in their illness and treatment history, which affects the outcome of treatment. An important predictive factor in addition to severity and duration (see Evidence section 2.1) is the amount of previous treatment. Definitions of treatment resistance vary although most describe it as a failure to respond to two or more adequate antidepressant treatment trials (Anderson, 2003). However, problems arise in defining what comprises an adequate treatment trial, which drugs are to be included and in taking account of psychological treatments. The largest prospective study investigating sequential treatment outcomes is the Sequenced Treatment Alternatives for the Relief of Depression (STAR*D), which found that response rates dropped from 49% to 16% and remission from 37% to 13% over four steps of treatment with early discontinuation for side effects increasing from 16% to 30% (Rush, *et al.*, 2006a). Studies of next-step treatments are mostly small, many are non-replicated and the stage of treatment resistance, methodology and patient populations differ making conclusions difficult to reach. Only RCT evidence will be considered as open studies are not interpretable.

When to decide that initial treatment has failed is by no means clear and the evidence is limited by different study definitions and durations. It has been reported that if there is a lack of improvement (defined as at least a 20–30% reduction in HDRS in different studies) at 4 and 6 weeks, only 20% and 10%, respectively will go on to eventual response (≥50% improvement) at 8 weeks (Nierenberg, *et al.*, 1995; Nierenberg, *et al.*, 2000). A signal detection analysis of three studies with different antidepressants found that non-improvement by week 6 identified ≥60% of non-remitters (HDRS >10) at 12 weeks with a false positive rate of ≥20% and little difference between antidepressant type (Sackeim, *et al.*, 2006). By contrast, an open study with fluoxetine reported that 23% of non-improvers at 8 weeks still remitted by 12 weeks (Quitkin, *et al.*, 2003). Another study reported that late responders (occurring between 4 and 12 weeks) had continuing improvement between weeks 3 and 4 whereas non-responders at 12 weeks had failed to improve after 3 weeks (Trivedi, *et al.*, 2005). While the elderly may be a little slower to respond than younger adults this does not appear to be clinically significant (Sackeim, *et al.*, 2006; Mandelli, *et al.*, 2007).

If a patient has not responded it is important to review whether the diagnosis is correct, whether there are concurrent medical or psychiatric conditions, and to check that the initial treatment has been adequately given. Estimates of medication non-adherence (either full or partial) differ widely with a median figure of about 40% in different reviews (Cramer and Rosenheck, 1998; Demyttenaere and Haddad, 2000). Identification of potentially remedial factors that are associated with poorer response such as chronic social difficulties and continuing life events (Ronalds, *et al.*, 1997; Mazure, *et al.*, 2000) may indicate therapeutic targets for intervention in addition to antidepressants.

3.2 Next-step drug treatment

Summary

There is a lack of direct evidence for the efficacy of increasing the dose after initial treatment non-response. Indirect evidence suggests there is a dose response for TCAs, venlafaxine and escitalopram (II) but not for other SSRIs.

Switching antidepressants, including to the same class, is associated with a wide range of response rates in different studies (12–70%) (I–II). The only switch strategy with some evidence for enhanced efficacy is from an SSRI to venlafaxine (I). For many antidepressants abrupt switching appears safe and well tolerated (II) but for some drugs (e.g. MAOIs to serotonin reuptake inhibitors and fluoxetine to TCA) there are dangerous pharmacodynamic or pharmacokinetic interactions (III).

There is evidence for the efficacy of augmentation of antidepressants with lithium (I), some atypical antipsychotics (olanzapine, risperidone, quetiapine and aripiprazole) (I–II) and, equivocally, tri-iodothyronine (I) but not buspirone (II). The combination of reuptake inhibitors with mianserin (I) and SSRIs with TCAs/noradrenaline reuptake inhibitors (II) does not appear to be effective. There is possible, but insecure, preliminary evidence for efficacy for augmentation with mirtazapine, tryptophan, methylphenidate, lamotrigine, modafinil, antiglucocorticoids and oestrogen (in perimenopausal women) (II). Augmentation with lithium and atypical antipsychotic is associated with significant side effects (I–II).

If a patient does not respond it is important to make sure that a dose of antidepressants that has been shown to be effective is being taken; determining plasma drug levels may be helpful for older TCAs where therapeutic plasma drug ranges have been described (Baumann, *et al.*, 2005). The three main drug strategies following non-response are: to (i) increase the dose; (ii) switch antidepressant; or (iii) augment/combine with

a second agent. A serious problem is the lack of medium and longer-term efficacy and safety data.

A systematic review found no consistent evidence for increased efficacy after dose escalation in non-responders compared with continuing lower doses for SSRIs in seven RCTs but, in most studies, the timing of dose increase was rather early (3–6 weeks) (Adli, *et al.*, 2005). Indirect evidence from differential dose studies in non-resistant patients suggests a possible slightly greater efficacy for higher dose TCAs (200–300 mg imipramine-dose equivalent *versus* standard doses) (Adli, *et al.*, 2005), venlafaxine 225–375 mg *versus* 75mg) (Rudolph, *et al.*, 1998) and escitalopram (20 mg *versus* 10 mg) (Burke, *et al.*, 2002). In spite of the limited evidence, increasing the dose, provided side effects and safety allow, may be a reasonable step especially as there is wide inter-individual variability in plasma concentration of antidepressants and associated uncertainty about what is an effective dose for an individual patient.

There are few RCTs with limited and differing methodology investigating the efficacy of switching antidepressant (Anderson, 2003; Ruhe, *et al.*, 2006). Placebo augmentation while continuing the same antidepressant is associated with 20–40% short-term response in non-responders to that point (Ferreri, *et al.*, 2001b; Carpenter, *et al.*, 2002a). Switching to a second SSRI in open studies and SSRI arms of RCTs shows widely varying response rates (25–70%) (Ruhe, *et al.*, 2006). Switching from a reuptake inhibitor to an MAOI and from an SSRI to venlafaxine is associated with short-term response rates >50% in some studies with switches between other antidepressants showing <50% response rates (Anderson, 2003; Ruhe, *et al.*, 2006) without a clear benefit between classes. Three studies [including STAR*D (Rush, *et al.*, 2006b)] with different methodology have randomised switching from an SSRI/predominantly SSRIs) to venlafaxine or another SSRI/predominantly SSRIs) and pooling these gives a modest significant advantage to venlafaxine (54% *versus* 45% remission NNT 13) (Ruhe, *et al.*, 2006). A comparison of switching to high (mean 309 mg) *versus* standard (mean 148 mg) dose venlafaxine after SSRI failure or intolerance found a tendency to faster and greater response, but poorer tolerability, at the high dose (Thase, *et al.*, 2006). Switching to tranylcypromine in the STAR*D study as a fourth stage treatment led to only a 12% response rate (McGrath, *et al.*, 2006a).

There are limited data on safe regimes for switching antidepressants. Direct switching (without washout) from an initial SSRI to another SSRI, nortriptyline, mirtazapine, bupropion, reboxetine, venlafaxine and duloxetine appears well tolerated and may reduce discontinuation symptoms (Wohlreich, *et al.*, 2005; Ruhe, *et al.*, 2006) and direct switching from citalopram to sertraline, venlafaxine and bupropion was used in the STAR*D study without apparent problem (Rush, *et al.*, 2006b). A small randomised open study found no difference in the severity of discontinuation symptoms between a 3-day and 14-day taper when switching from SSRIs to other antidepressants with significant discontinuation symptoms on shorter acting SSRIs but not fluoxetine (Tint, *et al.*, 2008). Potentially toxic interactions need to be considered especially when the initial drug has long-lasting effects (e.g. fluoxetine to TCA, MAOIs to serotonergic drugs) and it is recommended that appropriate reference books are consulted, such as the British National Formulary (BMJ and RPS, 2007) or the Maudsley Prescribing Guidelines (Taylor, *et al.*, 2007).

Adding a second agent tends to be called 'augmentation' when the drug is not primarily an antidepressant and 'combination' when two antidepressants are used. The strongest evidence remains for lithium augmentation of monoamine reuptake inhibitors; a recent meta-analysis of 10 small studies in treatment-resistant depression found a response rate of 41% *versus* 14 % (NNT 5) (Crossley and Bauer, 2007) with most studies using lithium in the dose range 600–1200 mg. It is unclear whether lithium added to non-reuptake inhibitors is effective (e.g. Bruijn, *et al.*, 1998). Lithium augmentation as the second stage in a four-step treatment programme in inpatients resulted in a 59% response rate (Birkenhager, *et al.*, 2006b) but the results were disappointing in the STAR*D study when lithium was added as a third stage treatment with only 16% responding and a 23% rate of discontinuation due to side effects (Nierenberg, *et al.*, 2006). Patient characteristics with high co-morbidity and degree of treatment resistance together with unknown adequacy of lithium treatment (only ascertained in 57% of patients, median concentration 0.6 mmol/L) could contribute to these differences. A small study in elderly inpatients with major depression reported that lithium augmentation after failure to respond to TCAs or venlafaxine was more effective than switching to an MAOI (response 47% *versus* 7%) (Kok, *et al.*, 2007).

A meta-analysis of augmentation of TCAs with triiodothyronine (T3), 25.0–37.5 μg, in four small RCTs of treatment-resistant depression found significant benefit with regard to improvement in HDRS score (effect size 0.6) but a non-significant improvement in response rate (NNT=13) (Aronson, *et al.*, 1996). A small subsequent study found no difference between lithium, T3, the combination and placebo in 2-week study in patients predominantly on SSRIs (Joffe, *et al.*, 2006). The STAR*D study found a non-significantly higher response rate on T3 (25–50 μg) than lithium (23% *versus* 16%, NNT 14) with significantly fewer patients discontinuing due to side effects (10% *versus* 23%, lithium NNH 8) (Nierenberg, *et al.*, 2006)

The rationale behind combining antidepressants is to broaden pharmacological action in the hope that multiple actions will be of benefit. The combination of a TCA with an MAOI was used historically for treatment-resistant depression but there is a lack of controlled evidence for benefit and the potential for dangerous interactions (Lader, 1983); however a small RCT combining amitriptyline and moclobemide did find greater efficacy than amitriptyline alone (Tanghe, *et al.*, 1997). The most common antidepressant combinations reported are: (i) an SSRI with mirtazapine, reboxetine, bupropion or a TCA; (ii) mirtazapine with a TCA or venlafaxine; and (iii) mianserin with a TCA or SSRI (Rojo, *et al.*, 2005). Clinical experience and open studies indicate that tolerability and safety are usually good but there is a lack of controlled data

examining the efficacy of most combinations (Rojo, *et al.*, 2005). Three small RCTs of mianserin added to a TCA or SSRI in patients not responding to antidepressant treatment were positive (Medhus, *et al.*, 1994; Maes, *et al.*, 1999; Ferreri, *et al.*, 2001a) but the fourth and largest with sertraline was not (Licht and Qvitzau, 2002). A pooled analysis of mianserin augmentation of SSRIs shows a non-significant advantage to the combination (three studies, response 66% *versus* 57%, NNT 13) with significant heterogeneity. A small RCT of augmentation by the related drug mirtazapine of predominantly SSRI non-responders found it to be significantly more effective than placebo (Carpenter, *et al.*, 2002b). There was no benefit from combining fluoxetine and desipramine compared with increasing the dose of fluoxetine in patients not responding to fluoxetine (Fava, *et al.*, 1994; Fava, *et al.*, 2002b); a small study claimed the same combination was more effective than either drug alone in non-resistant patients (Nelson, *et al.*, 2004) but taking baseline severity differences into account no efficacy advantage is apparent. Consistent with this, addition of the noradrenaline reuptake inhibitor, atomoxetine, was no better than placebo in patients with incomplete response to sertraline in a good sized study (remission 40% *versus* 38%) (Michelson, *et al.*, 2007). The results from STAR*D have cast limited light on the relative efficacy of combinations. Bupropion augmentation of citalopram as a second stage treatment was better tolerated and marginally more effective than buspirone (32% *versus* 27% response rate and superiority on some secondary efficacy outcomes) (Trivedi, *et al.*, 2006a). Combined mirtazapine and venlafaxine as a fourth stage treatment was non-significantly better than the MAOI tranylcypromine in terms of response (24% *versus* 12%) but led to significantly greater symptom reduction and fewer side-effect related dropouts (McGrath, *et al.*, 2006a).

The efficacy of antipsychotics as augmenting agents has received increasing attention. Two studies of typical antipsychotics did not find any benefit (Anderson, 2003) but a meta-analysis of 10 RCTs (published and conference presentations) of atypical antipsychotic augmentation in patients failing to respond to an antidepressants including olanzapine (five studies), quetiapine (four studies) and risperidone (two studies), mostly added to fluoxetine or venlafaxine showed a benefit for the combination (pooled response 57% *versus* 35%, NNT 5) (Papakostas, *et al.*, 2007b) with no significant heterogeneity. Discontinuation rates due to adverse effects were threefold higher in the augmented *versus* placebo groups. A caution in interpreting these results is that most studies are not peer-reviewed and some studies were not comparisons of augmentation against continuing the original antidepressant. In two large published studies olanzapine + fluoxetine tended to be better than fluoxetine but was no better than continuing the original antidepressant, nortriptyline (Shelton, *et al.*, 2005) or venlafaxine (Corya, *et al.*, 2006). Two methodologically identical studies of olanzapine augmentation in patients historically failing to respond to at least one antidepressant and to a prospective 8-week trial of fluoxetine found one study to be positive and one negative but when pooled, combined olanzapine + fluoxetine was more effective than both fluoxetine (response 40% *versus* 30%, NNT 10) and olanzapine (response 40% *versus* 26%, NNT 7) (Thase, *et al.*, 2007a). In a *post-hoc* analysis, failure to respond to an SSRI in the current episode was associated with a significant benefit from the combination over fluoxetine but not if patients had failed an antidepressant from another class. Taken together the olanzapine studies suggest that maximum benefit from olanzapine augmentation of SSRIs may be found when treatment failure has been limited to SSRIs rather than TCAs or SNRIs. In a good sized study, patients historically not responding to 1–3 previous antidepressants received 8-weeks, open prospective treatment with an SSRI or venlafaxine. In patients with inadequate response at 8 weeks continuing on the same treatment aripiprazole was more effective than placebo augmentation (response 34% *versus* 24%, NNT 10) and had good tolerability (Berman, *et al.*, 2007). Finally a small open randomised trial found quetiapine augmentation more effective than lithium augmentation (Doree, *et al.*, 2007).

There are few data using antiepileptics as augmenting agents in unipolar depression. A small RCT of lamotrigine + fluoxetine compared with fluoxetine in patients non-responsive to at least one previous treatment found significant benefit on secondary but not primary outcome measures (response 77% *versus* 40%, NNT 3) (Barbosa, *et al.*, 2003) and a randomised open comparison with lithium found a non-significantly better response to lamotrigine (53% *versus* 41%, NNT 9) (Schindler and Anghelescu, 2007). A small RCT of phenytoin *versus* placebo augmentation of antidepressants was negative (Shapira, *et al.*, 2006); we are not aware of RCTs of valproate or other antiepileptics.

Buspirone augmentation of SSRIs was not effective in two studies (Landen, *et al.*, 1998; Appelberg, *et al.*, 2001) although a secondary analysis of more severely depressed patients did report a benefit in one study (Appelberg, *et al.*, 2001). The STAR*D trial reported poorer tolerability and possibly slightly poorer efficacy compared with bupropion augmentation (see above, Trivedi, *et al.*, 2006a). Pindolol (7.5 mg daily) augmentation of SSRIs is probably not effective in treatment-resistant depression; two small studies were positive (Maes, *et al.*, 1999; Sokolski, *et al.*, 2004) but three, including the two largest were not (Moreno, *et al.*, 1997; Perez, *et al.*, 1999; Perry, *et al.*, 2004).

Manipulation of the glucocorticoid system may be of benefit in treatment-resistant depression but somewhat confusingly both antiglucocorticoid treatment and steroid agonists may have some efficacy (DeBattista, 2006). An RCT in non-resistant patients of 3-weeks treatment with the steroid synthesis inhibitor metyrapone added to nefazodone or fluvoxamine found better response at 5 weeks compared with placebo (58% *versus* 33%, NNT 4) (Jahn, *et al.*, 2004) and a small RCT of predominantly treatment-resistant patients found an advantage over placebo to the addition of dehydroepiandrosterone (DHEA) to ongoing treatment (Wolkowitz, *et al.*, 1999).

The addition of stimulant-like drugs has sometimes been used clinically but there is little controlled evidence. A small

RCT in non-responders to a variety of antidepressants showed a non-significant advantage to methylphenidate over placebo (response 40% *versus* 23%, NNT 6) (Patkar, *et al.*, 2006) and a very small study in the elderly found that methylphenidate accelerated the response to citalopram (Lavretsky, *et al.*, 2006). Modafinil, which has an unknown mechanism of action to reduce sleepiness, was significantly better than placebo in partial responders to SSRIs with persisting sleepiness or fatigue in pooled data from two RCTs (Fava, *et al.*, 2007). Other strategies with preliminary evidence for efficacy in treatment-resistant patients are tryptophan addition, especially to MAOIs (Anderson, 2003) and oestrogen in perimenopausal women (Morgan, *et al.*, 2005).

3.3 Next-step psychological treatment

Summary

There is limited evidence that augmenting with, or switching to, CBT may be effective in antidepressant non- or partial responders (II).

There is very little direct evidence for the efficacy of next-step psychological treatment. In the STAR*D study there was no difference in overall outcome between CBT augmentation and medication augmentation or CBT and medication switch although medication augmentation worked faster (Thase, *et al.*, 2007b). In patients with significant residual symptoms addition of CBT to ongoing medication resulted in greater full remission rates at 5 months than clinical management (25% *versus* 13% NNT 8–9) but a non-significant difference in symptom ratings (Paykel, *et al.*, 1999). However, a blindly rated study comparing CBT with lithium augmentation in partial responders to antidepressants found a non-significant advantage to the lithium group at the end of 8 weeks treatment, which was significant after a further 4 weeks follow up after both treatments had stopped (Kennedy, *et al.*, 2003). As discussed in Evidence section 2.2 indirect evidence suggests that combining antidepressants and CBT may be more effective than each individually in major depression of at least moderate and greater severity.

3.4 Next-step physical treatments

Summary

ECT is an effective short-term treatment and is more effective than antidepressants (I). rTMS may be an effective short-term treatment but is less effective than ECT for psychotic depression (II). VNS may be an effective longer-term treatment for patients with fewer than eight failed treatment trials (II). Ablative neurosurgery and deep brain stimulation (DBS) may be effective treatments (III) but there is only early experimental data for DBS.

The evidence for the general efficacy of physical treatments has been reviewed in Evidence section 2.2; here we address their use in depressed patients with treatment resistance.

Data are mixed as to whether treatment resistance is associated with reduced efficacy of ECT (Prudic, *et al.*, 1996; van den Broek, *et al.*, 2004; Husain, *et al.*, 2004b; de Vreede, *et al.*, 2005) but it is clear that medication-resistant patients can derive significant benefit with 82% of patients responding when ECT was used as the fourth step in a sequenced treatment study (Birkenhager, *et al.*, 2006a). ECT has greater efficacy than antidepressants (UK ECT Review Group, 2003) but, although many of these studies will have included patients who had failed drug treatment, only four of the 18 studies in the meta-analysis specified treatment-resistant patients. Of these, two out of three trials against antidepressants did show a significant advantage for ECT but one against lithium augmentation did not (UK ECT Review Group, 2003).

Many of the studies of rTMS in major depression have involved treatment-resistant patients. In comparison with ECT, rTMS was less effective in psychotically depressed patients in one study (Grunhaus, *et al.*, 2000); in non-psychotic patients three studies found equal short-term efficacy (Grunhaus, *et al.*, 2000; Grunhaus, *et al.*, 2003; Rosa, *et al.*, 2006) and one found rTMS less effective (Eranti, *et al.*, 2007). VNS may be effective in treatment-resistant patients as discussed in Evidence section 2.2 but an open study did not find a useful clinical response if there had been more than seven previous failed treatments (Sackeim, *et al.*, 2001b).

Deep brain stimulation (DBS) is an established neurosurgical treatment method for a range of neurological presentations, including movement disorders, but as a therapy for depression it is an experimental treatment supported by a small case series (Mayberg, *et al.*, 2005) and a case report (Jimenez, *et al.*, 2005).

There are no RCTs or high-quality, published systematic reviews of ablative neurosurgery for depression. Significant clinical experience has accrued within the specialist centres and narrative reviews are available describing the estimated consolidated outcomes for a range of ablative procedures (e.g. Royal College of Psychiatrists, 2000).

Exercise, light therapy and sleep deprivation are considered in Evidence section 2.2.

3.5 Next-step 'other' treatments

Summary

Omega-3 fatty acids may be an effective adjunct when added to current treatment in depressed patients not responding to antidepressants (I). Low folate status may reduce response to antidepressants and folate supplementation may enhance the efficacy of antidepressants although relationship to folate status is not clear (II). High intensity supervised exercise may be a useful adjunct to antidepressant treatment in more severe major depression (II).

There is some evidence for the use of EPA or EPA+DHA/fish oil as adjunctive treatment in three RCTs in depression not responding to antidepressants (Nemets, *et al.*, 2002; Peet and Horrobin, 2002; Su, *et al.*, 2003). A meta-analysis found that low folate status is associated with depressive symptoms

(11 studies, odds ratio 1.42) (Gilbody, *et al.*, 2007a) and in a secondary analysis low serum folate in major depressed patients not responding to open fluoxetine was associated with a subsequent poorer response to dose increase or lithium/desipramine augmentation (Papakostas, *et al.*, 2004). A systematic review found folate more effective than placebo supplementation of antidepressants in two small studies of non-resistant major depression (NNT 5) (Taylor, *et al.*, 2003). A small study 10 days of endurance training was more effective than stretching exercises as an adjuct to antidepressants in moderately to severely depressed inpatients (Knubben, *et al.*, 2007).

4 Relapse prevention, treatment of relapse and stopping treatment

Summary

A model of a reducing chance of relapse related to time in remission modified by individual risk factors is proposed (IV).

An influential model of the course of major depression proposes a continuum between depressive symptoms and major depression with phases of treatment going through response to remission that, if stable for 4–6 months, results in recovery (Frank, *et al.*, 1991). A return of depression is said to be relapse before recovery and recurrence thereafter, and a distinction is made between continuation treatment to prevent relapse and maintenance treatment to prevent recurrence. The assumption in the model is that a single depressive episode has a discrete duration followed by full remission; however this cannot be directly measured, is likely to vary between individuals and does not help in describing the return of major depression after persisting partial remission or continuing depressive symptoms. Although the model is helpful conceptually and in treatment trial design the distinction between remission *versus* recovery and relapse *versus* recurrence is often not possible and in this guideline we use the single term 'relapse' to mean re-emergence of significant depression. We propose a continuum model based on the chance of relapse over time, which will vary by individual depending on their risk factors and will influence the benefit they are likely to receive from staying on antidepressant treatment.

