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Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines

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Abstract

A revision of the 2008 British Association for Psychopharmacology evidence-based guidelines for treating depressive disorders with antidepressants was undertaken in order 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 September 2012. Key areas in treating depression were reviewed and the strength of evidence and clinical implications were considered. The guidelines were then revised after extensive feedback from participants and interested parties. A literature review is provided which identifies the quality of evidence upon which the recommendations are made. 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. Significant changes since the last guidelines were published in 2008 include the availability of new antidepressant treatment options, improved evidence supporting certain augmentation strategies (drug and non-drug), management of potential long-term side effects, updated guidance for prescribing in elderly and adolescent populations and updated guidance for optimal prescribing. Suggestions for future research priorities are also made.

Keywords

Antidepressants, depression, depressive disorder, treatment, evidence-based guidelines

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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 BAP guidelines for treating depressive disorders with antidepressants (Anderson et al., 2000, 2008) was undertaken in order to update the guidelines in the light of new evidence. As previously, every effort was taken to make recommendations explicitly evidence based.

Methodology

A consensus meeting was held under the auspices of the BAP in 2012 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 made by each co-author of the guidelines, followed by discussion within the whole group about the quality of evidence and its implications. Subsequently, the main authors revised the previous literature review from 2008 where necessary to incorporate significant developments and drafted revised recommendations and their strength based on the level of evidence. This was then circulated to all participants, user groups and other interested parties for feedback which was incorporated into the final version of the 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. Instead, each co-author was tasked with updating specific sections from the previous guidelines within their subspeciality, using major systematic reviews and RCTs from MEDLINE and EMBASE searches and from the Cochrane Database as well as cross-referencing from previous guidelines (e.g. American Psychiatric Association, 2010; Bauer et al., 2007; CANMAT, Kennedy et al., 2009; Ellis and Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Depression, 2004; National Institute for Clinical Excellence, 2009).

Presentation of data, levels of evidence, strength of recommendations and limitations

We have tried where possible to present effect sizes (ES) or numbers needed to treat (NNT) or harm (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). Numbers needed to treat of 5 or less 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 importance depends on context and needs to be judged in individual situations. In addition, the outcome measures used are ratings of depressive symptoms which only capture certain aspects of 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, 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 are the same as those used in the 2008 BAP guidelines. Although we have included meta-analytic evidence within the highest category, we acknowledge that meta-analyses are only as good as the underlying trials, which are of variable – and often poor – quality. Large, head-to-head RCTs are the ideal basis upon which to form judgements, but unfortunately are too often lacking in relation to the key questions of interest; there remain extensive gaps in the evidence base. Thus, we have taken the decision to include indirect meta-analytic comparisons (e.g. network meta-analysis methods) where other evidence is lacking, but we acknowledge that these are less robust than RCTs, or meta-analyses of RCTs, of direct comparisons. It is also important to note that it is difficult to compare response rates and effect sizes between studies for a large number of reasons; in particular we are mindful that some methodologies (such as the use of waiting list control) will tend to inflate the observed efficacy of some treatment modalities and cannot be compared directly with the more robust data obtained from more rigidly standardised, double-blind placebo-controlled studies. Where relevant we discuss this further in the appropriate sections of the evidence review. 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. As previously, 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 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

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.

disorders in adults, and do not cover depression occurring in bipolar disorder which are covered by another BAP guideline (Goodwin, 2009). Also, we no longer cover the use of antidepressants in pregnancy and the postnatal period, as this is the subject of a new BAP Guideline due to be published shortly. 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, and when accompanied by psychotic 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 updated 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-5; 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-5 major depression, including ICD-10 mild depressive episode with only four symptoms),
  - mild major depression (few symptoms beyond the minimum 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).
- Screening should only be considered where there are robust systems in place for integrated primary care management of depression (e.g. collaborative care) (D).
- Clinicians should be vigilant to the presence of depression in higher-risk groups (previous history of depression, established risk factors). They may consider integrating the use of brief case-finding questions (e.g. Whooley questions) in their consultation, and conduct a more thorough assessment on those where there is suspicion of untreated depression. However, screening even in high-risk groups is not supported by good evidence (D).
- Routinely check for a history of hypomania, mania, mixed affective or psychotic symptoms in patients diagnosed with depression (S).
- Treatment of major depression with antidepressants in primary care should ideally be in the context of

case management or collaborative care to improve outcomes (A). This should include:
  - scheduled follow-up (A),
  - routine assessment of depression severity to monitor progress (B),
  - an effective strategy to enhance adherence to medication (A),
  - standardised assessment of symptoms (S),
  - access to a mental health specialist when required (S).
- Where case management is used: case managers should ideally have a mental health background, and receive supervision (S); case management can be delivered over the telephone to enhance access and efficiency and can be integrated with Improving Access to Psychological Therapies (IAPT) services in the UK (D).
- 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),
  - if there are psychotic symptoms (S),
  - if there is a history, or clinical suspicion, of bipolar disorder (S),
  - in all cases where a child or adolescent is presenting with major depression (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, severity and symptom profile 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 symptom profile (A),
  - depression of any severity 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 there has been a partial or no response to other treatment (A), where the depression is severe (D) 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, patient choice and treatment availability (S).

2.2.1 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), behavioural activation (BA) (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 BA (A) to antidepressant treatment,
  - therapists using psychological and behavioural techniques should be experienced in treating depression (B).
- For major depression in the elderly:
  - The overall effect size for psychotherapy may be higher than for antidepressants (I),
  - Problem-solving therapy (PST) may be particularly suitable when treating depression associated with prominent executive dysfunction (II).
- For major depression in children and adolescents:
  - consider CBT or IPT for those not responding to initial structured supportive treatment (B),
  - the choice between drug and non-drug treatments should be based on individual assessment and availability of treatments (D),
  - combining drug and non-drug treatments 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).

2.2.2 **Physical treatments**

- Electroconvulsive therapy (ECT):
  - should be considered as a first-line treatment for major depression in urgent and emergency situations such as: depressive stupor; high risk of suicide; extreme levels of distress; and poor fluid intake (C). Bilateral ECT is the preferred choice in such circumstances (B),
  - is not recommended as a first-line treatment for major depression in non-urgent circumstances but could be considered where: patients express a clear choice; or the patient has relapsed and there has been a previous response to ECT; or psychotic features are present (D),
  - should be considered for treating major depression where first-line treatments are not possible or feasible. The risk–benefit balance needs to be evaluated, taking into account depression severity (including the presence of psychotic features) and degree of disability (S),
  - should be followed by continuation pharmacotherapy to reduce the risk of relapse or recurrence (A).
- Transcranial direct current stimulation (tDCS):
  - is not recommended as a first-line treatment for