4.1 Relapse prevention

Summary

Relapse rates are high in the months after remission and decline with time (I). Other important factors associated with increased risk of relapse including residual symptoms, number of previous episodes, chronicity and severity of last depressive episode, degree of treatment resistance and psychosis (II). In the elderly a greater degree of comorbid medical illness is associated with higher relapse rates (II). Antidepressants decrease the odds of relapse by about 70% and this appears largely independent of the underlying risk of relapse or type of antidepressant (I). The highest risk of relapse after antidepressant discontinuation occurs over the first 6 months (I). TCAs maintained at their acute treatment dose are more effective than lower 'maintenance doses' in prophylaxis (I). Weaker evidence suggests that minimum effective doses of SSRIs may be less effective than higher doses in preventing relapse in recurrent depression (II). Lithium may have similar efficacy in preventing relapse to antidepressants but evidence is limited (I). There are conflicting results about the relative efficacy of combining lithium with an antidepressant compared with an antidepressant alone (I) but the combination may be more effective in patients who required lithium augmentation (II) or are at high risk of relapse after responding to ECT (II). Lithium reduces the risk of suicide compared with antidepressants alone (I). After acute treatment with CBT there is continuing protection against subsequent relapse over the next 1–2 years (I). From limited evidence this may be comparable to continuation medication and better than discontinuing medication (II). Addition of CBT following initial antidepressant treatment increases the proportion of patients achieving full remission and reduces the risk of relapse over the next 1–3 years in patients with frequent relapse (I). Combining IPT with antidepressants in acute treatment reduces short-term relapse (II) and subsequent continuation IPT combined with antidepressants may reduce relapse compared with antidepressants alone (II). Continuation IPT monotherapy is less effective than antidepressants in preventing relapse after acute combination treatment (I). The efficacy of continuation ECT is as effective as drug treatment over 6 months (II) and some patients may do better on continuation ECT and antidepressants than on drug treatment alone over many years (II).

Rates of relapse following remission have been estimated as 20–24% by 2 months, 28–44% by 4 months, 27–50% by 6 months and 37–54% by 12 months from naturalistic follow-up studies (Belsher and Costello, 1988). A staggered placebo discontinuation RCT following 12–14 weeks open fluoxetine treatment showed a 49% relapse rate on placebo in the first 12 weeks and 23% in the following 12 weeks (Reimherr, *et al.*, 1998). A meta-analysis of discontinuation RCTs in patients with mainly recurrent depression found that 60% of patients on placebo relapsed in the year after randomisation and 29% relapsed in months 12–36 (Geddes, *et al.*, 2003). The risk of relapse is increased by a number of factors including number of previous episodes (Solomon, *et al.*, 2000; Kessing and Andersen, 2005), residual depressive symptoms (Paykel, *et al.*, 1995; Kanai, *et al.*, 2003; Dombrovski, *et al.*, 2007), depression severity (Ramana, *et al.*, 1995), longer episode duration (Dotoli, *et al.*, 2006; McGrath, *et al.*, 2006b), psychosis (Flint and Rifat, 1998; Kessing, 2003), degree of treatment resistance (Rush, *et al.*, 2006a), female sex (Kessing, 1998; Mueller, *et al.*, 1999; McGrath, *et al.*, 2006b), social stress/poor social adjustment (Reimherr, *et al.*, 2001; Kanai, *et al.*, 2003) and life-events (Paykel and Tanner, 1976; Ghaziuddin, *et al.*, 1990). Age and age of onset does not appear to be a consistent factor but the degree of comorbid medical illness appears associated with a considerably greater relapse rate, which may be particularly applicable in the elderly (Iosifescu, *et al.*, 2004b; Rey-

nolds, *et al.*, 2006). It has been suggested that an early 'placebo pattern' response is predictive of greater subsequent relapse (Stewart, *et al.*, 1998) but this has not been replicated (Nierenberg, *et al.*, 2004; McGrath, *et al.*, 2006b) and early response may in fact be associated with lower relapse rates (Linden, *et al.*, 1997; Dew, *et al.*, 2001; Nierenberg, *et al.*, 2004). The risk of relapse decreases as the duration of remission increases (Solomon, *et al.*, 2000; Franchini, *et al.*, 2000c).

Relapse prevention studies with antidepressants have shown a consistent benefit from continuing treatment compared with placebo, with the strongest evidence now from the newer antidepressants. Most modern antidepressants have data to at least 1 year and a meta-analysis of 31 RCTs found that antidepressants reduced the odds of relapse by 70% from 41% to 18% (NNT 4–5) over 6–36 months with no difference between the major classes of drug. Antidepressants had a slightly higher rate of dropout than placebo (18% *versus* 15%, NNT 33) (Geddes, *et al.*, 2003). This reduction in odds appeared largely independent of the underlying risk of relapse with similar values for the first 12 months and months 12–36, in spite of lower relapse rates in the latter period. The longest study to date has lasted 5 years showing sustained benefit from antidepressants but in very small numbers (Kupfer, *et al.*, 1992). Consistent with the RCT data, naturalistic studies have found that medication-adherent patients have better outcomes in terms of relapse or time to relapse than those stopping antidepressants (Dawson, *et al.*, 1998; Akerblad, *et al.*, 2006). After antidepressant discontinuation the greatest risk of relapse occurs in the first 6 months (Thase, 2006) but continues out to over 2 years (Frank, *et al.*, 1990).

Relapse still occurs, however, in patients continuing to take medication with a wide range of rates in published trials (Byrne and Rothschild, 1998); this has been termed tachyphylaxis, tolerance or 'poop-out' (Solomon, *et al.*, 2005). It is not clear if this is a true loss of effect to the drug, a loss of placebo effect, non-adherence or due to illness factors (Byrne and Rothschild, 1998; Thase, 2006). The long-term use of antidepressants may be better conceived of as modifying risk or severity of depressive relapse rather than 'curing' depression. Patients with greater adherence to medication do not necessarily have fewer relapses than those with poorer adherence but the time to relapse appears longer with fewer depressive symptoms overall (Katon, *et al.*, 2001; Akerblad, *et al.*, 2006). A retrospective study found that SSRIs were associated with slightly more relapse than TCAs or venlafaxine (14% *versus* 4%) (Posternak and Zimmerman, 2005a) but few studies have directly compared antidepressants and these are underpowered to detect a difference. No difference has been found in relapse rates where various different antidepressants were compared directly (Lonnqvist, *et al.*, 1995; Montgomery, *et al.*, 1998; Walters, *et al.*, 1999; Franchini, *et al.*, 2000a; Bump, *et al.*, 2001) except in one study in the elderly where phenelzine was better than nortriptyline or placebo (Georgotas, *et al.*, 1989). The suggestion that poop-out is specific to, or worse with, SSRIs than TCAs or dual action drugs seems premature (Thase, 2006).

A staggered placebo discontinuation RCT following remission with open fluoxetine treatment in non-selected depressed patients found significant benefit for continuing the antidepressant for 26 weeks following remission but not for longer (Reimherr, *et al.*, 1998). A naturalistic study found a significant protective effect of antidepressants up to 8 months after remission in patients with fewer than six lifetime episodes (Dawson, *et al.*, 1998) but continuing protection with highly recurrent depression. These studies are consistent with benefit from continuing antidepressants for a minimum of 6–9 months seems sensible after any episode of depression with persisting benefit in more recurrent depression (Geddes, *et al.*, 2003).

There is evidence that the concept of a lower 'maintenance dose' to remain well is mistaken with TCAs and related drugs. A 3-year study comparing relapse prevention with the TCA dose required to treat the acute episode against halving the dose found the lower dose less effective (Frank, *et al.*, 1993), maprotiline 75 mg was more effective than 37.5 mg over 1 year (Rouillon, *et al.*, 1991) and nortriptyline maintained at plasma levels of 80–120 ng/ml was more effective than 40–60 ng/ml over 3 years (Reynolds, *et al.*, 1999b). A naturalistic study also found that TCA dose reduction was associated with more relapse than maintaining the same dose (Dawson, *et al.*, 1998). The case with SSRIs, where there is a lack of evidence of dose response, is less clear; paroxetine 40 mg was more effective in preventing relapse than 20 mg over 28 months (Franchini, *et al.*, 2000a) but no difference was found between 50 mg and 100 mg of sertraline (Lepine, *et al.*, 2004). Nevertheless an open study of increased doses of SSRIs after relapse in patients with highly recurrent depression found 90% responded and subsequently 55% relapsed again over the following 2 years but with a milder severity (Franchini, *et al.*, 2000b) suggesting greater protection at higher doses. A 2-year study found that 60 mg of phenelzine was as effective as 45 mg in preventing relapse (Robinson, *et al.*, 1991).

Meta-analyses of lithium used as prophylaxis found a non-significant advantage for lithium over placebo in unipolar depression (three studies, relapse 40% *versus* 63%, NNT 4–5) (Burgess, *et al.*, 2001) and no difference compared with antidepressants (six studies, depressive relapse 42% *versus* 36%) (Cipriani, *et al.*, 2006). The benefit of combining lithium with an antidepressant over an antidepressant alone is not fully clear with earlier studies finding no benefit (e.g. Prien, *et al.*, 1984; Johnstone, *et al.*, 1990) but more recent studies in treatment-resistant patients responding to lithium augmentation (Bauer, *et al.*, 2000) or ECT (Sackeim, *et al.*, 2001a) found the combination more effective than an antidepressant alone in preventing relapse. The previously cited study by Prien, *et al.* (1984) found lithium less effective than imipramine in preventing relapse after stabilisation on the combination. A meta-analysis found that patients on lithium had a significant 85% reduction in suicide rate compared with those on antidepressants alone (eight studies 0.87% per year *versus* 1.48% per year) (Guzzetta, *et al.*, 2007) similar to that seen in bipolar disorder.

Hensley, *et al.* (2004) found that CBT performed better than maintenance TCAs pooling data from three small RCTs and after 1–2 years only 10% of patients on antidepressants remaining in remission compared with 35–50% of those who had received CBT. Gloaguen, *et al.* (1998), incorporating poorer quality studies reported an average 60% relapse rate for maintenance tricyclic antidepressants compared with 30% for CBT over 1–2 years in eight studies. However, these studies had a very high relapse rate on antidepressants compared with placebo-controlled relapse prevention studies with antidepressants (Geddes, *et al.*, 2003) raising questions about their generalisability and suggesting poor medication adherence. A recent RCT found that acute responders to CBT (with ≤3 subsequent booster sessions) were less likely to relapse over the following year compared with acute responders to medication who had their antidepressant withdrawn (31% *versus* 76%, NNT 2–3); patients compliant with continuation antidepressants had a 42% relapse rate (Hollon, *et al.*, 2005). Furthermore (mostly small) studies have investigated the effect of adding a course of CBT following initial improvement to medication and have shown efficacy in achieving full remission and in reducing relapse in those with recurrent depression, even if antidepressants are stopped (Paykel, 2007). A study of patients in remission found that augmentation with brief CBT significantly reduced relapse compared with treatment as usual alone over 2 years but only in those with more previous episodes (Bockting, *et al.*, 2005) (relapse 46% *versus* 72% in those with five or more previous episodes, NNT 4, but 63% *versus* 59% in fewer previous episodes); however the relapse rate on treatment as usual and in those with fewer episodes appears very high. Mindfulness CBT (MCBT) incorporates changing an individual's awareness of, and relationship to, unwanted thoughts and feelings. When given as an 8-week treatment during remission MCBT has also been found effective in reducing relapse in the following year compared with treatment as usual (the majority taking antidepressants) in patients with ≥3 previous episodes but not those with fewer episodes in two studies (NNTs 3–4) (Teasdale, *et al.*, 2000; Ma and Teasdale, 2004). Finally, a study of continuation CBT for 8 months following acute response to CBT in patients with recurrent depression reduced relapse over the following 16 months for those who hadn't achieved stable remission (Jarrett, *et al.*, 2001). These data provide support for continuing efficacy of CBT after acute treatment but its relative efficacy compared with maintenance antidepressants is difficult to interpret.

Combining IPT with medication in acute treatment was associated with better response rates and fewer relapses over the subsequent 3 months (3% *versus* 25%, NNT 5), with numerical but not statistical benefit sustained to 12 months (13% *versus* 29%, NNT 7) (Schramm, *et al.*, 2007). Relapse prevention studies with continuation IPT as monotherapy after acute combination treatment with an antidepressant suggests a modest (Frank, *et al.*, 1990; Reynolds, *et al.*, 1999a) or no (Reynolds, *et al.*, 2006) benefit compared with placebo. Continuation IPT monotherapy over 2 years was more effective in patients remitting with IPT alone than those who needed combined IPT and antidepressants acutely (relapse 26% *versus* 50%, NNT 4) (Frank, *et al.*, 2007). Over 3 years continuation IPT in combination with nortryptyline showed a trend to be better than nortriptyline alone after acute combination treatment (relapse 20% *versus* 43%, NNT 4–5) (Reynolds, *et al.*, 1999a). Continuation IPT given more frequently than monthly did not enhance efficacy (Frank, *et al.*, 2007).

Continuation ECT and nortriptyline + lithium were equally effective in preventing relapse over 6 months in a recent RCT (37% *versus* 32% relapse) (Kellner, *et al.*, 2006), which is better than the 65–84% relapse rate seen with patients maintained on placebo (see Evidence section 2.2). A retrospective case-note study found that the probability of patients remaining well over 5 years on continuation ECT was 73% compared with 18% of patients acutely treated with ECT and then maintained on medication (Gagne, *et al.*, 2000).

4.2 Treatment of relapse

Summary

A significant proportion of depressive relapses appear self-limiting over 3 months (II). Increasing the dose of the current antidepressant may be effective in the majority of patients (II). There is a lack of evidence for other strategies.

The treatment of patients relapsing while continuing on prophylactic treatment is a major clinical problem. One issue is whether to change treatment or persist with the current antidepressants. In a group of patients followed for up to 15 years after an index episode of depression and not on antidepressant therapy, 65% of those who relapsed did not seek treatment and had a median episode duration of 13 weeks. Overall 52% of patients (including those receiving and not receiving antidepressants) recovered in the first 3 months (Posternak, *et al.*, 2006b) suggesting that many patients have self-limiting episodes. We are not aware of any randomised data but open studies of increasing the dose of the current antidepressant (SSRIs/SNRIs) report 57–90% response rates (Fava, *et al.*, 1995; Franchini, *et al.*, 2000b; Schmidt, *et al.*, 2002; Fava, *et al.*, 2002a; Fava, *et al.*, 2006). We are not aware of any studies specifically looking at switching or combining drug treatments after relapse; a small study found that 4/5 patients responded to adding CBT (Fava, *et al.*, 2002a).

4.3 Stopping antidepressant drug treatment

Summary

Discontinuation symptoms may occur on abruptly stopping all classes of antidepressants with differences seen between classes of drugs (I–III). The incidence appears more common with higher doses (III) and longer duration up to about 9 weeks, when it appears to plateau (II). They are usually mild (I) and generally resolve rapidly with reinstatement (II). Among newer drugs paroxetine and venlafaxine appear particularly associated with discontinuation symptoms (I–II) with fluoxetine the least

(I). Symptoms begin within a few days of stopping and generally subside within a week (I) but a minority of patients may experience severe or prolonged symptoms (III). The optimum rate of taper to prevent discontinuation symptoms is unknown.

Acute discontinuation symptoms have been described with all of the main classes of antidepressants including TCAs, MAOIs, SSRIs, SNRIs and mirtazapine (see review by Haddad and Anderson, 2007). This needs to be distinguished from dependence; antidepressant use lacks key features of the dependence syndrome including tolerance, dose escalation, craving or compulsion (Haddad, 2005). In most patients discontinuation symptoms are self-limiting, of short duration but in a minority of cases they can be severe and last several weeks and there is the potential for misdiagnosis as relapse as depressive symptoms do occur (Haddad and Anderson, 2007; Tint, *et al.*, 2008). The mean time to onset of symptoms is about 2 days with resolution usually after 5–8 days. Discontinuation symptoms are variable and differ between classes of antidepressants but include sleep disturbance, gastrointestinal symptoms, affective symptoms and general somatic symptoms such as lethargy and headache. In addition drugs inhibiting serotonin reuptake are associated with sensory symptoms, such as electric shock feelings and paraesthesiae and disequilibrium symptoms. MAOIs may cause more severe symptoms including worsening depression and anxiety, confusion and psychotic symptoms. With most antidepressants, psychotic symptoms, mania and extrapyramidal symptoms have rarely been reported (Haddad and Anderson, 2007). The incidence varies between drugs, and paroxetine and venlafaxine have been associated with high rates whereas fluoxetine appears to have low rates, presumably due to its long half-life (Haddad and Anderson, 2007; Tint, *et al.*, 2008). Higher antidepressant dose and longer duration are more likely to lead to discontinuation symptoms but this appears to plateau at about 8–9 weeks (Committee on Safety of Medicines, 2004; Perahia, *et al.*, 2005).

It is presumed that tapering is an effective strategy to minimise discontinuation symptoms but there is a lack of evidence about this or the optimal rate of taper. A study randomising patients on SSRIs/venlafaxine to a 3 day or 14 day taper found a discontinuation syndrome in 46% of patients with no difference according to rate of taper (Tint, *et al.*, 2008). There have been case reports where reintroduction followed by a slower taper have been successful (Haddad and Anderson, 2007). Re-introduction of the same class of antidepressant appears to suppress symptoms rapidly (Ruhe, *et al.*, 2006) and with SSRIs (or SNRIs) an option is to switch to fluoxetine which can then be stopped abruptly due to its long half life.

The reasons for stopping antidepressants are complex and depend on stage of treatment (Demyttenaere, *et al.*, 2001). Common reasons are patient choice, including feeling better or dissatisfaction with efficacy or tolerability as well as the perceived need for continued prophylaxis. A factor that may not be considered is the consequence of relapse if antidepressants are stopped at a critical time in a person's life (e.g. examinations etc) given that the highest risk of relapse is in the 6 months after stopping (see above). We are not aware of controlled data on discontinuation of antidepressants after long-term use where there is also the issue of illness recurrence. The optimum rate to taper drug dose is unknown with opinions varying from a few weeks to 1 year (Greden, 1993).

5. Special considerations

5.1 Age

These have been reviewed as far as possible in the relevant sections, in particular Evidence sections 2 and 3 where efficacy of antidepressants and alternative treatments are discussed. There is a lack of evidence generally about next-step treatments, in children and adolescents, in the elderly, and prevention of relapse in children and adolescents. The elderly may also be particularly prone to specific adverse effects, e.g. hyponatraemia associated with SSRIs (Jacob and Spinler, 2006).

5.2 Comorbid medical illness

Summary

Increasing severity of comorbid medical illness and painful conditions is associated with poorer response to antidepressants and a greater risk of depressive relapse (II). SSRIs increase the risk of upper gastrointestinal bleeding particularly when co-administered with aspirin/non-steroidal anti-inflammatory drugs (I). TCAs may be associated with an increased risk of myocardial infarction (MI) (II). SSRIs, mirtazapine and bupropion do not increase the risk of cardiovascular events following MI (I–II).

The influence of comorbid medical illness on the outcome of depression is considered briefly in Evidence sections 2 and 4, with limited evidence suggesting a poorer response and greater relapse with increased severity of medical illness, and a poorer response with painful conditions (Bair, *et al.*, 2004). We are not aware of data indicating specific medical illness-related effects on efficacy beyond this (Peveler, *et al.*, 2002; Iosifescu, 2007) and the greatest concerns are with safety, tolerability and drug interactions.

SSRIs are now known to decrease platelet aggregability and activity, and prolong bleeding time with fluoxetine, paroxetine, and sertraline the most frequently implicated (Halperin and Reber, 2007) and non-SRI antidepressants should be favoured in patients with bleeding disorders. Two recent systematic reviews looking at the risk of SSRIs and upper gastrointestinal bleeding with or without aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) concluded that the evidence for an effect of SSRIs alone was weak, but that combination with NSAIDs greatly increased the risk compared with either drug alone, and that the combination should be avoided or ulcer-protective drugs should be used (Yuan, *et al.*, 2006; Mort, *et al.*, 2006).

An area of interest has been the use of antidepressants in people with cardiac disease because of the potentially cardiotoxic effects of TCAs and differing risk of fatality after overdose with different antidepressants as indicated by the fatal

toxicity index (see Evidence section 2.3 for discussion). TCAs have been associated with about a doubling in the risk of myocardial infarction (MI) in two cohort/case control studies (Cohen, *et al.*, 2000; Tata, *et al.*, 2005) but not in two others (Meier, *et al.*, 2001; Sauer, *et al.*, 2003). The results are conflicting for SSRIs with increased (Tata, *et al.*, 2005), decreased (Sauer, *et al.*, 2003) and unchanged (Meier, *et al.*, 2001) risk of MI found. In patients following an MI or suffering from unstable angina, three SSRI studies with sertraline (Glassman, *et al.*, 2002), fluoxetine (Strik, *et al.*, 2000) or mixed SSRIs (Taylor, *et al.*, 2005a) found no adverse effects on cardiovascular events or safety with some possible benefit in two (Glassman, *et al.*, 2002; Taylor, *et al.*, 2005a). Studies with mirtazapine (van Melle, *et al.*, 2007) and bupropion (Rigotti, *et al.*, 2006) have also found no difference in cardiac events compared with placebo when given post-MI.

It is beyond the scope of these guidelines to review specific drug interactions, which should be checked with an appropriate authority such as the British National Formulary (BMJ and RPS, 2007). As a general principle, choosing an antidepressant that is less likely to interfere with the metabolism of other drugs is advisable in patients on multiple medications (see Table 5).

5.3 Pregnancy and breast feeding

Summary

Pregnancy is not protective against onset or relapse of major depression (II), which has adverse effects for both mother and child development (II). Antidepressant use in pregnancy has been associated with an increased rate of spontaneous abortions and preterm labour (II). The balance of evidence is that there is no general increase in foetal malformations with first trimester exposure to TCAs (I) or SSRIs (I) except that paroxetine may be associated with a small increased risk of cardiovascular abnormalities (II). A small increased risk of persistant pulmonary hypertension of the newborn with SSRI-exposure after 20 weeks of pregnancy (II) needs replicating. A self-limiting neonatal behavioural syndrome with irritability, respiratory distress and poor feeding may occur after third trimester TCAs (III) and SSRIs, particularly paroxetine (II). Antidepressants vary in the amount that gets into breast milk with limited data on the effects on infant development (II/III). Serum lithium concentrations in infants are about a quarter of maternal levels although from limited evidence adverse effects have not been reported (III).

Major depression in the perinatal period often has an onset during pregnancy (Stowe, *et al.*, 2005) and in a naturalistic prospective study 68% of women on prophylactic antidepressant medication who stopped treatment relapsed compared with 26% who continued treatment (Cohen, *et al.*, 2006) suggesting that pregnancy is not protective against depressive relapse. The association between depressive symptoms in pregnancy and adverse birth outcomes (e.g. premature delivery, low birth weight) (Alder, *et al.*, 2007) may be due to confounding factors (Evans, *et al.*, 2007) and evidence related to major depression is limited. Nevertheless maternal depression is associated with impaired mother-baby interaction, lower cognitive and social function in the infant and increased behavioural and psychiatric problems in childhood (Mian, 2005) as well as the adverse consequences of depression to the mother.

Many published data examining the effects of antidepressants in pregnancy are based on case reports, case series and small controlled studies although increasingly registry studies are being used. Nevertheless a major problem is controlling for depression itself.

A meta-analysis of six cohort studies found that use of antidepressants was associated with a significantly increased rate of spontaneous abortions (12.4% *versus* 8.7%) with no apparent difference between class of drug (Hemels, *et al.*, 2005) and a recent small study found that prenatal antidepressant use was associated with lower gestational age at birth and an increased risk of preterm birth not accounted for by degree of depressive symptoms (Suri, *et al.*, 2007).

There is no evidence of an increased incidence of birth defects associated with prenatal exposure to TCAs (Simon, *et al.*, 2002a) although short-term neonatal behavioural symptoms, such as jitteriness, hyperexcitability, and feeding problems have been noted in case reports (Haddad and Anderson, 2007). An association between clomipramine and neonatal convulsions and a neonatal behavioural syndrome was found in the WHO database of adverse reactions but was not seen with other TCAs (Sanz, *et al.*, 2005).

Recent large case-control studies found no overall association between congenital malformations and first trimester SSRI exposure in four studies (Malm, *et al.*, 2005; Kallen and Otterblad, 2007; Alwan, *et al.*, 2007; Louik, *et al.*, 2007) and a slight increase in a fifth (Wogelius, *et al.*, 2006). Two studies found a link between first trimester paroxetine and cardiovascular defects (Kallen and Otterblad, 2007) or right ventricular outflow tract obstruction (Louik, *et al.*, 2007); a link with cardiovascular defects with paroxetine was also found in another database cohort study with an odds ratio of 1.82 (3.8% of live births) (GlaxoSmithKline, 2005). SSRIs in the third trimester are associated with a three times increased risk of a neonatal behavioural syndrome, including respiratory distress, irritability and feeding problems; these are usually mild and self-limiting and seem most likely with paroxetine (Sanz, *et al.*, 2005; Moses-Kolko, *et al.*, 2005). A recent case-control study reported an increased risk of persistent pulmonary hypertension of the newborn in infants exposed to an SSRI after the 20th week of gestation (Chambers, *et al.*, 2006) but the absolute risk is fairly low (about 1%) and the finding needs replicating.

Based on limited information, mirtazapine, bupropion, and venlafaxine do not appear to be major teratogens; little or no information is available on duloxetine (Way, 2007).

All antidepressants enter breast milk but the ratio between infant and maternal plasma levels varies greatly. A pooled analysis of 57 studies found that plasma levels of sertraline and nortryptyline are usually undetectable in breastfed infants,

with paroxetine levels somewhat higher, but citalopram and fluoxetine produced infant plasma levels above 10% of the maternal plasma level (22% and 17%, respectively) (Weissman, *et al.*, 2004). Doxepin has been associated with respiratory depression in case reports (Pons, *et al.*, 1994). There are few data available on long-term developmental outcomes; a small study found no effect of fluoxetine or TCAs in breastfed infants followed up to 6 years, whereas mothers' depression was associated with poorer cognitive and language achievement (Nulman, *et al.*, 2002). Lithium is excreted in high levels into breast milk and infant serum levels are about a quarter of maternal levels (Viguera, *et al.*, 2007). The usual recommendation is not to breast feed while taking lithium (Eberhard-Gran, *et al.*, 2006) although no adverse effects on infants were seen in a small cohort (Viguera, *et al.*, 2007).

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References

Aberg-Wistedt, A, Agren, H, Ekselius, L, Bengtsson, F, Akerblad, AC. (2000) Sertraline versus paroxetine in major depression: clinical outcome after six months of continuous therapy. J Clin Psychopharmacol *20*: 645–652

Adli, M, Baethge, C, Heinz, A, Langlitz, N, Bauer, M. (2005) Is dose escalation of antidepressants a rational strategy after a medium-dose treatment has failed? A systematic review. Eur Arch Psychiatry Clin Neurosci *255*: 387–400

Adli, M, Bauer, M, Rush, AJ. (2006) Algorithms and collaborative-care systems for depression: are they effective and why? A systematic review. Biol Psychiatry *59*: 1029–1038

Akerblad, AC, Bengtsson, F, von Knorring, L, Ekselius, L. (2006) Response, remission and relapse in relation to adherence in primary care treatment of depression: a 2-year outcome study. Int Clin Psychopharmacol *21*: 117–124

Akiskal, HS, Maser, JD, Zeller, PJ, Endicott, J, Coryell, W, Keller, M, Warshaw, M, Clayton, P, Goodwin, F. (1995) Switching from 'unipolar' to bipolar II. An 11-year prospective study of clinical and temperamental predictors in 559 patients. Arch Gen Psychiatry *52*: 114–123

Alder, J, Fink, N, Bitzer, J, Hosli, I, Holzgreve, W. (2007) Depression and anxiety during pregnancy: a risk factor for obstetric, fetal and neonatal outcome? A critical review of the literature. J Matern Fetal Neonatal Med *20*: 189–209

Alwan, S, Reefhuis, J, Rasmussen, SA, Olney, RS, Friedman, JM. (2007) Use of selective serotonin-reuptake inhibitors in pregnancy and the risk of birth defects. N Engl J Med *356*: 2684–2692

American Psychiatric Association. (2000a) Practice guideline for the treatment of patients with major depressive disorder (revision). Am J Psychiatry *157*(Suppl): 1–45

American Psychiatric Association. (2000b) Diagnostic and Statistical Manual of Mental Disorders (4th edn), Text Revision (DSM-IV-TR). American Psychiatric Association, Arlington, VA

Anderson, IM. (2000) Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. J Affect Disord *58*: 19–36

Anderson, IM. (2001) Meta-analytical studies on new antidepressants. Br Med Bull *57*: 161–178

Anderson, IM. (2003) Drug treatment of depression: reflections on the evidence. Adv Psychiatr Treat *9*: 11–20

Anderson, IM, Delvai, NA, Ashim, B, Ashim, S, Lewin, C, Singh, V, Sturman, D, Strickland, PL. (2007) Adjunctive fast repetitive transcranial magnetic stimulation in depression. Brit J Psychiatry *190*: 533–534

Anderson, IM, Edwards, JG. (2001) Guidelines for choice of selective serotonin reuptake inhibitor in depressive illness. Adv Psychiatr Treat *7*: 170–180

Anderson, IM, Nutt, DJ, Deakin, JFW. (2000) Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 1993 British Association for Psychopharmacology guidelines. J Psychopharmacol *14*: 3–20

Anderson, L, Lewis, G, Araya, R, Elgie, R, Harrison, G, Proudfoot, J, Schmidt, U, Sharp, D, Weightman, A, Williams, C. (2005) Self-help books for depression: how can practitioners and patients make the right choice? Brit J Gen Pract *55*: 387–392

Andrews, G, Poulton, R, Skoog, I. (2005) Lifetime risk of depression: restricted to a minority or waiting for most? Brit J Psychiatry *187*: 495–496

Anghelescu, IG, Kohnen, R, Szegedi, A, Klement, S, Kieser, M. (2006) Comparison of Hypericum extract WS 5570 and paroxetine in ongoing treatment after recovery from an episode of moderate to severe depression: results from a randomized multicenter study. Pharmacopsychiatry *39*: 213–219

Angst, J. (1985) Switch from depression to mania – a record study over decades between 1920 and 1982. Psychopathology *18*: 140–154

Angst, J, Amrein, R, Stabl, M. (1995) Moclobemide and tricyclic antidepressants in severe depression: meta-analysis and prospective studies. J Clin Psychopharmacol *15*: 16S–23S

Angst, J, Gamma, A, Benazzi, F, Ajdacic, V, Rossler, W. (2007) Melancholia and atypical depression in the Zurich study: epidemiology, clinical characteristics, course, comorbidity and personality. Acta Psychiatr Scand *115*(Suppl 433): 72–84

Angst, J, Scheidegger, P, Stabl, M. (1993) Efficacy of moclobemide in different patient groups. Results of new subscales of the Hamilton Depression Rating Scale. Clin Neuropharmacol *16*(Suppl 2): S55–S62

Angst, J, Stabl, M. (1992) Efficacy of moclobemide in different patient groups: a meta-analysis of studies. Psychopharmacol *106*(Suppl): S109–S113

Appelberg, BG, Syvalahti, EK, Koskinen, TE, Mehtonen, OP, Muhonen, TT, Naukkarinen, HH. (2001) Patients with severe depression may benefit from buspirone augmentation of selective serotonin reuptake inhibitors: results from a placebo-controlled, randomized, double-blind, placebo wash-in study. J Clin Psychiatry *62*: 448–452

Appleton, KM, Hayward, RC, Gunnell, D, Peters, TJ, Rogers, PJ, Kessler, D, Ness, AR. (2006) Effects of n-3 long-chain polyunsaturated fatty acids on depressed mood: systematic review of published trials. Am J Clin Nutr *84*: 1308–1316

Aronson, R, Offman, HJ, Joffe, RT, Naylor, CD. (1996) Triiodothyronine augmentation in the treatment of refractory depression. A meta-analysis. Arch Gen Psychiatry *53*: 842–848

Arroll, B, Khin, N, Kerse, N. (2003) Screening for depression in primary care with two verbally asked questions: cross sectional study. Brit Med J *327*: 1144–1146

Arroll, B, Macgillivray, S, Ogston, S, Reid, I, Sullivan, F, Williams, B, Crombie, I. (2005) Efficacy and tolerability of tricyclic

antidepressants and SSRIs compared with placebo for treatment of depression in primary care: a meta-analysis. Ann Fam Med *3*: 449–456

Baca, E, Garcia-Garcia, M, Porras-Chavarino, A. (2004) Gender differences in treatment response to sertraline versus imipramine in patients with nonmelancholic depressive disorders. Prog Neuropsychopharmacol Biol Psychiatry *28*: 57–65

Bair, MJ, Robinson, RL, Eckert, GJ, Stang, PE, Croghan, TW, Kroenke, K. (2004) Impact of pain on depression treatment response in primary care. Psychosom Med *66*: 17–22

Baldwin, DS, Anderson, IM, Nutt, DJ, Bandelow, B, Bond, A, Davidson, JR, den Boer, JA, Fineberg, NA, Knapp, M, Scott, J, Wittchen, HU. (2005) Evidence-based guidelines for the pharmacological treatment of anxiety disorders: recommendations from the British Association for Psychopharmacology. J Psychopharmacol *19*: 567–596

Baldwin, DS, Reines, EH, Guiton, C, Weiller, E. (2007) Escitalopram therapy for major depression and anxiety disorders. Ann Pharmacother *41*: 1583–1592

Ballenger, JC, Davidson, JR, Lecrubier, Y, Nutt, DJ, Kirmayer, LJ, Lepine, JP, Lin, KM, Tajima, O, Ono, Y. (2001) Consensus statement on transcultural issues in depression and anxiety from the International Consensus Group on Depression and Anxiety. J Clin Psychiatry *62*(Suppl 13): 47–55

Barbato, A, D'Avanzo, B. (2006) Marital therapy for depression. Cochrane Database Syst Rev. *2*: CD004188. doi: 10.1002/14651858.CD004188.pub2

Barbosa, L, Berk, M, Vorster, M. (2003) A double-blind, randomized, placebo-controlled trial of augmentation with lamotrigine or placebo in patients concomitantly treated with fluoxetine for resistant major depressive episodes. J Clin Psychiatry *64*: 403–407

Barrett, JE, Barrett, JA, Oxman, TE, Gerber, PD. (1988) The prevalence of psychiatric disorders in a primary care practice. Arch Gen Psych *45*: 1100–1106

Barrett, JE, Williams, JW, Oxman, TE, Frank, E, Katon, W, Sullivan, M, Hegel, MT, Cornell, JE, Sengupta, AS. (2001) Treatment of dysthymia and minor depression in primary care: a randomized trial in patients aged 18 to 59 years. J Fam Pract *50*: 405–412

Bateman, DN. (2003) Poisonous substances: antidepressants. Medicine *31*: 32–34

Bauer, M, Bschor, T, Kunz, D, Berghofer, A, Strohle, A, Muller-Oerlinghausen, B. (2000) Double-blind, placebo-controlled trial of the use of lithium to augment antidepressant medication in continuation treatment of unipolar major depression. Am J Psychiatry *157*: 1429–1435

Bauer, M, Bschor, T, Pfennig, A, Whybrow, PC, Angst, J, Versiani, M, Moller, HJ. (2007) World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for biological treatment of unipolar depressive disorders in primary care. World J Biol Psychiatry *8*: 67–104

Baumann, P, Ulrich, S, Eckermann, G, Gerlach, M, Kuss, HJ, Laux, G, Muller-Oerlinghausen, B, Rao, ML, Riederer, P, Zernig, G, Hiemke, C. (2005) The AGNP-TDM Expert Group Consensus Guidelines: focus on therapeutic monitoring of antidepressants. Dialogues Clin Neurosci *7*: 231–247

Beasley, CM. Dornseif, BE, Bosomworth, JC, Sayler, ME, Rampey, AH, Heiligenstein, JH, Thompson, VL, Murphy, DJ, Masica, DN (1991) Fluoxetine and suicide: a meta-analysis of controlled trials of treatment for depression. Brit Med J *303*: 685–692

Belsher, G, Costello, CG. (1988) Relapse after recovery from unipolar depression: a critical review. Psychol Bull *104*: 84–96

Benedetti, F, Colombo, C, Pontiggia, A, Bernasconi, A, Florita, M, Smeraldi, E. (2003) Morning light treatment hastens the antidepressant effect of citalopram: a placebo-controlled trial. J Clin Psychiatry *64*: 648–653

Benkelfat, C, Poirier, MF, Leouffre, P, Gay, C, Loo, H. (1987) Dexamethasone suppression test and the response to antidepressant depending on their central monoaminergic action in major depression. Can J Psychiatry *32*: 175–178

Berlanga, C, Flores-Ramos, M. (2006) Different gender response to serotonergic and noradrenergic antidepressants. A comparative study of the efficacy of citalopram and reboxetine. J Affect Disord *95*: 119–123

Berman, RM, Marcus, RN, Swanink, R, McQuade, RD, Carson, WH, Corey-Lisle, PK, Khan, A. (2007) The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychiatry *68*: 843–853

Birkenhager, TK, van den Broek, WW, Moleman, P, Bruijn, JA. (2006a) Outcome of a 4-step treatment algorithm for depressed inpatients. J Clin Psychiatry *67*: 1266–1271

Birkenhager, TK, van den Broek, WW, Moleman, P, Bruijn, JA. (2006b) Outcome of a 4-step treatment algorithm for depressed inpatients. J Clin Psychiatry *67*: 1266–1271

Bjerkenstedt, L, Edman, GV, Alken, RG, Mannel, M. (2005) Hypericum extract LI 160 and fluoxetine in mild to moderate depression: a randomized, placebo-controlled multi-center study in outpatients. Eur Arch Psychiatry Clin Neurosci *255*: 40–47

Blacker, CV, Clare, AW. (1988) The prevalence and treatment of depression in general practice. Psychopharmacol *95*(Suppl): S14–S17

Brit Med J and RPS (2007) British National Formulary. London

Bockting, CL, Schene, AH, Spinhoven, P, Koeter, MW, Wouters, LF, Huyser, J, Kamphuis, JH. (2005) Preventing relapse/recurrence in recurrent depression with cognitive therapy: a randomized controlled trial. J Consult Clin Psychol *73*: 647–657

Bollini, P, Pampallona, S, Tibaldi, G, Kupelnick, B, Munizza, C. (1999) Effectiveness of antidepressants. Meta-analysis of dose-effect relationships in randomised clinical trials. Brit J Psychiatry *174*: 297–303

Bostwick, JM, Pankratz, VS. (2000) Affective disorders and suicide risk: a reexamination. Am J Psychiatry *157*: 1925–1932

Bower, P, Gilbody, S, Richards, D, Fletcher, J, Sutton, A. (2006) Collaborative care for depression in primary care. Making sense of a complex intervention: systematic review and meta-regression. Brit J Psychiatry *189*: 484–493

Bower, P, Rowland, N, Hardy, R. (2003) The clinical effectiveness of counselling in primary care: a systematic review and meta-analysis. Psychol Med *33*: 203–215

Brenes, GA, Williamson, JD, Messier, SP, Rejeski, WJ, Pahor, M, Ip, E, Penninx, BW. (2007) Treatment of minor depression in older adults: a pilot study comparing sertraline and exercise. Aging Ment Health *11*: 61–68

Bridge, JA, Iyengar, S, Salary, CB, Barbe, RP, Birmaher, B, Pincus, HA, Ren, L, Brent, DA. (2007) Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. JAMA *297*: 1683–1696

Brown, WA. (2007) Treatment response in melancholia. Acta Psychiatr Scand *115*(Suppl 433): 125–129

Brown, WA, Johnson, MF, Chen, MG. (1992) Clinical features of depressed patients who do and do not improve with placebo. Psychiatry Res *41*: 203–214

Browne, G, Steiner, M, Roberts, J, Gafni, A, Byrne, C, Dunn, E, Bell, B, Mills, M, Chalklin, L, Wallik, D, Kraemer, J. (2002) Sertraline and/or interpersonal psychotherapy for patients with dysthymic disorder in primary care: 6-month comparison with longitudinal 2-year follow-up of effectiveness and costs. J Affect Disord *68*: 317–330

Bruijn, JA, Moleman, P, Mulder, PG, van den Broek, WW. (1998) Comparison of 2 treatment strategies for depressed inpatients: imipramine and lithium addition or mirtazapine and lithium addition. J Clin Psychiatry *59*: 657–663

Bryant, SG, Fisher, S, Kluge, RM. (1987) Long-term versus short-term amitriptyline side effects as measured by a postmarketing surveillance system. J Clin Psychopharmacol *7*: 78–82

Buckley, NA, McManus, PR. (2002) Fatal toxicity of serotoninergic and other antidepressant drugs: analysis of United Kingdom mortality data. Brit Med J *325*: 1332–1333

Bump, GM, Mulsant, BH, Pollock, BG, Mazumdar, S, Begley, AE, Dew, MA, Reynolds, CF. (2001) Paroxetine versus nortriptyline in the continuation and maintenance treatment of depression in the elderly. Depress Anxiety *13*: 38–44

Burgess, S, Geddes, J, Hawton, K, Townsend, E, Jamison, K, Goodwin, G. (2001) Lithium for maintenance treatment of mood disorders. Cochrane Database Syst Rev. *2*: CD003013. doi: 10.1002/14651858.CD003013

Burke, WJ, Gergel, I, Bose, A. (2002) Fixed-dose trial of the single isomer SSRI escitalopram in depressed outpatients. J Clin Psychiatry *63*: 331–336

Burns, D. (1999) Feeling good – the new mood therapy. Avon Books, New York

Byrne, SE, Rothschild, AJ. (1998) Loss of antidepressant efficacy during maintenance therapy: possible mechanisms and treatments. J Clin Psychiatry *59*: 279–288

Carpenter, LL, Yasmin, S, Price, LH. (2002a) A double-blind, placebo-controlled study of antidepressant augmentation with mirtazapine. Biol Psychiatry *51*: 183–188

Carpenter, LL, Yasmin, S, Price, LH. (2002b) A double-blind, placebo-controlled study of antidepressant augmentation with mirtazapine. Biol Psychiatry *51*: 183–188

Casacalenda, N, Perry, JC, Looper, K. (2002) Remission in major depressive disorder: a comparison of pharmacotherapy, psychotherapy, and control conditions. Am J Psychiatry *159*: 1354–1360

Chambers, CD, Hernandez-Diaz, S, Van Marter, LJ, Werler, MM, Louik, C, Jones, KL, Mitchell, AA. (2006) Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. N Engl J Med *354*: 579–587

Cheeta, S, Schifano, F, Oyefeso, A, Webb, L, Ghodse, AH. (2004) Antidepressant-related deaths and antidepressant prescriptions in England and Wales, 1998–2000. Brit J Psychiatry *184*: 41–47

Chilvers, C, Dewey, M, Fielding, K, Gretton, V, Miller, P, Palmer, B, Weller, D, Churchill, R, Williams, I, Bedi, N, Duggan, C, Lee, A, Harrison, G. (2001) Antidepressant drugs and generic counselling for treatment of major depression in primary care: randomised trial with patient preference arms. Brit Med J *322*: 772–775

Cipriani, A, Smith, K, Burgess, S, Carney, S, Goodwin, G, Geddes, J. (2006) Lithium versus antidepressants in the long-term treatment of unipolar affective disorder. Cochrane Database Syst Rev *4*: CD003492. doi: 10.1002/14651858.CD003492.pub2

Clarke, G, Debar, L, Lynch, F, Powell, J, Gale, J, O'Connor, E, Ludman, E, Bush, T, Lin, EH, Von Korff, M, Hertert, S. (2005) A randomized effectiveness trial of brief cognitive-behavioral therapy for depressed adolescents receiving antidepressant medication. J Am Acad Child Adolesc Psychiatry *44*: 888–898

Clayton, AH, Zajecka, J, Ferguson, JM, Filipiak-Reisner, JK, Brown, MT, Schwartz, GE. (2003) Lack of sexual dysfunction with the selective noradrenaline reuptake inhibitor reboxetine during treatment for major depressive disorder. Int Clin Psychopharmacol *18*: 151–156

Cohen, HW, Gibson, G, Alderman, MH. (2000) Excess risk of myocardial infarction in patients treated with antidepressant medications: association with use of tricyclic agents. Am J Med *108*: 2–8

Cohen, J. (1988) Statistical power analysis for the behavioral sciences, 2nd edn. Lawrence Earlbaum Associates, Hillsdale, NJ

Cohen, LS, Altshuler, LL, Harlow, BL, Nonacs, R, Newport, DJ, Viguera, AC, Suri, R, Burt, VK, Hendrick, V, Reminick, AM, Loughead, A, Vitonis, AF, Stowe, ZN. (2006) Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. JAMA *295*: 499–507

Cole, MG, Bellavance, F, Mansour, A. (1999) Prognosis of depression in elderly community and primary care populations: a systematic review and meta-analysis. Am J Psychiatry *156*: 1182–1189

Committee on Safety of Medicines. (2004) Report of the CSM Expert Working Group on the safety of selective serotonin reuptake inhibitor antidepressants. http://www.mhra.gov.uk/home/groups/pl–p/documents/drugsafetymessage/con019472.pdf.

Corya, SA, Williamson, D, Sanger, TM, Briggs, SD, Case, M, Tollefson, G. (2006) A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, fluoxetine, and venlafaxine in treatment-resistant depression. Depress Anxiety *23*: 364–372

Cramer, JA, Rosenheck, R. (1998) Compliance with medication regimens for mental and physical disorders. Psychiatr Serv *49*: 196–201

Crossley, NA, Bauer, M. (2007) Acceleration and augmentation of antidepressants with lithium for depressive disorders: two meta-analyses of randomized, placebo-controlled trials. J Clin Psychiatry *68*: 935–940

Cuijpers, P, Smit, F, van Straten, A. (2007a) Psychological treatments of subthreshold depression: a meta-analytic review. Acta Psychiatr Scand *115*: 434–441

Cuijpers, P, van Straten, A, Warmerdam, L. (2007b) Behavioral activation treatments of depression: a meta-analysis. Clin Psychol Rev *27*: 318–326

Cuijpers, P, van Straten, A, Warmerdam, L. (2007c) Problem solving therapies for depression: a meta-analysis. Eur Psychiatry *22*: 9–15

Dannon, PN, Dolberg, OT, Schreiber, S, Grunhaus, L. (2002) Three and six-month outcome following courses of either ECT or rTMS in a population of severely depressed individuals-preliminary report. Biol Psychiatry *51*: 687–690

Davidson, JRT, Meltzer-Brody, SE. (1999) The underrecognition and undertreatment or depression: what is the breadth and depth of the problem? J Clin Psychiatry *60*(Suppl 7): 4–9

Dawson, MY, Michalak, EE, Waraich, P, Anderson, JE, Lam, RW. (2004) Is remission of depressive symptoms in primary care a realistic goal? A meta-analysis. BMC Fam Pract *5*:19

Dawson, R, Lavori, PW, Coryell, WH, Endicott, J, Keller, MB. (1998) Maintenance strategies for unipolar depression: an observational study of levels of treatment and recurrence. J Affect Disord *49*: 31–44

de Mello, MF, de Jesus, MJ, Bacaltchuk, J, Verdeli, H, Neugebauer, R. (2005) A systematic review of research findings on the efficacy of interpersonal therapy for depressive disorders. Eur Arch Psychiatry Clin Neurosci *255*: 75–82

de Vreede, IM, Burger, H, van Vliet, IM. (2005) Prediction of response to ECT with routinely collected data in major depression. J Affect Disord *86*: 323–327

DeBattista, C. (2005) Executive dysfunction in major depressive disorder. Expert Rev Neurother *5*: 79–83

DeBattista, C. (2006) Augmentation and combination strategies for depression. J Psychopharmacol *20* (Suppl 3): 11–18

DeBattista, C, Belanoff, J, Glass, S, Khan, A, Horne, RL, Blasey, C, Carpenter, LL, Alva, G. (2006) Mifepristone versus placebo in the treatment of psychosis in patients with psychotic major depression. Biol Psychiatry *60*: 1343–1349

DeBattista, C, Solvason, B, Poirier, J, Kendrick, E, Loraas, E. (2005) A placebo-controlled, randomized, double-blind study of adjunctive bupropion sustained release in the treatment of SSRI-induced sexual dysfunction. J Clin Psychiatry *66*: 844–848

Debonnel, G, Saint-Andre, E, Hebert, C, de Montigny, C, Lavoie, N, Blier, P. (2007) Differential physiological effects of a low dose and high doses of venlafaxine in major depression. Int J Neuropsychopharmacol *10*: 51–61

Delgado, PL. (2004) Common pathways of depression and pain. J Clin Psychiatry *65*(Suppl 12): 16–19

Delgado, PL, Brannan, SK, Mallinckrodt, CH, Tran, PV, McNamara, RK, Wang, F, Watkin, JG, Detke, MJ. (2005) Sexual functioning assessed in 4 double-blind placebo- and paroxetine-controlled trials of duloxetine for major depressive disorder. J Clin Psychiatry *66*: 686–692

Demyttenaere, K, Albert, A, Mesters, P, Dewe, W, De Bruyckere, K, Sangeleer, M. (2005) What happens with adverse events during 6 months of treatment with selective serotonin reuptake inhibitors? J Clin Psychiatry *66*: 859–863

Demyttenaere, K, Enzlin, P, Dewe, W, Boulanger, B, De Bie, J, De Troyer, W, Mesters, P. (2001) Compliance with antidepressants in a primary care setting, 1: Beyond lack of efficacy and adverse events. J Clin Psychiatry *62*(Suppl 22): 30–33

Demyttenaere, K, Haddad, P. (2000) Compliance with antidepressant therapy and antidepressant discontinuation symptoms. Acta Psychiatr Scand *101*(Suppl 403): 50–56

Derubeis, RJ, Gelfand, LA, Tang, TZ, Simons, AD. (1999) Medications versus cognitive behavior therapy for severely depressed outpatients: mega-analysis of four randomized comparisons. Am J Psychiatry *156*: 1007–1013

Derubeis, RJ, Hollon, SD, Amsterdam, JD, Shelton, RC, Young, PR, Salomon, RM, O'Reardon, JP, Lovett, ML, Gladis, MM, Brown, LL, Gallop, R. (2005) Cognitive therapy vs medications in the treatment of moderate to severe depression. Arch Gen Psychiatry *62*: 409–416

Detke, MJ, Wiltse, CG, Mallinckrodt, CH, McNamara, RK, Demitrack, MA, Bitter, I. (2004) Duloxetine in the acute and long-term treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. Eur Neuropsychopharmacol *14*: 457–470

Dew, MA, Reynolds, CF, Mulsant, B, Frank, E, Houck, PR, Mazumdar, S, Begley, A, Kupfer, DJ. (2001) Initial recovery patterns may predict which maintenance therapies for depression will keep older adults well. J Affect Disord *65*: 155–166

Dimidjian, S, Hollon, SD, Dobson, KS, Schmaling, KB, Kohlenberg, RJ, Addis, ME, Gallop, R, McGlinchey, JB, Markley, DK, Gollan, JK, Atkins, DC, Dunner, DL, Jacobson, NS. (2006) Randomized trial of behavioral activation, cognitive therapy, and antidepressant medication in the acute treatment of adults with major depression. J Consult Clin Psychol *74*: 658–670

Dombrovski, AY, Mulsant, BH, Houck, PR, Mazumdar, S, Lenze, EJ, Andreescu, C, Cyranowski, JM, Reynolds, CF. (2007) Residual symptoms and recurrence during maintenance treatment of late-life depression. J Affect Disord *103*: 77–82

Doree, JP, Des, RJ, Lew, V, Gendron, A, Elie, R, Stip, E, Tourjman, SV. (2007) Quetiapine augmentation of treatment-resistant depression: a comparison with lithium. Curr Med Res Opin *23*: 333–341

Dotoli, D, Spagnolo, C, Bongiorno, F, Zanardi, R, Serretti, A, Smeraldi, E, Franchini, L. (2006) Relapse during a 6-month continuation treatment with fluvoxamine in an Italian population: the role of clinical, psychosocial and genetic variables. Prog Neuropsychopharmacol Biol Psychiatry *30*: 442–448

Dowrick, C, Buchan, I. (1995) Twelve month outcome of depression in general practice: does detection or disclosure make a difference? Brit Med J *311*: 1274–1276

Dubini, A, Bosc, M, Polin, V. (1997) Noradrenaline-selective versus serotonin-selective antidepressant therapy: differential effects on social functioning. J Psychopharmacol *11*: S17–S23

Dunn, AL, Trivedi, MH, Kampert, JB, Clark, CG, Chambliss, HO. (2005) Exercise treatment for depression: efficacy and dose response. Am J Prev Med *28*: 1–8

Dunn, RL, Donoghue, JM, Ozminkowski, RJ, Stephenson, D, Hylan, TR. (1999) Longitudinal patterns of antidepressant prescribing in primary care in the UK: comparison with treatment guidelines. J Psychopharmacol *13*: 136–143

Dunner, DL, Rush, AJ, Russell, JM, Burke, M, Woodard, S, Wingard, P, Allen, J. (2006) Prospective, long-term, multicenter study of the naturalistic outcomes of patients with treatment-resistant depression. J Clin Psychiatry *67*: 688–695

Eberhard-Gran, M, Eskild, A, Opjordsmoen, S. (2006) Use of psychotropic medications in treating mood disorders during lactation : practical recommendations. CNS Drugs *20*: 187–198

Eichelbaum, M, Ingelman-Sundberg, M, Evans, WE. (2006) Pharmacogenomics and individualized drug therapy. Annu Rev Med *57*: 119–137

Ekers, D, Richards, D, Gilbody, S. (2008) A meta-analysis of randomized trials of behavioural treatment of depression. Psychol Med *38*: 611–623.

Elkin, I, Shea, MT, Watkins, JT, Imber, SD, Sotsky, SM, Collins, JF, Glass, DR, Pilkonis, PA, Leber, WR, Docherty, JP. (1989) National Institute of Mental Health Treatment of Depression Collaborative Research Program. General effectiveness of treatments. Arch Gen Psychiatry *46*: 971–982

Epperson, CN, Terman, M, Terman, JS, Hanusa, BH, Oren, DA, Peindl, KS, Wisner, KL. (2004) Randomized clinical trial of bright light therapy for antepartum depression: preliminary findings. J Clin Psychiatry *65*: 421–425

Eranti, S, Mogg, A, Pluck, G, Landau, S, Purvis, R, Brown, RG, Howard, R, Knapp, M, Philpot, M, Rabe-Hesketh, S, Romeo, R, Rothwell, J, Edwards, D, McLoughlin, DM. (2007) A randomized, controlled trial with 6-month follow-up of repetitive transcranial magnetic stimulation and electroconvulsive therapy for severe depression. Am J Psychiatry *164*: 73–81

Evans, J, Heron, J, Patel, RR, Wiles, N. (2007) Depressive symptoms during pregnancy and low birth weight at term: longitudinal study. Brit J Psychiatry *191*: 84–85

Ezquiaga, E, Garcia, A, Bravo, F, Pallares, T. (1998) Factors associated with outcome in major depression: A 6-month prospective study. Soc Psychiatry Psychiatr Epidemiol *33*: 552–557

Fava, GA, Ruini, C, Rafanelli, C, Grandi, S. (2002a) Cognitive behavior approach to loss of clinical effect during long-term antidepressant treatment: a pilot study. Am J Psychiatry *159*: 2094–2095

Fava, M, Alpert, J, Nierenberg, A, Lagomasino, I, Sonawalla, S, Tedlow, J, Worthington, J, Baer, L, Rosenbaum, JF. (2002b) Double-blind study of high-dose fluoxetine versus lithium or desipramine augmentation of fluoxetine in partial responders and non-responders to fluoxetine. J Clin Psychopharmacol *22*: 379–387

Fava, M, Alpert, J, Nierenberg, AA, Mischoulon, D, Otto, MW, Zajecka, J, Murck, H, Rosenbaum, JF. (2005) A Double-blind, randomized trial of St John's wort, fluoxetine, and placebo in major depressive disorder. J Clin Psychopharmacol *25*: 441–447

Fava, M, Detke, MJ, Balestrieri, M, Wang, F, Raskin, J, Perahia, D. (2006) Management of depression relapse: re-initiation of duloxetine treatment or dose increase. J Psychiatr Res *40*: 328–336

Fava, M, Rappe, SM, Pava, JA, Nierenberg, AA, Alpert, JE, Rosenbaum, JF. (1995) Relapse in patients on long-term fluoxetine treatment: response to increased fluoxetine dose. J Clin Psychiatry *56*: 52–55

Fava, M, Rosenbaum, JF, McGrath, PJ, Stewart, JW, Amsterdam, JD, Quitkin, FM. (1994) Lithium and tricyclic augmentation of fluoxetine treatment for resistant major depression: a double-blind, controlled study. Am J Psychiatry *151*: 1372–1374

Fava, M, Thase, ME, DeBattista, C, Doghramji, K, Arora, S, Hughes, RJ. (2007) Modafinil augmentation of selective serotonin reuptake inhibitor therapy in MDD partial responders with persistent fatigue and sleepiness. Ann Clin Psychiatry *19*: 153–159

Fava, M, Uebelacker, LA, Alpert, JE, Nierenberg, AA, Pava, JA, Rosenbaum, JF. (1997) Major depressive subtypes and treatment response. Biol Psychiatry *42*: 568–576

Fergusson, D, Doucette, S, Glass, KC, Shapiro, S, Healy, D, Hebert, P, Hutton, B. (2005) Association between suicide attempts and selective serotonin reuptake inhibitors: systematic review of randomised controlled trials. Brit Med J *330*: 396–402

Ferreri, M, Lavergne, F, Berlin, I, Payan, C, Puech, AJ. (2001b) Benefits from mianserin augmentation of fluoxetine in patients with major depression non-responders to fluoxetine alone. Acta Psychiatr Scand *103*: 66–72

Ferreri, M, Lavergne, F, Berlin, I, Payan, C, Puech, AJ. (2001a) Benefits from mianserin augmentation of fluoxetine in patients with major depression non-responders to fluoxetine alone. Acta Psychiatr Scand *103*: 66–72

Flint, AJ, Rifat, SL. (1998) Two-year outcome of psychotic depression in late life. Am J Psychiatry *155*: 178–183

Flores, BH, Kenna, H, Keller, J, Solvason, HB, Schatzberg, AF. (2006) Clinical and biological effects of mifepristone treatment for psychotic depression. Neuropsychopharmacol *31*: 628–636

Franchini, L, Gasperini, M, Zanardi, R, Smeraldi, E. (2000a) Four-year follow-up study of sertraline and fluvoxamine in long-term treatment of unipolar subjects with high recurrence rate. J Affect Disord *58*: 233–236

Franchini, L, Rossini, D, Bongiorno, F, Spagnolo, C, Smeraldi, E, Zanardi, R. (2000c) Will a second prophylactic treatment with a higher dosage of the same antidepressant either prevent or delay new depressive episodes? Psychiatry Res *96*: 81–85

Franchini, L, Rossini, D, Bongiorno, F, Spagnolo, C, Smeraldi, E, Zanardi, R. (2000b) Will a second prophylactic treatment with a higher dosage of the same antidepressant either prevent or delay new depressive episodes? Psychiatry Res *96*: 81–85

Franchini, L, Serretti, A, Gasperini, M, Smeraldi, E. (1998) Familial concordance of fluvoxamine response as a tool for differentiating mood disorder pedigrees. J Psychiatr Res *32*: 255–259

Frank, E, Kupfer, DJ, Buysse, DJ, Swartz, HA, Pilkonis, PA, Houck, PR, Rucci, P, Novick, DM, Grochocinski, VJ, Stapf, DM. (2007) Randomized trial of weekly, twice-monthly, and monthly interpersonal psychotherapy as maintenance treatment for women with recurrent depression. Am J Psychiatry *164*: 761–767

Frank, E, Kupfer, DJ, Perel, JM, Cornes, C, Jarrett, DB, Mallinger, AG, Thase, ME, McEachran, AB, Grochocinski, VJ. (1990) Three-year outcomes for maintenance therapies in recurrent depression. Arch Gen Psychiatry *47*: 1093–1099

Frank, E, Kupfer, DJ, Perel, JM, Cornes, C, Mallinger, AG, Thase, ME, McEachran, AB, Grochocinski, VJ. (1993) Comparison of full-dose versus half-dose pharmacotherapy in the maintenance treatment of recurrent depression. J Affect Disord *27*: 139–145

Frank, E, Prien, RF, Jarrett, RB, Keller, MB, Kupfer, DJ, Lavori, PW, Rush, AJ, Weissman, MM. (1991) Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Remission, recovery, relapse, and recurrence. Arch Gen Psychiatry *48*: 851–855

Frazer, CJ, Christensen, H, Griffiths, KM. (2005) Effectiveness of treatments for depression in older people. Med J Aust *182*: 627–632

Freeling, P, Rao, BM, Paykel, ES, Sireling, LI, Burton, RH. (1985) Unrecognised depression in general practice. Brit Med J *290*: 1880–1883

Freeman, MP, Hibbeln, JR, Wisner, KL, Davis, JM, Mischoulon, D, Peet, M, Keck, PE, Marangell, LB, Richardson, AJ, Lake, J, Stoll, AL. (2006) Omega-3 fatty acids: evidence basis for treatment and future research in psychiatry. J Clin Psychiatry *67*: 1954–1967

Freemantle, N, Anderson, IM, Young, P. (2000) Predictive value of pharmacological activity for the relative efficacy of antidepressant drugs. Meta-regression analysis. Brit J Psychiatry *177*: 292–302

Furukawa, TA, McGuire, H, Barbui, C. (2002) Meta-analysis of effects and side effects of low dosage tricyclic antidepressants in depression: systematic review. Brit Med J *325*: 991–1000

Furukawa, TA, Streiner, DL, Young, LT. (2001) Is antidepressant-benzodiazepine combination therapy clinically more useful? A meta-analytic study. J Affect Disord *65*: 173–177

Gagne, GG, Furman, MJ, Carpenter, LL, Price, LH. (2000) Efficacy of continuation ECT and antidepressant drugs compared to long-term antidepressants alone in depressed patients. Am J Psychiatry *157*: 1960–1965

Gartlehner, G, Hansen, RA, Carey, TS, Lohr, KN, Gaynes, BN, Randolph, LC. (2005) Discontinuation rates for selective serotonin reuptake inhibitors and other second-generation antidepressants in outpatients with major depressive disorder: a systematic review and meta-analysis. Int Clin Psychopharmacol *20*: 59–69

Gastpar, M, Singer, A, Zeller, K. (2006) Comparative efficacy and safety of a once-daily dosage of hypericum extract STW3-VI and citalopram in patients with moderate depression: a double-blind, randomised, multicentre, placebo-controlled study. Pharmacopsychiatry *39*: 66–75

Geddes, JR, Carney, SM, Davies, C, Furukawa, TA, Kupfer, DJ, Frank, E, Goodwin, GM. (2003) Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. Lancet *361*: 653–661

Gensichen, J, Beyer, M, Muth, C, Gerlach, FM, Von Korff, M, Ormel, J. (2006) Case management to improve major depression in primary health care: a systematic review. Psychol Med *36*: 7–14

George, MS, Rush, AJ, Marangell, LB, Sackeim, HA, Brannan, SK, Davis, SM, Howland, R, Kling, MA, Moreno, F, Rittberg, B, Dunner, D, Schwartz, T, Carpenter, L, Burke, M, Ninan, P, Goodnick, P. (2005) A one-year comparison of vagus nerve stimulation with treatment as usual for treatment-resistant depression. Biol Psychiatry *58*: 364–373

Georgotas, A, McCue, RE, Cooper, TB. (1989) A placebo-controlled comparison of nortriptyline and phenelzine in maintenance therapy of elderly depressed patients. Arch Gen Psychiatry *46*: 783–786

Ghaziuddin, M, Ghaziuddin, N, Stein, GS. (1990) Life events and the recurrence of depression. Can J Psychiatry *35*: 239–242

Gibbons, RD, Brown, CH, Hur, K, Marcus, SM, Bhaumik, DK, Erkens, JA, Herings, RM, Mann, JJ. (2007) Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents. Am J Psychiatry *164*: 1356–1363

Gibbons, RD, Hur, K, Bhaumik, DK, Mann, JJ. (2005) The relationship between antidepressant medication use and rate of suicide. Arch Gen Psychiatry *62*: 165–172

Gibbons, RD, Hur, K, Bhaumik, DK, Mann, JJ. (2006) The relationship between antidepressant prescription rates and rate of early adolescent suicide. Am J Psychiatry *163*: 1898–1904

Giedke, H, Schwarzler, F. (2002) Therapeutic use of sleep deprivation in depression. Sleep Med Rev *6*: 361–377

Gilbody, S, Bower, P, Fletcher, J, Richards, D, Sutton, AJ. (2006a) Collaborative care for depression: a cumulative meta-analysis and review of longer-term outcomes. Arch Intern Med *166*: 2314–2321

Gilbody, S, Bower, P, Whitty, P. (2006b) Costs and consequences of enhanced primary care for depression: systematic review of randomised economic evaluations. Brit J Psychiatry *189*: 297–308

Gilbody, S, House, AO, Sheldon, TA. (2005) Screening and case finding instruments for depression. Cochrane Database Syst Rev *4*: CD002792. doi: 10.1002/14651858.CD002792.pub2

Gilbody, S, Lightfoot, T, Sheldon, T. (2007a) Is low folate a risk factor for depression? A meta-analysis and exploration of heterogeneity. J Epidemiol Community Health *61*: 631–637

Gilbody, S, Richards, D, Brealey, S, Hewitt, C. (2007b) Screening for depression in medical settings with the Patient Health Questionnaire (PHQ): a diagnostic meta-analysis. J Gen Intern Med *22*: 1596–1602

Gill, D, Hatcher, S. (1999) A systematic review of the treatment of depression with antidepressant drugs in patients who also have a physical illness. J Psychosom Res *47*: 131–143

Glassman, AH, O'Connor, CM, Califf, RM, Swedberg, K, Schwartz, P, Bigger, JT, Krishnan, KR, van Zyl, LT, Swenson, JR, Finkel, MS, Landau, C, Shapiro, PA, Pepine, CJ, Mardekian, J, Harrison, WM, Barton, D, Mclvor, M. (2002) Sertraline treatment of major depression in patients with acute MI or unstable angina. JAMA *288*: 701–709

GlaxoSmithKline. (2005) Updated Preliminary Report on Bupropion and Other Antidepressants, including Paroxetine, in Pregnancy and the Occurrence of Cardiovascular and Major Congenital Malformation (EPIP083). http://ctr.gsk.co.uk/Summary/paroxetine/epip083part2.pdf

Gloaguen, V, Cottraux, J, Cucherat, M, Blackburn, IM. (1998) A meta-analysis of the effects of cognitive therapy in depressed patients. J Affect Disord *49*: 59–72

Goldberg, D, Bridges, K, Grayson, D. (1988) Detecting anxiety and depression in general medical settings. Brit Med J *297*: 897–899

Goldberg, D, Privett, M, Ustun, B, Simon, G, Linden, M. (1998) The effects of detection and treatment on the outcome of major depression in primary care: a naturalistic study in 15 cities. Brit J Gen Pract *48*: 1840–1844

Golden, RN, Gaynes, BN, Ekstrom, RD, Hamer, RM, Jacobsen, FM, Suppes, T, Wisner, KL, Nemeroff, CB. (2005) The efficacy of light therapy in the treatment of mood disorders: a review and meta-analysis of the evidence. Am J Psychiatry *162*: 656–662

Goldstein, DJ, Lu, Y, Detke, MJ, Wiltse, C, Mallinckrodt, C, Demitrack, MA. (2004) Duloxetine in the treatment of depression: a double-blind placebo-controlled comparison with paroxetine. J Clin Psychopharmacol *24*: 389–399

Goodwin, GM. (2003) Evidence-based guidelines for treating bipolar disorder: recommendations from the British Association for Psychopharmacology. J Psychopharmacol *17*: 149–173

Goodyer, I, Dubicka, B, Wilkinson, P, Kelvin, R, Roberts, C, Byford, S, Breen, S, Ford, C, Barrett, B, Leech, A, Rothwell, J, White, L, Harrington, R. (2007) Selective serotonin reuptake inhibitors (SSRIs) and routine specialist care with and without cognitive behaviour therapy in adolescents with major depression: randomised controlled trial. Brit Med J *335*: 142–150

Greden, JF. (1993) Antidepressant maintenance medications: when to discontinue and how to stop. J Clin Psychiatry *54*(Suppl): 39–45

Gregorian, RS, Golden, KA, Bahce, A, Goodman, C, Kwong, WJ, Khan, ZM. (2002) Antidepressant-induced sexual dysfunction. Ann Pharmacother *36*: 1577–1589

Greist, J, McNamara, RK, Mallinckrodt, CH, Rayamajhi, JN, Raskin, J. (2004) Incidence and duration of antidepressant-induced nausea: duloxetine compared with paroxetine and fluoxetine. Clin Ther *26*: 1446–1455

Grunhaus, L, Dannon, PN, Schreiber, S, Dolberg, OH, Amiaz, R, Ziv, R, Lefkifker, E. (2000) Repetitive transcranial magnetic stimulation is as effective as electroconvulsive therapy in the treatment of nondelusional major depressive disorder: an open study. Biol Psychiatry *47*: 314–324

Grunhaus, L, Schreiber, S, Dolberg, OT, Polak, D, Dannon, PN. (2003) A randomized controlled comparison of electroconvulsive therapy and repetitive transcranial magnetic stimulation in severe and resistant nonpsychotic major depression. Biol Psychiatry *53*: 324–331

Guaiana, G, Barbui, C, Hotopf, M. (2003) Amitriptyline versus other types of pharmacotherapy for depression. Cochrane Database Syst Rev *2*: CD004186. doi: 10.1002/14651858.CD004186.pub2

Gunn, J, Diggens, J, Hegarty, K, Blashki, G. (2006) A systematic review of complex system interventions designed to increase recovery from depression in primary care. BMC Health Serv Res *6*: 88–xx

Gunnell, D, Saperia, J, Ashby, D. (2005) Selective serotonin reuptake inhibitors (SSRIs) and suicide in adults: meta-analysis of drug company data from placebo controlled, randomised controlled trials submitted to the MHRA's safety review. Brit Med J *330*: 385

Guzzetta, F, Tondo, L, Centorrino, F, Baldessarini, RJ. (2007) Lithium treatment reduces suicide risk in recurrent major depressive disorder. J Clin Psychiatry *68*: 380–383

Haby, MM, Donnelly, M, Corry, J, Vos, T. (2006) Cognitive behavioural therapy for depression, panic disorder and generalized anxiety disorder: a meta-regression of factors that may predict outcome. Aust N Z J Psychiatry *40*: 9–19

Haby, MM, Tonge, B, Littlefield, L, Carter, R, Vos, T. (2004) Cost-effectiveness of cognitive behavioural therapy and selective serotonin reuptake inhibitors for major depression in children and adolescents. Aust N Z J Psychiatry *38*: 579–591

Haddad, PM. (2005) Do antidepressants cause dependence? Epidemiol Psichiatr Soc *14*: 58–62

Haddad, PM, Anderson, IM. (2007) Recognising and managing antidepressant discontinuation symptoms. Adv Psychiatr Treat *13*: 447–457

Hall, WD, Lucke, J. (2006) How have the selective serotonin reuptake inhibitor antidepressants affected suicide mortality? Aust N Z J Psychiatry *40*: 941–950

Halperin, D, Reber, G. (2007) Influence of antidepressants on hemostasis. Dialogues Clin Neurosci *9*: 47–59

Hammerlein, A, Derendorf, H, Lowenthal, DT. (1998) Pharmacokinetic and pharmacodynamic changes in the elderly. Clinical implications. Clin Pharmacokinet *35*: 49–64

Hannaford, PC, Thompson, C, Simpson, M. (1996) Evaluation of an educational programme to improve the recognition of psychological illness by general practitioners. Brit J Gen Pract *46*: 333–337

Haynes, RB, Devereaux, PJ, Guyatt, GH. (2002) Physicians' and patients' choices in evidence based practice. Brit Med J *324*: 1350

Hazell, P, O'Connell, D, Heathcote, D, Henry, D. (2002) Tricyclic drugs for depression in children and adolescents. Cochrane Database Syst Rev *3*: CD002317. doi: 10.1002/14651858.CD002317

Healy, D, McMonagle, T. (1997) The enhancement of social functioning as a therapeutic principle in the management of depression. J Psychopharmacol *11*: S25–S31

Heiligenstein, JH, Tollefson, GD, Faries, DE. (1994) Response patterns of depressed outpatients with and without melancholia: a double-blind, placebo-controlled trial of fluoxetine versus placebo. J Affect Disord *30*: 163–173

Hemels, ME, Einarson, A, Koren, G, Lanctot, KL, Einarson, TR. (2005) Antidepressant use during pregnancy and the rates of spontaneous abortions: a meta-analysis. Ann Pharmacother *39*: 803–809

Henkel, V, Mergl, R, Allgaier, AK, Kohnen, R, Moller, HJ, Hegerl, U. (2006) Treatment of depression with atypical features: a meta-analytic approach. Psychiatry Res *141*: 89–101

Hensley, PL, Nadiga, D, Uhlenhuth, EH. (2004) Long-term effectiveness of cognitive therapy in major depressive disorder. Depress Anxiety *20*: 1–7

Herrmann, LL, Ebmeier, KP. (2006) Factors modifying the efficacy of transcranial magnetic stimulation in the treatment of depression: a review. J Clin Psychiatry *67*: 1870–1876

Hildebrandt, MG, Steyerberg, EW, Stage, KB, Passchier, J, Kragh-Soerensen, P. (2003) Are gender differences important for the clinical effects of antidepressants? Am J Psychiatry *160*: 1643–1650

Hoehn-Saric, R, Ninan, P, Black, DW, Stahl, S, Greist, JH, Lydiard, B, McElroy, S, Zajecka, J, Chapman, D, Clary, C, Harrison, W. (2000) Multicenter double-blind comparison of sertraline and desipramine for concurrent obsessive-compulsive and major depressive disorders. Arch Gen Psychiatry *57*: 76–82

Hoffman, L, Enders, J, Luo, J, Segal, R, Pippins, J, Kimberlin, C. (2003) Impact of an antidepressant management program on medication adherence. Am J Manag Care *9*: 70–80

Hollon, SD, Derubeis, RJ, Shelton, RC, Amsterdam, JD, Salomon, RM, O'Reardon, JP, Lovett, ML, Young, PR, Haman, KL, Freeman, BB, Gallop, R. (2005) Prevention of relapse following cognitive therapy vs medications in moderate to severe depression. Arch Gen Psychiatry *62*: 417–422

Hrobjartsson, A, Gotzsche, PC. (2004) Is the placebo powerless? Update of a systematic review with 52 new randomized trials comparing placebo with no treatment. J Intern Med *256*: 91–100

Hudson, JI, Wohlreich, MM, Kajdasz, DK, Mallinckrodt, CH, Watkin, JG, Martynov, OV. (2005) Safety and tolerability of duloxetine in the treatment of major depressive disorder: analysis of pooled data from eight placebo-controlled clinical trials. Hum Psychopharmacol *20*: 327–341

Husain, MM, Rush, AJ, Fink, M, Knapp, R, Petrides, G, Rummans, T, Biggs, MM, O'Connor, K, Rasmussen, K, Litle, M, Zhao, W, Bernstein, HJ, Smith, G, Mueller, M, McClintock, SM, Bailine, SH, Kellner, CH. (2004a) Speed of response and remission in major depressive disorder with acute electroconvulsive therapy (ECT): a Consortium for Research in ECT (CORE) report. J Clin Psychiatry *65*: 485–491

Husain, SS, Kevan, IM, Linnell, R, Scott, AI. (2004b) Electroconvulsive therapy in depressive illness that has not responded to drug treatment. J Affect Disord *83*: 121–126

Iosifescu, DV. (2007) Treating depression in the medically ill. Psychiatr Clin North Am *30*: 77–90

Iosifescu, DV, Bankier, B, Fava, M. (2004a) Impact of medical comorbid disease on antidepressant treatment of major depressive disorder. Curr Psychiatry Rep *6*: 193–201

Iosifescu, DV, Nierenberg, AA, Alpert, JE, Papakostas, GI, Perlis, RH, Sonawalla, S, Fava, M. (2004b) Comorbid medical illness and relapse of major depressive disorder in the continuation phase of treatment. Psychosomatics *45*: 419–425

Isbister, GK, Bowe, SJ, Dawson, A, Whyte, IM. (2004) Relative toxicity of selective serotonin reuptake inhibitors (SSRIs) in overdose. J Toxicol Clin Toxicol *42*: 277–285

Jacob, S, Spinler, SA. (2006) Hyponatremia associated with selective serotonin-reuptake inhibitors in older adults. Ann Pharmacother *40*: 1618–1622

Jahn, H, Schick, M, Kiefer, F, Kellner, M, Yassouridis, A, Wiedemann, K. (2004) Metyrapone as additive treatment in major depression: a double-blind and placebo-controlled trial. Arch Gen Psychiatry *61*: 1235–1244

Jarrett, RB, Kraft, D, Doyle, J, Foster, BM, Eaves, GG, Silver, PC. (2001) Preventing recurrent depression using cognitive therapy with and without a continuation phase: a randomized clinical trial. Arch Gen Psychiatry *58*: 381–388

Jenkins, R, Lewis, G, Bebbington, P, Brugha, T, Farrell, M, Gill, B, Meltzer, H. (1997) The National Psychiatric Morbidity Surveys of Great Britain – initial findings from the household surveys. Psychol Med *27*: 775–789

Jick, H, Kaye, JA, Jick, SS. (2004) Antidepressants and the risk of suicidal behaviors. JAMA *292*: 338–343

Jimenez, F, Velasco, F, Salin-Pascual, R, Hernandez, JA, Velasco, M, Criales, JL, Nicolini, H. (2005) A patient with a resistant major depression disorder treated with deep brain stimulation in the inferior thalamic peduncle. Neurosurgery *57*: 585–593

Joffe, RT, Sokolov, ST, Levitt, AJ. (2006) Lithium and triiodothyronine augmentation of antidepressants. Can J Psychiatry *51*: 791–793

Johnstone, EC, Owens, DG, Lambert, MT, Crow, TJ, Frith, CD, Done, DJ. (1990) Combination tricyclic antidepressant and lithium maintenance medication in unipolar and bipolar depressed patients. J Affect Disord *20*: 225–233

Joyce, PR, Mulder, RT, Luty, SE, McKenzie, JM, Miller, AL, Rogers, GR, Kennedy, MA. (2003a) Age-dependent antidepressant pharmacogenomics: polymorphisms of the serotonin transporter and G

protein beta3 subunit as predictors of response to fluoxetine and nortriptyline. Int J Neuropsychopharmacol *6*: 339–346

Joyce, PR, Mulder, RT, Luty, SE, McKenzie, JM, Rae, AM. (2003b) A differential response to nortriptyline and fluoxetine in melancholic depression: the importance of age and gender. Acta Psychiatr Scand *108*: 20–23

Joyce, PR, Mulder, RT, Luty, SE, Sullivan, PF, McKenzie, JM, Abbott, RM, Stevens, IF. (2002) Patterns and predictors of remission, response and recovery in major depression treated with fluoxetine or nortriptyline. Aust N Z J Psychiatry *36*: 384–391

Judd, LL. (1997) The clinical course of unipolar major depressive disorders. Arch Gen Psychiatry *54*: 989–991

Judd, LL, Akiskal, HS, Maser, JD, Zeller, PJ, Endicott, J, Coryell, W, Paulus, MP, Kunovac, JL, Leon, AC, Mueller, TI, Rice, JA, Keller, MB. (1998a) A prospective 12-year study of subsyndromal and syndromal depressive symptoms in unipolar major depressive disorders. Arch Gen Psychiatry *55*: 694–700

Judd, LL, Akiskal, HS, Maser, JD, Zeller, PJ, Endicott, J, Coryell, W, Paulus, MP, Kunovac, JL, Leon, AC, Mueller, TI, Rice, JA, Keller, MB. (1998b) A prospective 12-year study of subsyndromal and syndromal depressive symptoms in unipolar major depressive disorders. Arch Gen Psychiatry *55*: 694–700

Judd, LL, Rapaport, MH, Yonkers, KA, Rush, AJ, Frank, E, Thase, ME, Kupfer, DJ, Plewes, JM, Schettler, PJ, Tollefson, G. (2004) Randomized, placebo-controlled trial of fluoxetine for acute treatment of minor depressive disorder. Am J Psychiatry *161*: 1864–1871

Kallen, BA, Otterblad, OP. (2007) Maternal use of selective serotonin re-uptake inhibitors in early pregnancy and infant congenital malformations. Birth Defects Res A Clin Mol Teratol 79: 301–308

Kaltenthaler, E, Brazier, J, De Nigris, E, Tumur, I, Ferriter, M, Beverley, C, Parry, G, Rooney, G, Sutcliffe, P. (2006) Computerised cognitive behaviour therapy for depression and anxiety update: a systematic review and economic evaluation. Health Technol Assess *10*: 1–168

Kanai, T, Takeuchi, H, Furukawa, TA, Yoshimura, R, Imaizumi, T, Kitamura, T, Takahashi, K. (2003) Time to recurrence after recovery from major depressive episodes and its predictors. Psychol Med *33*: 839–845

Karp, JF, Scott, J, Houck, P, Reynolds, CF, Kupfer, DJ, Frank, E. (2005) Pain predicts longer time to remission during treatment of recurrent depression. J Clin Psychiatry *66*: 591–597

Kasper, S, Anghelescu, IG, Szegedi, A, Dienel, A, Kieser, M. (2006) Superior efficacy of St John's wort extract WS 5570 compared to placebo in patients with major depression: a randomized, double-blind, placebo-controlled, multi-center trial. BMC Med *4*: 14–xx

Katon, W, Robinson, P, Von Korff, M, Lin, E, Bush, T, Ludman, E, Simon, G, Walker, E. (1996) A multifaceted intervention to improve treatment of depression in primary care. Arch Gen Psychiatry *53*: 924–932

Katon, W, Rutter, C, Ludman, EJ, Von Korff, M, Lin, E, Simon, G, Bush, T, Walker, E, Unutzer, J. (2001) A randomized trial of relapse prevention of depression in primary care. Arch Gen Psychiatry *58*: 241–247

Katon, W, Von Korff, M, Lin, E, Simon, G, Walker, E, Bush, T, Ludman, E. (1997) Collaborative management to achieve depression treatment guidelines. J Clin Psychiatry *58*(Suppl): 20–23

Katz, MM, Tekell, JL, Bowden, CL, Brannan, S, Houston, JP, Berman, N, Frazer, A. (2004) Onset and early behavioral effects of pharmacologically different antidepressants and placebo in depression. Neuropsychopharmacol *29*: 566–579

Keller, MB, McCullough, JP, Klein, DN, Arnow, B, Dunner, DL, Gelenberg, AJ, Markowitz, JC, Nemeroff, CB, Russell, JM, Thase, ME, Trivedi, MH, Zajecka, J. (2000) A comparison of nefazodone, the cognitive behavioural-analysis system of psychotherapy, and their combination for the treatment of chronic depression. N Engl J Med *342*: 1462–1470

Kellner, CH, Knapp, RG, Petrides, G, Rummans, TA, Husain, MM, Rasmussen, K, Mueller, M, Bernstein, HJ, O'Connor, K, Smith, G, Biggs, M, Bailine, SH, Malur, C, Yim, E, McClintock, S, Sampson, S, Fink, M. (2006) Continuation electroconvulsive therapy vs pharmacotherapy for relapse prevention in major depression: a multisite study from the Consortium for Research in Electroconvulsive Therapy (CORE). Arch Gen Psychiatry *63*: 1337–1344

Kendell, RE. (1968) The classification of depressive illness. Maudsley Monographs 18 (1st edn), Oxford University Press, Oxford

Kennedy, N, Foy, K. (2005) The impact of residual symptoms on outcome of major depression. Curr Psychiatry Rep *7*: 441–446

Kennedy, SH, Andersen, HF, Lam, RW. (2006) Efficacy of escitalopram in the treatment of major depressive disorder compared with conventional selective serotonin reuptake inhibitors and venlafaxine XR: a meta-analysis. J Psychiatry Neurosci *31*: 122–131

Kennedy, SH, Segal, ZV, Cohen, NL, Levitan, RD, Gemar, M, Bagby, RM. (2003) Lithium carbonate versus cognitive therapy as sequential combination treatment strategies in partial responders to antidepressant medication: an exploratory trial. J Clin Psychiatry *64*: 439–444

Kessing, LV. (1998) Recurrence in affective disorder. II. Effect of age and gender. Brit J Psychiatry *172*: 29–34

Kessing, LV. (2003) Subtypes of depressive episodes according to ICD-10: prediction of risk of relapse and suicide. Psychopathol *36*: 285–291

Kessing, LV. (2007) Epidemiology of subtypes of depression. Acta Psychiatr Scand *433*(Suppl): 85–89

Kessing, LV, Andersen, PK. (2005) Predictive effects of previous episodes on the risk of recurrence in depressive and bipolar disorders. Curr Psychiatry Rep *7*: 413–420

Kessler, D, Bennewith, O, Lewis, G, Sharp, D. (2002) Detection of depression and anxiety in primary care: follow up study. Brit Med J *325*: 1016–1017

Kessler, RC, Berglund, P, Demler, O, Jin, R, Koretz, D, Merikangas, KR, Rush, AJ, Walters, EE, Wang, PS. (2003) The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA *289*: 3095–3105

Khan, A, Bose, A, Alexopoulos, GS, Gommoll, C, Li, D, Gandhi, C. (2007) Double-blind comparison of escitalopram and duloxetine in the acute treatment of major depressive disorder. Clin Drug Investig *27*: 481–492

Khan, A, Brodhead, AE, Kolts, RL, Brown, WA. (2005a) Severity of depressive symptoms and response to antidepressants and placebo in antidepressant trials. J Psychiatr Res *39*: 145–150

Khan, A, Brodhead, AE, Schwartz, KA, Kolts, RL, Brown, WA. (2005b) Sex differences in antidepressant response in recent antidepressant clinical trials. J Clin Psychopharmacol *25*: 318–324

Khan, A, Dager, SR, Cohen, S, Avery, DH, Scherzo, B, Dunner, DL. (1991) Chronicity of depressive episode in relation to antidepressant-placebo response. Neuropsychopharmacol *4*: 125–130

Kirsch, I, Scoboria, A, Moore, TJ. (2002) Antidepressants and placebos: secrets, revelations, and unanswered questions. prevention and

treatment 5: Article 33. http://journals.apa.org/prevention/volume5/toc–jul15–02.htm

Klein, DF. (2006) The flawed basis for FDA post-marketing safety decisions: the example of anti-depressants and children. Neuropsychopharmacol *31*: 689–699

Knubben, K, Reischies, FM, Adli, M, Schlattmann, P, Bauer, M, Dimeo, F. (2007) A randomised, controlled study on the effects of a short-term endurance training programme in patients with major depression. Brit J Sports Med *41*: 29–33

Knuppel, L, Linde, K. (2004) Adverse effects of St John's Wort: a systematic review. J Clin Psychiatry *65*: 1470–1479

Koerselman, F, Laman, DM, van Duijn, H, van Duijn, MA, Willems, MA. (2004) A 3-month, follow-up, randomized, placebo-controlled study of repetitive transcranial magnetic stimulation in depression. J Clin Psychiatry *65*: 1323–1328

Kok, RM, Vink, D, Heeren, TJ, Nolen, WA. (2007) Lithium augmentation compared with phenelzine in treatment-resistant depression in the elderly: an open, randomized, controlled trial. J Clin Psychiatry *68*: 1177–1185

Kornstein, SG, Schatzberg, AF, Thase, ME, Yonkers, KA, McCullough, JP, Keitner, GI, Gelenberg, AJ, Davis, SM, Harrison, WM, Keller, MB. (2000) Gender differences in treatment response to sertraline versus imipramine in chronic depression. Am J Psychiatry *157*: 1445–1452

Kornstein, SG, Wohlreich, MM, Mallinckrodt, CH, Watkin, JG, Stewart, DE. (2006) Duloxetine efficacy for major depressive disorder in male vs. female patients: data from 7 randomized, double-blind, placebo-controlled trials. J Clin Psychiatry *67*: 761–770

Kovacs, M. (1996) Presentation and course of major depressive disorder during childhood and later years of the life span. J Am Acad Child Adolesc Psychiatry *35*: 705–715

Kraft, JB, Peters, EJ, Slager, SL, Jenkins, GD, Reinalda, MS, McGrath, PJ, Hamilton, SP. (2007) Analysis of association between the serotonin transporter and antidepressant response in a large clinical sample. Biol Psychiatry *61*: 734–742

Kroenke, K, Spitzer, RL, Williams, JB. (2001) The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med *16*: 606–613

Kupfer, DJ, Frank, E, Perel, JM, Cornes, C, Mallinger, AG, Thase, ME, McEachran, AB, Grochocinski, VJ. (1992) Five-year outcome for maintenance therapies in recurrent depression. Arch Gen Psychiatry *49*: 769–773

Lader, M. (1983) Combined use of tricyclic antidepressants and monoamine oxidase inhibitors. J Clin Psychiatry *44*: 20–24

Lam, RW, Gorman, CP, Michalon, M, Steiner, M, Levitt, AJ, Corral, MR, Watson, GD, Morehouse, RL, Tam, W, Joffe, RT. (1995) Multicenter, placebo-controlled study of fluoxetine in seasonal affective disorder. Am J Psychiatry *152*: 1765–1770

Lam, RW, Levitt, AJ, Levitan, RD, Enns, MW, Morehouse, R, Michalak, EE, Tam, EM. (2006) The Can-SAD study: a randomized controlled trial of the effectiveness of light therapy and fluoxetine in patients with winter seasonal affective disorder. Am J Psychiatry *163*: 805–812

Landen, M, Bjorling, G, Agren, H, Fahlen, T. (1998) A randomized, double-blind, placebo-controlled trial of buspirone in combination with an SSRI in patients with treatment-refractory depression. J Clin Psychiatry *59*: 664–668

Langworth, S, Bodlund, O, Agren, H. (2006) Efficacy and tolerability of reboxetine compared with citalopram: a double-blind study in patients with major depressive disorder. J Clin Psychopharmacol *26*: 121–127

Lauritzen, L, Odgaard, K, Clemmesen, L, Lunde, M, Ohrstrom, J, Black, C, Bech, P. (1996) Relapse prevention by means of paroxetine in ECT-treated patients with major depression: a comparison with imipramine and placebo in medium-term continuation therapy. Acta Psychiatr Scand *94*: 241–251

Lavretsky, H, Park, S, Siddarth, P, Kumar, A, Reynolds, CF. (2006) Methylphenidate-enhanced antidepressant response to citalopram in the elderly: a double-blind, placebo-controlled pilot trial. Am J Geriatr Psychiatry *14*: 181–185

Lawlor, DA, Hopker, SW. (2001) The effectiveness of exercise as an intervention in the management of depression: systematic review and meta-regression analysis of randomised controlled trials. Brit Med J *322*: 763–767

Lee, P, Shu, L, Xu, X, Wang, CY, Lee, MS, Liu, CY, Hong, JP, Ruschel, S, Raskin, J, Colman, SA, Harrison, GA. (2007) Once-daily duloxetine 60 mg in the treatment of major depressive disorder: multicenter, double-blind, randomized, paroxetine-controlled, non-inferiority trial in China, Korea, Taiwan and Brazil. Psychiatry Clin Neurosci *61*: 295–307

Leichsenring, F, Rabung, S, Leibing, E. (2004) The efficacy of short-term psychodynamic psychotherapy in specific psychiatric disorders: a meta-analysis. Arch Gen Psychiatry *61*: 1208–1216

Leinonen, E, Skarstein, J, Behnke, K, Agren, H, Helsdingen, JT. (1999) Efficacy and tolerability of mirtazapine versus citalopram: a double-blind, randomized study in patients with major depressive disorder. Nordic Antidepressant Study Group. Int Clin Psychopharmacol *14*: 329–337

Lepine, JP, Caillard, V, Bisserbe, JC, Troy, S, Hotton, JM, Boyer, P. (2004) A randomized, placebo-controlled trial of sertraline for prophylactic treatment of highly recurrent major depressive disorder. Am J Psychiatry *161*: 836–842

Lewinsohn, PM, Solomon, A, Seeley, JR, Zeiss, A. (2000) Clinical implications of 'subthreshold' depressive symptoms. J Abnorm Psychol *109*: 345–351

Licht, RW, Qvitzau, S. (2002) Treatment strategies in patients with major depression not responding to first-line sertraline treatment. A randomised study of extended duration of treatment, dose increase or mianserin augmentation. Psychopharmacol (Berl) *161*: 143–151

Lima, MS, Moncrieff, J. (2000) Drugs versus placebo for dysthymia. Cochrane Database Syst Rev *1*: CD001130. doi: 10.1002/14651858.CD001130

Lin, EH, Simon, GE, Katzelnick, DJ, Pearson, SD. (2001) Does physician education on depression management improve treatment in primary care? J Gen Intern Med *16*: 614–619

Lin, EH, Von Korff, M, Ludman, EJ, Rutter, C, Bush, TM, Simon, GE, Unutzer, J, Walker, E, Katon, WJ. (2003) Enhancing adherence to prevent depression relapse in primary care. Gen Hosp Psychiatry *25*: 303–310

Lin, P, Campbell, DG, Chaney, EF, Liu, CF, Heagerty, P, Felker, BL, Hedrick, SC. (2005) The influence of patient preference on depression treatment in primary care. Ann Behav Med *30*: 164–173

Linde, K, Berner, M, Egger, M, Mulrow, C. (2005) St John's wort for depression: meta-analysis of randomised controlled trials. Brit J Psychiatry *186*: 99–107

Linden, M, Baier, D, Gothe, H, Kohnen, R. (1997) What happens to patients after the end of a clinical trial? Systematic follow-up observational study of an open moclobemide trial in major depression. Pharmacopsychiatry *30*: 35–43

Lonnqvist, J, Sihvo, S, Syvalahti, E, Sintonen, H, Kiviruusu, O, Pitkanen, H. (1995) Moclobemide and fluoxetine in the prevention

of relapses following acute treatment of depression. Acta Psychiatr Scand *91*: 189–194

Louik, C, Lin, AE, Werler, MM, Hernandez-Diaz, S, Mitchell, AA. (2007) First-trimester use of selective serotonin-reuptake inhibitors and the risk of birth defects. N Engl J Med *356*: 2675–2683

Loving, RT, Kripke, DF, Elliott, JA, Knickerbocker, NC, Grandner, MA. (2005) Bright light treatment of depression for older adults. BMC Psychiatry *5*: 41–xx

Luty, SE, Carter, JD, McKenzie, JM, Rae, AM, Frampton, CM, Mulder, RT, Joyce, PR. (2007) Randomised controlled trial of interpersonal psychotherapy and cognitive-behavioural therapy for depression. Brit J Psychiatry *190*: 496–502

Ma, SH, Teasdale, JD. (2004) Mindfulness-based cognitive therapy for depression: replication and exploration of differential relapse prevention effects. J Consult Clin Psychol *72*: 31–40

Macgillivray, S, Arroll, B, Hatcher, S, Ogston, S, Reid, I, Sullivan, F, Williams, B, Crombie, I. (2003) Efficacy and tolerability of selective serotonin reuptake inhibitors compared with tricyclic antidepressants in depression treated in primary care: systematic review and meta-analysis. Brit Med J *326*: 1014–1017

Maes, M, Libbrecht, I, van Hunsel, F, Campens, D, Meltzer, HY. (1999) Pindolol and mianserin augment the antidepressant activity of fluoxetine in hospitalized major depressed patients, including those with treatment resistance. J Clin Psychopharmacol *19*: 177–182

Malm, H, Klaukka, T, Neuvonen, PJ. (2005) Risks associated with selective serotonin reuptake inhibitors in pregnancy. Obstet Gynecol *106*: 1289–1296

Mandelli, L, Serretti, A, Zanardi, R, Rossini, D, De Ronchi, D, Tarricone, I, Colombo, C. (2007) Antidepressant response in the elderly. Psychiatry Res *152*: 37–44

Marangell, LB, Martinez, JM, Zboyan, HA, Kertz, B, Kim, HF, Puryear, LJ. (2003) A double-blind, placebo-controlled study of the omega-3 fatty acid docosahexaenoic acid in the treatment of major depression. Am J Psychiatry *160*: 996–998

March, J, Silva, S, Petrycki, S, Curry, J, Wells, K, Fairbank, J, Burns, B, Domino, M, McNulty, S, Vitiello, B, Severe, J. (2004) Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. JAMA *292*: 807–820

Martenyi, F, Dossenbach, M, Mraz, K, Metcalfe, S. (2001) Gender differences in the efficacy of fluoxetine and maprotiline in depressed patients: a double-blind trial of antidepressants with serotonergic or norepinephrinergic reuptake inhibition profile. Eur Neuropsychopharmacol *11*: 227–232

Martinez, C, Rietbrock, S, Wise, L, Ashby, D, Chick, J, Moseley, J, Evans, S, Gunnell, D. (2005) Antidepressant treatment and the risk of fatal and non-fatal self harm in first episode depression: nested case-control study. Brit Med J *330*: 389–393

Martiny, K. (2004) Adjunctive bright light in non-seasonal major depression. Acta Psychiatr Scand *425*(Suppl): 7–28

Martiny, K, Lunde, M, Simonsen, C, Clemmensen, L, Poulsen, DL, Solstad, K, Bech, P. (2004) Relapse prevention by citalopram in SAD patients responding to 1 week of light therapy. A placebo-controlled study. Acta Psychiatr Scand *109*: 230–234

Martiny, K, Lunde, M, Unden, M, Dam, H, Bech, P. (2006) The lack of sustained effect of bright light, after discontinuation, in non-seasonal major depression. Psychol Med *36*: 1247–1252

Masand, PS, Gupta, S. (2002) Long-term side effects of newer-generation antidepressants: SSRIS, venlafaxine, nefazodone, bupropion, and mirtazapine. Ann Clin Psychiatry *14*: 175–182

Mather, AS, Rodriguez, C, Guthrie, MF, McHarg, AM, Reid, IC, McMurdo, ME. (2002) Effects of exercise on depressive symptoms in older adults with poorly responsive depressive disorder: randomised controlled trial. Brit J Psychiatry *180*: 411–415

Mayberg, HS, Lozano, AM, Voon, V, McNeely, HE, Seminowicz, D, Hamani, C, Schwalb, JM, Kennedy, SH. (2005) Deep brain stimulation for treatment-resistant depression. Neuron *45*: 651–660

Mazure, CM, Bruce, ML, Maciejewski, PK, Jacobs, SC. (2000) Adverse life events and cognitive-personality characteristics in the prediction of major depression and antidepressant response. Am J Psychiatry *157*: 896–903

McEnany, GW, Lee, KA. (2005) Effects of light therapy on sleep, mood, and temperature in women with nonseasonal major depression. Issues Ment Health Nurs *26*: 781–794

McGrath, PJ, Stewart, JW, Fava, M, Trivedi, MH, Wisniewski, SR, Nierenberg, AA, Thase, ME, Davis, L, Biggs, MM, Shores-Wilson, K, Luther, JF, Niederehe, G, Warden, D, Rush, AJ. (2006a) Tranylcypromine versus venlafaxine plus mirtazapine following three failed antidepressant medication trials for depression: a STAR*D report. Am J Psychiatry *163*: 1531–1541

McGrath, J, Stewart, JW, Quitkin, FM, Chen, Y, Alpert, JE, Nierenberg, AA, Fava, M, Cheng, J, Petkova, E. (2006b) Predictors of relapse in a prospective study of fluoxetine treatment of major depression. Am J Psychiatry *163*: 1542–1548

McLaughlin, T, Hogue, SL, Stang, PE. (2007) Once-daily bupropion associated with improved patient adherence compared with twice-daily bupropion in treatment of depression. Am J Ther *14*: 221–225

Mead, N, MacDonald, W, Bower, P, Lovell, K, Richards, D, Roberts, C, Bucknall, A. (2005) The clinical effectiveness of guided self-help versus waiting-list control in the management of anxiety and depression: a randomized controlled trial. Psychol Med *35*: 1633–1643

Medhus, A, Heskestad, S, Tjemsland, L. (1994) Mianserin added to tricyclic antidepressant in depressed patients not responding to a tricyclic antidepressant alone. A randomised, placebo-controlled, double-blind trial. Nord J Psychiatry *48*: 355–358

Medicines and Healthcare Products Regulatory Authority. (2006) Venlafaxine (Efexor) – summary of basis for regulatory position. http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023840&RevisionSelectionMethod=LatestReleased.

Meier, CR, Schlienger, RG, Jick, H. (2001) Use of selective serotonin reuptake inhibitors and risk of developing first-time acute myocardial infarction. Brit J Clin Pharmacol *52*: 179–184

Melvin, GA, Tonge, BJ, King, NJ, Heyne, D, Gordon, MS, Klimkeit, E. (2006) A comparison of cognitive-behavioral therapy, sertraline, and their combination for adolescent depression. J Am Acad Child Adolesc Psychiatry *45*: 1151–1161

Mian, AI. (2005) Depression in pregnancy and the postpartum period: balancing adverse effects of untreated illness with treatment risks. J Psychiatr Pract *11*: 389–396

Michelson, D, Adler, LA, Amsterdam, JD, Dunner, DL, Nierenberg, AA, Reimherr, FW, Schatzberg, AF, Kelsey, DK, Williams, DW. (2007) Addition of atomoxetine for depression incompletely responsive to sertraline: a randomized, double-blind, placebo-controlled study. J Clin Psychiatry *68*: 582–587

Miller, P, Chilvers, C, Dewey, M, Fielding, K, Gretton, V, Palmer, B, Weller, D, Churchill, R, Williams, I, Bedi, N, Duggan, C, Lee, A,

Harrison, G. (2003) Counseling versus antidepressant therapy for the treatment of mild to moderate depression in primary care: economic analysis. Int J Technol Assess Health Care *19*: 80–90

Mitchell, AJ, Subramaniam, H. (2005) Prognosis of depression in old age compared to middle age: a systematic review of comparative studies. Am J Psychiatry *162*: 1588–1601

Modell, JG, Rosenthal, NE, Harriett, AE, Krishen, A, Asgharian, A, Foster, VJ, Metz, A, Rockett, CB, Wightman, DS. (2005) Seasonal affective disorder and its prevention by anticipatory treatment with bupropion XL. Biol Psychiatry *58*: 658–667

Moller, SE, de Beurs, P, Timmerman, L, Tan, BK, Leijnse-Ybema, HJ, Stuart, MH, Petersen, HE. (1986) Plasma tryptophan and tyrosine ratios to competing amino acids in relation to antidepressant response to citalopram and maprotiline. A preliminary study. Psychopharmacol *88*: 96–100

Moncrieff, J, Kirsch, I. (2005) Efficacy of antidepressants in adults. Brit Med J *331*: 155–157

Montejo, AL, Llorca, G, Izquierdo, JA, Rico-Villademoros, F. (2001) Incidence of sexual dysfunction associated with antidepressant agents: a prospective multicenter study of 1022 outpatients. Spanish Working Group for the Study of Psychotropic-Related Sexual Dysfunction. J Clin Psychiatry *62*(Suppl 3): 10–21

Montgomery, SA, Reimitz, PE, Zivkov, M. (1998) Mirtazapine versus amitriptyline in the long-term treatment of depression: a double-blind placebo-controlled study. Int Clin Psychopharmacol *13*: 63–73

Moreno, FA, Gelenberg, AJ, Bachar, K, Delgado, PL. (1997) Pindolol augmentation of treatment-resistant depressed patients. J Clin Psychiatry *58*: 437–439

Morgan, ML, Cook, IA, Rapkin, AJ, Leuchter, AF. (2005) Estrogen augmentation of antidepressants in perimenopausal depression: a pilot study. J Clin Psychiatry *66*: 774–780

Morgan, O, Griffiths, C, Baker, A, Majeed, A. (2004) Fatal toxicity of antidepressants in England and Wales, 1993–2002. Health Stat Q *23*: 18–24

Mort, JR, Aparasu, RR, Baer, RK. (2006) Interaction between selective serotonin reuptake inhibitors and nonsteroidal antiinflammatory drugs: review of the literature. Pharmacotherapy *26*: 1307–1313

Moscovitch, A, Blashko, CA, Eagles, JM, Darcourt, G, Thompson, C, Kasper, S, Lane, RM. (2004) A placebo-controlled study of sertraline in the treatment of outpatients with seasonal affective disorder. Psychopharmacol (Berl) *171*: 390–397

Moses-Kolko, EL, Bogen, D, Perel, J, Bregar, A, Uhl, K, Levin, B, Wisner, KL. (2005) Neonatal signs after late in utero exposure to serotonin reuptake inhibitors: literature review and implications for clinical applications. JAMA *29* 3: 2372–2383

Mottram, P, Wilson, K, Strobl, J. (2006) Antidepressants for depressed elderly. Cochrane Database Syst Rev *1*: CD003491. doi: 10.1002/14651858.CD003491.pub2

Moussavi, S, Chatterji, S, Verdes, E, Tandon, A, Patel, V, Ustun, B. (2007) Depression, chronic diseases, and decrements in health: results from the World Health Surveys. Lancet *370*: 851–858

Mueller, TI, Leon, AC, Keller, MB, Solomon, DA, Endicott, J, Coryell, W, Warshaw, M, Maser, JD. (1999) Recurrence after recovery from major depressive disorder during 15 years of observational follow-up. Am J Psychiatry *156*: 1000–1006

Mufson, L, Sills, R. (2006) Interpersonal Psychotherapy for depressed adolescents (IPT-A): an overview. Nord J Psychiatry *60*: 431–437

Muller, MJ, Himmerich, H, Kienzle, B, Szegedi, A. (2003) Differentiating moderate and severe depression using the Montgomery-Asberg depression rating scale (MADRS). J Affect Disord *77*: 255–260

Murphy, GM, Hollander, SB, Rodrigues, HE, Kremer, C, Schatzberg, AF. (2004) Effects of the serotonin transporter gene promoter polymorphism on mirtazapine and paroxetine efficacy and adverse events in geriatric major depression. Arch Gen Psychiatry *61*: 1163–1169

Murray, CJ, Lopez, AD. (1997) Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. Lancet *349*: 1498–1504

National Institute for Clinical Excellence. (2004) Clinical Guideline 23. Depression: the management of depression in primary and secondary care. http://www.nice.org.uk/page.aspx?o=guidelines.completed.

Navarro, V, Gasto, C, Torres, X, Marcos, T, Pintor, L. (2001) Citalopram versus nortriptyline in late-life depression: a 12-week randomized single-blind study. Acta Psychiatr Scand *103*: 435–440

Nelson, JC, Mazure, CM, Jatlow, PI, Bowers, MB, Price, LH. (2004) Combining norepinephrine and serotonin reuptake inhibition mechanisms for treatment of depression: a double-blind, randomized study. Biol Psychiatry *55*: 296–300

Nelson, JC, Portera, L, Leon, AC. (2005a) Are there differences in the symptoms that respond to a selective serotonin or norepinephrine reuptake inhibitor? Biol Psychiatry *57*: 1535–1542

Nelson, JC, Portera, L, Leon, AC. (2005b) Residual symptoms in depressed patients after treatment with fluoxetine or reboxetine. J Clin Psychiatry *66*: 1409–1414

Nemeroff, CB, Entsuah, R, Benattia, I, Demitrack, M, Sloan, DM, Thase, ME. (2007) Comprehensive Analysis of Remission (COMPARE) with Venlafaxine versus SSRIs. Biol Psychiatry doi:10.1016/j.biopsych.2007.06.027

Nemets, B, Stahl, Z, Belmaker, RH. (2002) Addition of omega-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder. Am J Psychiatry *159*: 477–479

Nemets, H, Nemets, B, Apter, A, Bracha, Z, Belmaker, RH. (2006) Omega-3 treatment of childhood depression: a controlled, double-blind pilot study. Am J Psychiatry *163*: 1098–1100

Nicholson, A, Kuper, H, Hemingway, H. (2006) Depression as an aetiologic and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146 538 participants in 54 observational studies. Eur Heart J *27*: 2763–2774

Nierenberg, AA, Farabaugh, AH, Alpert, JE, Gordon, J, Worthington, JJ, Rosenbaum, JF, Fava, M. (2000) Timing of onset of antidepressant response with fluoxetine treatment. Am J Psychiatry *157*: 1423–1428

Nierenberg, AA, Fava, M, Trivedi, MH, Wisniewski, SR, Thase, ME, McGrath, PJ, Alpert, JE, Warden, D, Luther, JF, Niederehe, G, Lebowitz, B, Shores-Wilson, K, Rush, AJ. (2006) A comparison of lithium and T(3) augmentation following two failed medication treatments for depression: a STAR*D report. Am J Psychiatry *163*: 1519–1530

Nierenberg, AA, McLean, NE, Alpert, JE, Worthington, JJ, Rosenbaum, JF, Fava, M. (1995) Early nonresponse to fluoxetine as a predictor of poor 8-week outcome. Am J Psychiatry *152*: 1500–1503

Nierenberg, AA, Quitkin, FM, Kremer, C, Keller, MB, Thase, ME. (2004) Placebo-controlled continuation treatment with mirtazapine: acute pattern of response predicts relapse. Neuropsychopharmacol *29*: 1012–1018

Nihalani, ND, Schwartz, TL. (2007) Mifepristone, a glucocorticoid antagonist for the potential treatment of psychotic major depression. Curr Opin Investig Drugs *8*: 563–569

Nulman, I, Rovet, J, Stewart, DE, Wolpin, J, Pace-Asciak, P, Shuhaiber, S, Koren, G. (2002) Child development following exposure to tricyclic antidepressants or fluoxetine throughout fetal life: a prospective, controlled study. Am J Psychiatry *159*: 1889–1895

O'Brien, JT, Lloyd, A, McKeith, I, Gholkar, A, Ferrier, N. (2004) A longitudinal study of hippocampal volume, cortisol levels, and cognition in older depressed subjects. Am J Psychiatry *161*: 2081–2090

O'Reilly, RL, Bogue, L, Singh, SM. (1994) Pharmacogenetic response to antidepressants in a multicase family with affective disorder. Biol Psychiatry *36*: 467–471

Ohayon, MM, Schatzberg, AF. (2003) Using chronic pain to predict depressive morbidity in the general population. Arch Gen Psychiatry *60*: 39–47

Ottevanger, EA. (1991) The efficacy of fluvoxamine in patients with severe depression. Brit J Clin Res *2*: 125–132

Pagnin, D. de Q V, Pini S, Cassano G B (2004) Efficacy of ECT in depression: a meta-analytic review. J ECT *20*: 13–20

Pampallona, S, Bollini, P, Tibaldi, G, Kupelnick, B, Munizza, C. (2004) Combined pharmacotherapy and psychological treatment for depression: a systematic review. Arch Gen Psychiatry *61*: 714–719

Papakostas, GI, Fava, M. (2007) A meta-analysis of clinical trials comparing milnacipran, a serotonin-norepinephrine reuptake inhibitor, with a selective serotonin reuptake inhibitor for the treatment of major depressive disorder. Eur Neuropsychopharmacol *17*: 32–36

Papakostas, GI, Kornstein, SG, Clayton, AH, Soares, CN, Hallett, LA, Krishen, A, Tucker, VL. (2007a) Relative antidepressant efficacy of bupropion and the selective serotonin reuptake inhibitors in major depressive disorder: gender-age interactions. Int Clin Psychopharmacol *22*: 226–229

Papakostas, GI, Petersen, T, Mischoulon, D, Ryan, JL, Nierenberg, AA, Bottiglieri, T, Rosenbaum, JF, Alpert, JE, Fava, M. (2004) Serum folate, vitamin B12, and homocysteine in major depressive disorder, Part 1: predictors of clinical response in fluoxetine-resistant depression. J Clin Psychiatry *65*: 1090–1095

Papakostas, GI, Shelton, RC, Smith, J, Fava, M. (2007b) Augmentation of antidepressants with atypical antipsychotic medications for treatment-resistant major depressive disorder: a meta-analysis. J Clin Psychiatry *68*: 826–831

Papakostas, GI, Thase, ME, Fava, M, Craig, NJ, Shelton, RC. (2007c) Are antidepressant drugs that combine serotonergic and noradrenergic mechanisms of action nore effective than the selective serotonin reuptake inhibitors in treating major depressive disorder? A meta-analysis of studies of newer agents. Biol Psychiatry *62*: 1217–1227

Papanikolaou, K, Richardson, C, Pehlivanidis, A, Papadopoulou-Daifoti, Z. (2006) Efficacy of antidepressants in child and adolescent depression: a meta-analytic study. J Neural Transm *113*: 399–415

Pare, CM, Mack, JW. (1971) Differentiation of two genetically specific types of depression by the response to antidepressant drugs. J Med Genet *8*: 306–309

Parker, G. (2000) Classifying depression: should paradigms lost be regained? Am J Psychiatry *157*: 1195–1203

Parker, G. (2002) Differential effectiveness of newer and older antidepressants appears mediated by an age effect on the phenotypic expression of depression. Acta Psychiatr Scand *106*: 168–170

Parker, G, Roy, K, Wilhelm, K, Mitchell, P. (2001) Assessing the comparative effectiveness of antidepressant therapies: a prospective clinical practice study. J Clin Psychiatry *62*: 117–125

Partonen, T, Lonnqvist, J. (1996) Moclobemide and fluoxetine in treatment of seasonal affective disorder. J Affect Disord *41*: 93–99

Patkar, AA, Masand, PS, Pae, CU, Peindl, K, Hooper-Wood, C, Mannelli, P, Ciccone, P. (2006) A randomized, double-blind, placebo-controlled trial of augmentation with an extended release formulation of methylphenidate in outpatients with treatment-resistant depression. J Clin Psychopharmacol *26*: 653–656

Paykel, ES. (2007) Cognitive therapy in relapse prevention in depression. Int J Neuropsychopharmacol *10*: 131–136

Paykel, ES, Hollyman, JA, Freeling, P, Sedgwick, P. (1988) Predictors of therapeutic benefit from amitriptyline in mild depression: a general practice placebo-controlled trial. J Affect Disord *14*: 83–95

Paykel, ES, Priest, RG. (1992) Recognition and management of depression in general practice: consensus statement. Brit Med J *305*: 1198–1202

Paykel, ES, Ramana, R, Cooper, Z, Hayhurst, H, Kerr, J, Barocka, A. (1995) Residual symptoms after partial remission: an important outcome in depression. Psychol Med *25*: 1171–1180

Paykel, ES, Scott, J, Teasdale, JD, Johnson, AL, Garland, A, Moore, R, Jenaway, A, Cornwall, PL, Hayhurst, H, Abbott, A, Pope, M. (1999) Prevention of relapse in residual depression by cognitive therapy. Arch Gen Psychiatry *56*: 829–835

Paykel, ES, Tanner, J. (1976) Life events, depressive relapse and maintenance treatment. Psychol Med *6*: 481–485

Peet, M, Horrobin, DF. (2002) A dose-ranging study of the effects of ethyl-eicosapentaenoate in patients with ongoing depression despite apparently adequate treatment with standard drugs. Arch Gen Psychiatry *59*: 913–919

Perahia, DG, Kajdasz, DK, Desaiah, D, Haddad, PM. (2005) Symptoms following abrupt discontinuation of duloxetine treatment in patients with major depressive disorder. J Affect Disord *89*: 207–212

Perahia, DG, Pritchett, YL, Kajdasz, DK, Bauer, M, Jain, R, Russell, JM, Walker, DJ, Spencer, KA, Froud, DM, Raskin, J, Thase, ME. (2008) A randomized, double-blind comparison of duloxetine and venlafaxine in the treatment of patients with major depressive disorder. J Psychiatr Res *42*: 22–34

Perahia, DG, Wang, F, Mallinckrodt, CH, Walker, DJ, Detke, MJ. (2006) Duloxetine in the treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. Eur Psychiatry *21*: 367–378

Perez, V, Soler, J, Puigdemont, D, Alvarez, E, Artigas, F. (1999) A double-blind, randomized, placebo-controlled trial of pindolol augmentation in depressive patients resistant to serotonin reuptake inhibitors. Arch Gen Psychiatry *56*: 375–379

Perry, EB, Berman, RM, Sanacora, G, Anand, A, Lynch-Colonese, K, Charney, DS. (2004) Pindolol augmentation in depressed patients resistant to selective serotonin reuptake inhibitors: a double-blind, randomized, controlled trial. J Clin Psychiatry *65*: 238–243

Peveler, R, Carson, A, Rodin, G. (2002) Depression in medical patients. Brit Med J *325*: 149–152

Peveler, R, George, C, Kinmonth, AL, Campbell, M, Thompson, C. (1999) Effect of antidepressant drug counselling and information leaflets on adherence to drug treatment in primary care: randomised controlled trial. Brit Med J *319*: 612–615

Peveler, R, Kendrick, T, Buxton, M, Longworth, L, Baldwin, D, Moore, M, Chatwin, J, Goddard, J, Thornett, A, Smith, H, Campbell, M, Thompson, C. (2005) A randomised controlled trial to compare the cost-effectiveness of tricyclic antidepressants, selective serotonin reuptake inhibitors and lofepramine. Health Technol Assess *9*: 1–134

Pinquart, M, Duberstein, PR, Lyness, JM. (2006) Treatments for later-life depressive conditions: a meta-analytic comparison of pharmacotherapy and psychotherapy. Am J Psychiatry *163*: 1493–1501

Pons, G, Rey, E, Matheson, I. (1994) Excretion of psychoactive drugs into breast milk. Pharmacokinetic principles and recommendations. Clin Pharmacokinet *27*: 270–289

Porter, RJ, Mulder, RT, Joyce, PR, Luty, SE. (2005) Tryptophan and tyrosine availability and response to antidepressant treatment in major depression. J Affect Disord *86*: 129–134

Posternak, MA, Miller, I. (2001) Untreated short-term course of major depression: a meta-analysis of outcomes from studies using wait-list control groups. J Affect Disord *66*: 139–146

Posternak, MA, Solomon, DA, Leon, AC, Mueller, TI, Shea, MT, Endicott, J, Keller, MB. (2006b) The naturalistic course of unipolar major depression in the absence of somatic therapy. J Nerv Ment Dis *194*: 324–329

Posternak, MA, Solomon, DA, Leon, AC, Mueller, TI, Shea, MT, Endicott, J, Keller, MB. (2006a) The naturalistic course of unipolar major depression in the absence of somatic therapy. J Nerv Ment Dis *194*: 324–329

Posternak, MA, Zimmerman, M. (2005a) Dual reuptake inhibitors incur lower rates of tachyphylaxis than selective serotonin reuptake inhibitors: a retrospective study. J Clin Psychiatry *66*: 705–707

Posternak, MA, Zimmerman, M. (2005b) Is there a delay in the antidepressant effect? A meta-analysis. J Clin Psychiatry *66*: 148–158

Posternak, MA, Zimmerman, M. (2007b) Therapeutic effect of follow-up assessments on antidepressant and placebo response rates in antidepressant efficacy trials: meta-analysis. Brit J Psychiatry *190*: 287–292

Posternak, MA, Zimmerman, M. (2007a) Therapeutic effect of follow-up assessments on antidepressant and placebo response rates in antidepressant efficacy trials: meta-analysis. Brit J Psychiatry *190*: 287–292

Prien, RF, Kupfer, DJ, Mansky, PA, Small, JG, Tuason, VB, Voss, CB, Johnson, WE. (1984) Drug therapy in the prevention of recurrences in unipolar and bipolar affective disorders. Report of the NIMH Collaborative Study Group comparing lithium carbonate, imipramine, and a lithium carbonate-imipramine combination. Arch Gen Psychiatry *41*: 1096–1104

Priest, RG, Vize, C, Roberts, A, Roberts, M, Tylee, A. (1996) Lay people's attitudes to treatment of depression: results of opinion poll for Defeat Depression Campaign just before its launch. Brit Med J *313*: 858–859

Prudic, J, Haskett, RF, Mulsant, B, Malone, KM, Pettinati, HM, Stephens, S, Greenberg, R, Rifas, SL, Sackeim, HA. (1996) Resistance to antidepressant medications and short-term clinical response to ECT. Am J Psychiatry *153*: 985–992

Quitkin, FM, Petkova, E, McGrath, PJ, Taylor, B, Beasley, C, Stewart, J, Amsterdam, J, Fava, M, Rosenbaum, J, Reimherr, F, Fawcett, J, Chen, Y, Klein, D. (2003) When should a trial of fluoxetine for major depression be declared failed? Am J Psychiatry *160*: 734–740

Quitkin, FM, Rabkin, JD, Markowitz, JM, Stewart, JW, McGrath, PJ, Harrison, W. (1987) Use of pattern analysis to identify true drug response. A replication. Arch Gen Psychiatry *44*: 259–264

Quitkin, FM, Rabkin, JG, Ross, D, Stewart, JW. (1984) Identification of true drug response to antidepressants. Use of pattern analysis. Arch Gen Psychiatry *41*: 782–786

Quitkin, FM, Stewart, JW, McGrath, PJ. (2001) Gender differences in treatment response. Am J Psychiatry *158*: 1531–1533

Ramana, R, Paykel, ES, Cooper, Z, Hayhurst, H, Saxty, M, Surtees, PG. (1995) Remission and relapse in major depression: a two-year prospective follow-up study. Psychol Med *25*: 1161–1170

Ramana, R, Paykel, ES, Surtees, PG, Melzer, D, Mehta, MA. (1999) Medication received by patients with depression following the acute episode: adequacy and relation to outcome. Brit J Psychiatry *174*:128–134

Reimherr, FW, Amsterdam, JD, Quitkin, FM, Rosenbaum, JF, Fava, M, Zajecka, J, Beasley, CM, Michelson, D, Roback, P, Sundell, K. (1998) Optimal length of continuation therapy in depression: a prospective assessment during long-term fluoxetine treatment. Am J Psychiatry *155*: 1247–1253

Reimherr, FW, Strong, RE, Marchant, BK, Hedges, DW, Wender, PH. (2001) Factors affecting return of symptoms 1 year after treatment in a 62-week controlled study of fluoxetine in major depression. J Clin Psychiatry *62*(Suppl 22): 16–23

Revicki, DA, Simon, GE, Chan, K, Katon, W, Heiligenstein, J. (1998) Depression, health-related quality of life, and medical cost outcomes of receiving recommended levels of antidepressant treatment. J Fam Pract *47*: 446–452

Reynolds, CF, Dew, MA, Pollock, BG, Mulsant, BH, Frank, E, Miller, MD, Houck, PR, Mazumdar, S, Butters, MA, Stack, JA, Schlernitzauer, MA, Whyte, EM, Gildengers, A, Karp, J, Lenze, E, Szanto, K, Bensasi, S, Kupfer, DJ. (2006) Maintenance treatment of major depression in old age. N Engl J Med *354*: 1130–1138

Reynolds, CF, Frank, E, Perel, JM, Imber, SD, Cornes, C, Miller, MD, Mazumdar, S, Houck, PR, Dew, MA, Stack, JA, Pollock, BG, Kupfer, DJ. (1999a) Nortriptyline and interpersonal psychotherapy as maintenance therapies for recurrent major depression: a randomized controlled trial in patients older than 59 years. JAMA *281*: 39–45

Reynolds, CF, Perel, JM, Frank, E, Cornes, C, Miller, MD, Houck, PR, Mazumdar, S, Stack, JA, Pollock, BG, Dew, MA, Kupfer, DJ. (1999b) Three-year outcomes of maintenance nortriptyline treatment in late-life depression: a study of two fixed plasma levels. Am J Psychiatry *156*: 1177–1181

Richards, A, Barkham, M, Cahill, J, Richards, D, Williams, C, Heywood, P. (2003) PHASE: a randomised, controlled trial of supervised self-help cognitive behavioural therapy in primary care. Brit J Gen Pract *53*: 764–770

Rigotti, NA, Thorndike, AN, Regan, S, McKool, K, Pasternak, RC, Chang, Y, Swartz, S, Torres-Finnerty, N, Emmons, KM, Singer, DE. (2006) Bupropion for smokers hospitalized with acute cardiovascular disease. Am J Med *119*: 1080–1087

Rihmer, Z, Arato, M, Gyorgy, S, Revai, K, Demeter, E. (1985) Dexamethasone suppression test as an aid for selection of specific antidepressant drugs in patients with endogenous depression. Pharmacopsychiatry *18*: 306–308

Robinson, DS, Lerfald, SC, Bennett, B, Laux, D, Devereaux, E, Kayser, A, Corcella, J, Albright, D. (1991) Continuation and maintenance treatment of major depression with the monoamine oxidase inhibitor phenelzine: a double-blind placebo-controlled discontinuation study. Psychopharmacol Bull *27*: 31–39

Robinson, P, Katon, W, Von Korff, M, Bush, T, Simon, G, Lin, E, Walker, E. (1997) The education of depressed primary care patients: what do patients think of interactive booklets and a video? J Fam Pract *44*: 562–571

Rohan, KJ, Lindsey, KT, Roecklein, KA, Lacy, TJ. (2004) Cognitive-behavioral therapy, light therapy, and their combination in treating seasonal affective disorder. J Affect Disord *80*: 273–283

Rojo, JE, Ros, S, Aguera, L, de la Gandara, J, de Pedro, JM. (2005) Combined antidepressants: clinical experience. Acta Psychiatr Scand *112*(Suppl 428): 25–31

Ronalds, C, Creed, F, Stone, K, Webb, S, Tomenson, B. (1997) The outcome of anxiety and depressive disorders in general practice. Brit J Psychiatry *171*: 427–433

Rosa, MA, Gattaz, WF, Pascual-Leone, A, Fregni, F, Rosa, MO, Rumi, DO, Myczkowski, M, Silva, MF, Mansur, C, Rigonatti, SP, Jacobsen, TM, Marcolin, MA. (2006) Comparison of repetitive transcranial magnetic stimulation and electroconvulsive therapy in unipolar non-psychotic refractory depression: a randomized, single-blind study. Int J Neuropsychopharmacol *9*: 667–676

Rose, D, Fleischmann, P, Wykes, T, Leese, M, Bindman, J. (2003) Patients' perspectives on electroconvulsive therapy: systematic review. Brit Med J *326*: 1363

Rose, G, Barker, DJ. (1978) Epidemiology for the uninitiated. What is a case? Dichotomy or continuum? Brit Med J *2*: 873–874

Rost, K, Zhang, M, Fortney, J, Smith, J, Coyne, J, Smith, GRJ. (1998) Persistently poor outcomes of undetected major depression in primary care. Gen Hosp Psychiatry *20*: 12–20

Rouillon, F, Serrurier, D, Miller, HD, Gerard, MJ. (1991) Prophylactic efficacy of maprotiline on unipolar depression relapse. J Clin Psychiatry *52*: 423–431

Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Depression. (2004) Australian and New Zealand clinical practice guidelines for the treatment of depression. Aust N Z J Psychiatry *38*: 389–407

Royal College of Psychiatrists. (2000) Neurosurgery for mental disorder. Report from the Neurosurgery Working Group of the Royal College of Psychiatrists. Council Report CR89. Royal College of Psychiatrists, London

Rudolph, RL, Fabre, LF, Feighner, JP, Rickels, K, Entsuah, R, Derivan, AT. (1998) A randomized, placebo-controlled, dose-response trial of venlafaxine hydrochloride in the treatment of major depression. J Clin Psychiatry *59*: 116–122

Ruhe, HG, Huyser, J, Swinkels, JA, Schene, AH. (2006) Switching antidepressants after a first selective serotonin reuptake inhibitor in major depressive disorder: a systematic review. J Clin Psychiatry *67*: 1836–1855

Rush, AJ, Marangell, LB, Sackeim, HA, George, MS, Brannan, SK, Davis, SM, Howland, R, Kling, MA, Rittberg, BR, Burke, WJ, Rapaport, MH, Zajecka, J, Nierenberg, AA, Husain, MM, Ginsberg, D, Cooke, RG. (2005) Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial. Biol Psychiatry *58*: 347–354

Rush, AJ, Trivedi, MH, Wisniewski, SR, Nierenberg, AA, Stewart, JW, Warden, D, Niederehe, G, Thase, ME, Lavori, PW, Lebowitz, BD, McGrath, PJ, Rosenbaum, JF, Sackeim, HA, Kupfer, DJ, Luther, J, Fava, M. (2006a) Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry *163*: 1905–1917

Rush, AJ, Trivedi, MH, Wisniewski, SR, Stewart, JW, Nierenberg, AA, Thase, ME, Ritz, L, Biggs, MM, Warden, D, Luther, JF, Shores-Wilson, K, Niederehe, G, Fava, M. (2006b) Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. N Engl J Med *354*: 1231–1242

Rutz, W. (1999) Improvement of care for people suffering from depression: the need for comprehensive education. Int Clin Psychopharmacol *14*(Suppl 3): S27–S33

Rutz, W, von Knorring, L, Walinder, J. (1992) Long-term effects of an educational program for general practitioners given by the Swedish Committee for the Prevention and Treatment of Depression. Acta Psychiatr Scand *85*: 83–88

Sackeim, HA, Brannan, SK, John, RA, George, MS, Marangell, LB, Allen, J. (2007a) Durability of antidepressant response to vagus nerve stimulation (VNSTM). Int J Neuropsychopharmacol *10*: 817–826

Sackeim, HA, Haskett, RF, Mulsant, BH, Thase, ME, Mann, JJ, Pettinati, HM, Greenberg, RM, Crowe, RR, Cooper, TB, Prudic, J. (2001a) Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: a randomized controlled trial. JAMA *285*: 1299–1307

Sackeim, HA, Prudic, J, Fuller, R, Keilp, J, Lavori, PW, Olfson, M. (2007b) The cognitive effects of electroconvulsive therapy in community settings. Neuropsychopharmacol *32*: 244–254

Sackeim, HA, Roose, SP, Lavori, PW. (2006) Determining the duration of antidepressant treatment: application of signal detection methodology and the need for duration adaptive designs (DAD). Biol Psychiatry *59*: 483–492

Sackeim, HA, Rush, AJ, George, MS, Marangell, LB, Husain, MM, Nahas, Z, Johnson, CR, Seidman, S, Giller, C, Haines, S, Simpson, RK, Goodman, RR. (2001b) Vagus nerve stimulation (VNS) for treatment-resistant depression: efficacy, side effects, and predictors of outcome. Neuropsychopharmacol *25*: 713–728

Salkovskis, P, Rimes, K, Stephenson, D, Sacks, G, Scott, J. (2006) A randomized controlled trial of the use of self-help materials in addition to standard general practice treatment of depression compared to standard treatment alone. Psychol Med *36*: 325–333

Sanz, EJ, las-Cuevas, C, Kiuru, A, Bate, A, Edwards, R. (2005) Selective serotonin reuptake inhibitors in pregnant women and neonatal withdrawal syndrome: a database analysis. Lancet *365*: 482–487

Sauer, WH, Berlin, JA, Kimmel, SE. (2003) Effect of antidepressants and their relative affinity for the serotonin transporter on the risk of myocardial infarction. Circulation *108*: 32–36

Schindler, F, Anghelescu, IG. (2007) Lithium versus lamotrigine augmentation in treatment resistant unipolar depression: a randomized, open-label study. Int Clin Psychopharmacol *22*: 179–182

Schmidt, ME, Fava, M, Zhang, S, Gonzales, J, Raute, NJ, Judge, R. (2002) Treatment approaches to major depressive disorder relapse. Part 1: dose increase. Psychother Psychosom *71*: 190–194

Schramm, E, van Calker, D, Dykierek, P, Lieb, K, Kech, S, Zobel, I, Leonhart, R, Berger, M. (2007) An intensive treatment program of interpersonal psychotherapy plus pharmacotherapy for depressed inpatients: acute and long-term results. Am J Psychiatry *164*: 768–777

Schwenk, TL, Coyne, JC, Fechner, BS. (1996) Differences between detected and undetected patients in primary care and depressed psychiatric patients. Gen Hosp Psychiatry *18*: 407–415

Scott, AIF. (2005) The ECT Handbook: The Third Report of the Royal College of Psychiatrists' Special Committee on ECT (Council Report CR128, 2nd edn), London

Scott, J. (1996) Cognitive therapy of affective disorders: a review. J Affect Disord *37*: 1–11

Serrano-Blanco, A, Gabarron, E, Garcia-Bayo, I, Soler-Vila, M, Carames, E, Penarrubia-Maria, MT, Pinto-Meza, A, Haro, JM. (2006) Effectiveness and Cost-effectiveness of antidepressant treatment in primary health care: a six-month randomised study comparing fluoxetine to imipramine. J Affect Disord *91*: 153–163

Serretti, A, Kato, M, De Ronchi, D, Kinoshita, T. (2007) Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with selective serotonin reuptake inhibitor efficacy in depressed patients. Mol Psychiatry *12*: 247–257

Shapira, B, Nemets, B, Trachtenberg, A, Belmaker, RH. (2006) Phenytoin as an augmentation for SSRI failures: a small controlled study. J Affect Disord *96*: 123–126

Shaw, BF, Elkin, I, Yamaguchi, J, Olmsted, M, Vallis, TM, Dobson, KS, Lowery, A, Sotsky, SM, Watkins, JT, Imber, SD. (1999) Therapist competence ratings in relation to clinical outcome in cognitive therapy of depression. J Consult Clin Psychol *67*: 837–846

Shekelle, PG, Woolf, SH, Eccles, M, Grimshaw, J. (1999) Developing guidelines. Brit Med J *318*: 593–596

Shelton, RC, Williamson, DJ, Corya, SA, Sanger, TM, Van Campen, LE, Case, M, Briggs, SD, Tollefson, GD. (2005) Olanzapine/fluoxetine combination for treatment-resistant depression: a controlled study of SSRI and nortriptyline resistance. J Clin Psychiatry *66*: 1289–1297

Silvers, KM, Woolley, CC, Hamilton, FC, Watts, PM, Watson, RA. (2005) Randomised double-blind placebo-controlled trial of fish oil in the treatment of depression. Prostaglandins Leukot Essent Fatty Acids *72*: 211–218

Simon, GE, Cunningham, ML, Davis, RL. (2002a) Outcomes of prenatal antidepressant exposure. Am J Psychiatry *159*: 2055–2061

Simon, GE, Fleck, M, Lucas, R, Bushnell, DM. (2004) Prevalence and predictors of depression treatment in an international primary care study. Am J Psychiatry *161*: 1626–1634

Simon, GE, Goldberg, D, Tiemens, BG, Ustun, TB. (1999a) Outcomes of recognized and unrecognized depression in an international primary care study. Gen Hosp Psychiatry *21*: 97–105

Simon, GE, Goldberg, DP, Von Korff, M, Ustun, TB. (2002b) Understanding cross-national differences in depression prevalence. Psychol Med *32*: 585–594

Simon, GE, Heiligenstein, JH, Revicki, DA, VonKorff, M, Katon, W, Ludman, E, Grothaus, L, Wagner, EH. (1999b) Long-term outcomes of initial antidepressant drug treatment choice in a 'real world' randomized trial. Arch Fam Med *8*: 319–325

Simon, GE, Lin, EH, Katon, W, Saunders, K, VonKorff, M, Walker, E, Bush, T, Robinson, P. (1995) Outcomes of 'inadequate' antidepressant treatment. J Gen Intern Med *10*: 663–670

Simon, GE, Ludman, EJ, Operskalski, BH. (2006a) Randomized trial of a telephone care management program for outpatients starting antidepressant treatment. Psychiatr Serv *57*: 1441–1445

Simon, GE, Savarino, J. (2007) Suicide attempts among patients starting depression treatment with medications or psychotherapy. Am J Psychiatry *164*: 1029–1034

Simon, GE, Savarino, J, Operskalski, B, Wang, PS. (2006b) Suicide risk during antidepressant treatment. Am J Psychiatry *163*: 41–47

Simon, GE, VonKorff, M, Rutter, C, Wagner, E. (2000) Randomised trial of monitoring, feedback, and management of care by telephone to improve treatment of depression in primary care. Brit Med J *320*: 550–554

Singh, NA, Clements, KM, Singh, MA. (2001) The efficacy of exercise as a long-term antidepressant in elderly subjects: a randomized, controlled trial. J Gerontol A Biol Sci Med Sci *56*: M497–M504

Singh, NA, Stavrinos, TM, Scarbek, Y, Galambos, G, Liber, C, Fiatarone Singh, MA. (2005) A randomized controlled trial of high versus low intensity weight training versus general practitioner care for clinical depression in older adults. J Gerontol A Biol Sci Med Sci *60*: 768–776

Smith, D, Dempster, C, Freemantle, N, Anderson, I. (2002) The efficacy and tolerability of venlafaxine compared with selective serotonin reuptake inhibitors and other antidepressants: a meta-analysis. Brit J Psychiatry *180*: 396–404

Sobin, C, Prudic, J, Devanand, DP, Nobler, MS, Sackeim, HA. (1996) Who responds to electroconvulsive therapy? A comparison of effective and ineffective forms of treatment. Brit J Psychiatry *169*: 322–328

Sokolski, KN, Conney, JC, Brown, BJ, DeMet, EM. (2004) Once-daily high-dose pindolol for SSRI-refractory depression. Psychiatry Res *125*: 81–86

Solomon, DA, Keller, MB, Leon, AC, Mueller, TI, Lavori, PW, Shea, MT, Coryell, W, Warshaw, M, Turvey, C, Maser, JD, Endicott, J. (2000) Multiple recurrences of major depressive disorder. Am J Psychiatry *157*: 229–233

Solomon, DA, Leon, AC, Mueller, TI, Coryell, W, Teres, JJ, Posternak, MA, Judd, LL, Endicott, J, Keller, MB. (2005) Tachyphylaxis in unipolar major depressive disorder. J Clin Psychiatry *66*: 283–290

Sotsky, SM, Glass, DR, Shea, MT, Pilkonis, PA, Collins, JF, Elkin, I, Watkins, JT, Imber, SD, Leber, WR, Moyer, J. (1991) Patient predictors of response to psychotherapy and pharmacotherapy: findings in the NIMH Treatment of Depression Collaborative Research Program. Am J Psychiatry *148*: 997–1008

Spek, V, Cuijpers, P, Nyklicek, I, Riper, H, Keyzer, J, Pop, V. (2007) Internet-based cognitive behaviour therapy for symptoms of depression and anxiety: a meta-analysis. Psychol Med *37*: 319–328

Stassen, HH, Angst, J, Delini-Stula, A. (1996) Delayed onset of action of antidepressant drugs? Survey of results of Zurich meta-analyses. Pharmacopsychiatry *29*: 87–96

Stein, DJ, Baldwin, DS, Dolberg, OT, Despiegel, N, Bandelow, B. (2006) Which factors predict placebo response in anxiety disorders and major depression? An analysis of placebo-controlled studies of escitalopram. J Clin Psychiatry *67*: 1741–1746

Stewart, JW, McGrath, PJ, Quitkin, FM, Harrison, W, Markowitz, J, Wager, S, Leibowitz, MR. (1989) Relevance of DMS-III depressive subtype and chronicity of antidepressant efficacy in atypical depression. Differential response to phenelzine, imipramine, and placebo. Arch Gen Psychiatry *46*: 1080–1087

Stewart, JW, McGrath, PJ, Quitkin, FM, Rabkin, JG, Harrison, W, Wager, S, Nunes, E, Ocepek-Welikson, K, Tricamo, E. (1993) Chronic depression: response to placebo, imipramine, and phenelzine. J Clin Psychopharmacol *13*: 391–396

Stewart, JW, Quitkin, FM, Liebowitz, MR, McGrath, PJ, Harrison, WM, Klein, DF. (1983) Efficacy of desipramine in depressed outpatients. Response according to research diagnosis criteria diagnoses and severity of illness. Arch Gen Psychiatry *40*: 202–207

Stewart, JW, Quitkin, FM, McGrath, PJ, Amsterdam, J, Fava, M, Fawcett, J, Reimherr, F, Rosenbaum, J, Beasley, C, Roback, P. (1998) Use of pattern analysis to predict differential relapse of remitted patients with major depression during 1 year of treatment with fluoxetine or placebo. Arch Gen Psychiatry *55*: 334–343

Stowe, ZN, Hostetter, AL, Newport, DJ. (2005) The onset of postpartum depression: Implications for clinical screening in obstetrical and primary care. Am J Obstet Gynecol *192*: 522–526

Strik, JJ, Honig, A, Lousberg, R, Lousberg, AH, Cheriex, EC, Tuynman-Qua, HG, Kuijpers, PM, Wellens, HJ, Van Praag, HM. (2000) Efficacy and safety of fluoxetine in the treatment of patients with major depression after first myocardial infarction: findings from a double-blind, placebo-controlled trial. Psychosom Med *62*: 783–789

Su, KP, Huang, SY, Chiu, CC, Shen, WW. (2003) Omega-3 fatty acids in major depressive disorder. A preliminary double-blind, placebo-controlled trial. Eur Neuropsychopharmacol *13*: 267–271

Sullivan, MD, Katon, WJ, Russo, JE, Frank, E, Barrett, JE, Oxman, TE, Williams, JW. (2003) Patient beliefs predict response to paroxetine among primary care patients with dysthymia and minor depression. J Am Board Fam Pract *16*: 22–31

Suri, R, Altshuler, L, Hellemann, G, Burt, VK, Aquino, A, Mintz, J. (2007) Effects of antenatal depression and antidepressant treatment on gestational age at birth and risk of preterm birth. Am J Psychiatry *164*: 1206–1213

Sutor, B, Rummans, TA, Jowsey, SG, Krahn, LE, Martin, MJ, O'Connor, MK, Philbrick, KL, Richardson, JW. (1998) Major depression in medically ill patients. Mayo Clin Proc *73*: 329–337

Szegedi, A, Kohnen, R, Dienel, A, Kieser, M. (2005) Acute treatment of moderate to severe depression with hypericum extract WS 5570 (St John's wort): randomised controlled double blind non-inferiority trial versus paroxetine. Brit Med J *330*: 503

Szegedi, A, Muller, MJ, Anghelescu, I, Klawe, C, Kohnen, R, Benkert, O. (2003) Early improvement under mirtazapine and paroxetine predicts later stable response and remission with high sensitivity in patients with major depression. J Clin Psychiatry *64*: 413–420

Taner, E, Demir, EY, Cosar, B. (2006) Comparison of the effectiveness of reboxetine versus fluoxetine in patients with atypical depression: a single-blind, randomized clinical trial. Adv Ther *23*: 974–987

Tanghe, A, Steeman, J, Bollen, E, Renynghe de Voxvrie, G, Dendooven, M, Haazen, L. (1997) Moclobeminde and amitriptyline, alone or in combination, in therapy resistant depression. Hum Psychopharmacol *12*: 509–510

Tata, LJ, West, J, Smith, C, Farrington, P, Card, T, Smeeth, L, Hubbard, R. (2005) General population based study of the impact of tricyclic and selective serotonin reuptake inhibitor antidepressants on the risk of acute myocardial infarction. Heart *91*: 465–471

Tavares, JV, Drevets, WC, Sahakian, B. (2003) Cognition in mania and depression. Psychol Med *33*: 959–967

Taylor, CB, Youngblood, ME, Catellier, D, Veith, RC, Carney, RM, Burg, MM, Kaufmann, PG, Shuster, J, Mellman, T, Blumenthal, JA, Krishnan, R, Jaffe, AS. (2005a) Effects of antidepressant medication on morbidity and mortality in depressed patients after myocardial infarction. Arch Gen Psychiatry *62*: 792–798

Taylor, D, Paton, C, Kerwin, R. (2007) The Maudsley Prescribing Guidelines (9th edn), Informa Healthcare, London

Taylor, MJ, Carney, S, Geddes, J, Goodwin, G. (2003) Folate for depressive disorders. Cochrane Database Syst Rev *2*: CD003390. doi: 10.1002/14651858.CD003390

Taylor, MJ, Freemantle, N, Geddes, JR, Bhagwagar, Z. (2006) Early onset of selective serotonin reuptake inhibitor antidepressant action: systematic review and meta-analysis. Arch Gen Psychiatry *63*: 1217–1223

Taylor, MJ, Rudkin, L, Hawton, K. (2005b) Strategies for managing antidepressant-induced sexual dysfunction: systematic review of randomised controlled trials. J Affect Disord *88*: 241–254

Teasdale, JD, Segal, ZV, Williams, JM, Ridgeway, VA, Soulsby, JM, Lau, MA. (2000) Prevention of relapse/recurrence in major depression by mindfulness-based cognitive therapy. J Consult Clin Psychol *68*: 615–623

Thanacoody, HK, Thomas, SH. (2005) Tricyclic antidepressant poisoning: cardiovascular toxicity. Toxicol Rev *24*: 205–214

Thase, ME, Lu, Y, Joliat, MJ, Treuer, T, Detke, MJ. (2003) Remission in placebo-controlled trials of duloxetine with an SSRI comparator. Poster presentation at International Forum for Mood and Anxiety Disorders, Nov 19–21, Monte Carlo

Thase, ME. (2006) Preventing relapse and recurrence of depression: a brief review of therapeutic options. CNS Spectr *11*: 12–21

Thase, ME, Corya, SA, Osuntokun, O, Case, M, Henley, DB, Sanger, TM, Watson, SB, Dube, S. (2007a) A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, and fluoxetine in treatment-resistant major depressive disorder. J Clin Psychiatry *68*: 224–236

Thase, ME, Entsuah, AR, Rudolph, RL. (2001) Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. Brit J Psychiatry *178*: 234–241

Thase, ME, Friedman, ES, Biggs, MM, Wisniewski, SR, Trivedi, MH, Luther, JF, Fava, M, Nierenberg, AA, McGrath, PJ, Warden, D, Niederehe, G, Hollon, SD, Rush, AJ. (2007b) Cognitive therapy versus medication in augmentation and switch strategies as second–step treatments: a STAR*D report. Am J Psychiatry *164*: 739–752

Thase, ME, Greenhouse, JB, Frank, E, Reynolds, CF, Pilkonis, PA, Hurley, K, Grochocinski, V, Kupfer, DJ. (1997) Treatment of major depression with psychotherapy or psychotherapy-pharmacotherapy combinations. Arch Gen Psychiatry *54*: 1009–1015

Thase, ME, Haight, BR, Richard, N, Rockett, CB, Mitton, M, Modell, JG, VanMeter, S, Harriett, AE, Wang, Y. (2005) Remission rates following antidepressant therapy with bupropion or selective serotonin reuptake inhibitors: a meta-analysis of original data from 7 randomized controlled trials. J Clin Psychiatry *66*: 974–981

Thase, ME, Shelton, RC, Khan, A. (2006) Treatment with venlafaxine extended release after SSRI nonresponse or intolerance: a randomized comparison of standard- and higher-dosing strategies. J Clin Psychopharmacol *26*: 250–258

Thase, ME, Trivedi, MH, Rush, AJ. (1995) MAOIs in the contemporary treatment of depression. Neuropsychopharmacol *12*: 185–219

Thiels, C, Linden, M, Grieger, F, Leonard, J. (2005) Gender differences in routine treatment of depressed outpatients with the selective serotonin reuptake inhibitor sertraline. Int Clin Psychopharmacol *20*: 1–7

Thompson, C, Kinmonth, AL, Stevens, L, Peveler, RC, Stevens, A, Ostler, KJ, Pickering, RM, Baker, NG, Henson, A, Preece, J, Cooper, D, Campbell, MJ. (2000) Effects of a clinical-practice guideline and practice-based education on detection and outcome of depression in primary care: Hampshire Depression Project randomised controlled trial. Lancet *355*: 185–191

Thompson, C, Ostler, K, Peveler, RC, Baker, N, Kinmonth, AL. (2001) Dimensional perspective on the recognition of depressive symptoms in primary care: The Hampshire Depression Project 3. Brit J Psychiatry *179*: 317–323

Tiemens, BG, Ormel, J, Simon, GE. (1996) Occurrence, recognition, and outcome of psychological disorders in primary care. Am J Psychiatry *153*: 636–644

Tiemens, BG, VonKorff, M, Lin, EHB. (1999) Diagnosis of depression by primary care physicians versus a structured diagnostic interview: understanding discordance. Gen Hosp Psychiatry *21*: 87–96

Timmerman, L, de Beurs, P, Tan, BK, Leijnse-Ybema, H, Sanchez, C, Hopfner Petersen, HE, Cohen Stuart, MH. (1987) A double-blind comparative clinical trial of citalopram vs maprotiline in hospitalized depressed patients. Int Clin Psychopharmacol *2*: 239–253

Tint, A, Haddad, PM, Anderson, IM. (2008) The effect of rate of antidepressant tapering on the incidence of discontinuation symptoms: a randomised study. J Psychopharmacol *22*: 330–332

Tollefson, GD, Holman, SL. (1993) Analysis of the Hamilton Depression Rating Scale factors from a double-blind, placebo-controlled trial of fluoxetine in geriatric major depression. Int Clin Psychopharmacol *8*: 253–259

Tomaszewska, W, Peselow, ED, Barouche, F, Fieve, RR. (1996) Antecedent life events, social supports and response to antidepressants in depressed patients. Acta Psychiatr Scand *94*: 352–357

Trivedi, MH, Fava, M, Wisniewski, SR, Thase, ME, Quitkin, F, Warden, D, Ritz, L, Nierenberg, AA, Lebowitz, BD, Biggs, MM, Luther, JF, Shores-Wilson, K, Rush, AJ. (2006a) Medication augmentation after the failure of SSRIs for depression. N Engl J Med *354*: 1243–1252

Trivedi, MH, Morris, DW, Grannemann, BD, Mahadi, S. (2005) Symptom clusters as predictors of late response to antidepressant treatment. J Clin Psychiatry *66*: 1064–1070

Trivedi, MH, Rush, AJ, Crismon, ML, Kashner, TM, Toprac, MG, Carmody, TJ, Key, T, Biggs, MM, Shores-Wilson, K, Witte, B, Suppes, T, Miller, AL, Altshuler, KZ, Shon, SP. (2004) Clinical results for patients with major depressive disorder in the Texas Medication Algorithm Project. Arch Gen Psychiatry *61*: 669–680

Trivedi, MH, Rush, AJ, Wisniewski, SR, Nierenberg, AA, Warden, D, Ritz, L, Norquist, G, Howland, RH, Lebowitz, B, McGrath, PJ, Shores-Wilson, K, Biggs, MM, Balasubramani, GK, Fava, M. (2006b) Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry *163*: 28–40

Tsai, YF, Wong, TK, Juang, YY, Tsai, HH. (2004) The effects of light therapy on depressed elders. Int J Geriatr Psychiatry *19*: 545–548

Tuunainen, A, Kripke, DF, Endo, T. (2004) Light therapy for non-seasonal depression. Cochrane Database Syst Rev *2*: CD004050. doi: 10.1002/14651858.CD004050.pub2

Tylee, A, Freeling, P, Kerry, S, Burns, T. (1995) How does the content of consultations affect the recognition by general practitioners of major depression in women? Brit J Gen Pract *45*: 575–578

Uebelhack, R, Gruenwald, J, Graubaum, HJ, Busch, R. (2004) Efficacy and tolerability of Hypericum extract STW 3-VI in patients with moderate depression: a double-blind, randomized, placebo-controlled clinical trial. Adv Ther *21*: 265–275

UK ECT Review Group. (2003) Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. Lancet *361*: 799–808

Valenstein, M, Taylor, KK, Austin, K, Kales, HC, McCarthy, JF, Blow, FC. (2004) Benzodiazepine use among depressed patients treated in mental health settings. Am J Psychiatry *161*: 654–661

Vallejo, J, Gasto, C, Catalan, R, Bulbena, A, Menchon, JM. (1991) Predictors of antidepressant treatment outcome in melancholia: Psychosocial, clinical and biological indicators. J Affect Disord *21*: 151–162

van den Broek, WW, Birkenhager, TK, Mulder, PG, Bruijn, JA, Moleman, P. (2006) Imipramine is effective in preventing relapse in electroconvulsive therapy-responsive depressed inpatients with prior pharmacotherapy treatment failure: a randomized, placebo-controlled trial. J Clin Psychiatry *67*: 263–268

van den Broek, WW, de Lely, A, Mulder, PG, Birkenhager, TK, Bruijn, JA. (2004) Effect of antidepressant medication resistance on short-term response to electroconvulsive therapy. J Clin Psychopharmacol *24*: 400–403

van Melle, JP, de Jonge, P, Honig, A, Schene, AH, Kuyper, AM, Crijns, HJ, Schins, A, Tulner, D, van den Berg, MP, Ormel, J. (2007) Effects of antidepressant treatment following myocardial infarction. Brit J Psychiatry *190*: 460–466

van Schaik, DJ, Klijn, AF, van Hout, HP, van Marwijk, HW, Beekman, AT, de Haan, M, van Dyck, R. (2004) Patients' preferences in the treatment of depressive disorder in primary care. Gen Hosp Psychiatry *26*: 184–189

Vergouwen, AC, Bakker, A, Burger, H, Verheij, TJ, Koerselman, F. (2005) A cluster randomized trial comparing two interventions to improve treatment of major depression in primary care. Psychol Med *35*: 25–33

Vergouwen, AC, Bakker, A, Katon, WJ, Verheij, TJ, Koerselman, F. (2003) Improving adherence to antidepressants: a systematic review of interventions. J Clin Psychiatry *64*: 1415–1420

Viguera, AC, Newport, DJ, Ritchie, J, Stowe, Z, Whitfield, T, Mogielnicki, J, Baldessarini, RJ, Zurick, A, Cohen, LS. (2007) Lithium in breast milk and nursing infants: clinical implications. Am J Psychiatry *164*: 342–345

Von Korff, M, Goldberg, D. (2001) Improving outcomes in depression. Brit Med J *323*: 948–949

Wade, A, Gembert, K, Florea, I. (2007) A comparative study of the efficacy of acute and continuation treatment with escitalopram versus duloxetine in patients with major depressive disorder. Curr Med Res Opin *23*: 1605–1614

Walsh, BT, Seidman, SN, Sysko, R, Gould, M. (2002) Placebo response in studies of major depression: variable, substantial, and growing. JAMA *278*: 1840–1847

Walsh, BT, Sysko, R. (2005) Placebo control groups in trials of major depressive disorder among older patients. J Clin Psychopharmacol *25*: S29–S33

Walters, G, Reynolds, CF, Mulsant, BH, Pollock, BG. (1999) Continuation and maintenance pharmacotherapy in geriatric depression: an open-trial comparison of paroxetine and nortriptyline in patients older than 70 years. J Clin Psychiatry *60*(Suppl 20): 21–25

Wampold, BE, Minami, T, Baskin, TW, Callen, TS. (2002) A meta-(re)analysis of the effects of cognitive therapy versus 'other therapies' for depression. J Affect Disord *68*: 159–165

Waraich, P, Goldner, EM, Somers, JM, Hsu, L. (2004) Prevalence and incidence studies of mood disorders: a systematic review of the literature. Can J Psychiatry *49*: 124–138

Way, CM. (2007) Safety of newer antidepressants in pregnancy. Pharmacotherapy *27*: 546–552

Weinmann, S, Becker, T, Koesters, M. (2007) Re-evaluation of the efficacy and tolerability of venlafaxine vs SSRI: meta-analysis. Psychopharmacol doi: 10.1007/s00213-007-0975-9

Weissman, AM, Levy, BT, Hartz, AJ, Bentler, S, Donohue, M, Ellingrod, VL, Wisner, KL. (2004) Pooled analysis of antidepressant levels in lactating mothers, breast milk, and nursing infants. Am J Psychiatry *161*: 1066–1078

Weissman, MM, Bland, RC, Canino, GJ, Faravelli, C, Greenwald, S, Hwu, H-G, Joyce, PR, Karem, EG, Lee, C-K, Lellouch, J, Lepine, JP, Newman, SC, Rubio-Stipec, M, Wells, JE, Wickramaratne, PJ, Wittchen, H-U, Yeh, E-K. (1996) Cross-national epidemiology of major depression and bipolar disorder. JAMA *276*: 293–299

Wells, KB, Golding, JM, Burnham, MA. (1988) Psychiatric disorder in a sample of the general population with and without chronic medical conditions. Am J Psychiatry *145*: 976–981

Whittington, CJ, Kendall, T, Fonagy, P, Cottrell, D, Cotgrove, A, Boddington, E. (2004) Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. Lancet 363: 1341–1345

Whooley, MA, Avins, AL, Miranda, J, Browner, WS. (1997) Case-finding instruments for depression. Two questions are as good as many. Gen Intern Med *12*: 439–445

Whyte, IM, Dawson, AH, Buckley, NA. (2003) Relative toxicity of venlafaxine and selective serotonin reuptake inhibitors in overdose compared to tricyclic antidepressants. QJM *96*: 369–374

Wijkstra, J, Lijmer, J, Balk, F, Geddes, J, Nolen, WA. (2005) Pharmacological treatment for psychotic depression. Cochrane Database Syst Rev *4*: CD004044. doi: 10.1002/14651858.CD004044.pub2

Wilkinson, MJ, Barczak, P. (1988) Psychiatric screening in general practice: comparison of the general health questionnaire and the hospital anxiety depression scale. J R Coll Gen Pract *38*: 311–313

Williams, JW, Barrett, J, Oxman, T, Frank, E, Katon, W, Sullivan, M, Cornell, J, Sengupta, A. (2000) Treatment of dysthymia and minor depression in primary care: A randomized controlled trial in older adults. JAMA *284*: 1519–1526

Wilson, K, Mottram, P, Sivanranthan, A, Nightingale, A. (2001) Antidepressant versus placebo for depressed elderly. Cochrane Database Syst Rev *3*: CD000561. doi: 10.1002/14651858.CD000561

Wittchen, HU, Hofler, M, Meister, W. (2001) Prevalence and recognition of depressive syndromes in German primary care settings: poorly recognized and treated? Int Clin Psychopharmacol *16*: 121–135

Wogelius, P, Norgaard, M, Gislum, M, Pedersen, L, Munk, E, Mortensen, PB, Lipworth, L, Sorensen, HT. (2006) Maternal use of selective serotonin reuptake inhibitors and risk of congenital malformations. Epidemiol *17*: 701–704

Wohlreich, MM, Mallinckrodt, CH, Watkin, JG, Wilson, MG, Greist, JH, Delgado, PL, Fava, M. (2005) Immediate switching of antidepressant therapy: results from a clinical trial of duloxetine. Ann Clin Psychiatry *17*: 259–268

Wolkowitz, OM, Reus, VI, Keebler, A, Nelson, N, Friedland, M, Brizendine, L, Roberts, E. (1999) Double-blind treatment of major depression with dehydroepiandrosterone. Am J Psychiatry *156*: 646–649

World Health Organization. (1992) The ICD-10 Classification of Mental and Behavioural Disorders – Clinical Descriptions and Diagnostic Guidelines, Geneva

Yildiz, A, Pauler, DK, Sachs, GS. (2004) Rates of study completion with single versus split daily dosing of antidepressants: a meta-analysis. J Affect Disord *78*: 157–162

Yuan, Y, Tsoi, K, Hunt, RH. (2006) Selective serotonin reuptake inhibitors and risk of upper GI bleeding: confusion or confounding? Am J Med *119*: 719–727

Yyldyz, A, Sachs, GS. (2001) Administration of antidepressants. Single versus split dosing: a meta-analysis. J Affect Disord *66*: 199–206

Zigmond, AS, Snaith, RD. (1983) The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand *67*: 361–370

Zimmerman, M, Chelminski, I, Posternak, MA. (2005) Generalizability of antidepressant efficacy trials: differences between depressed psychiatric outpatients who would or would not qualify for an efficacy trial. Am J Psychiatry *162*: 1370–1372

Zimmerman, M, Mattia, JI, Posternak, MA. (2002) Are subjects in pharmacological treatment trials of depression representative of patients in routine clinical practice? Am J Psychiatry *159*: 469–473.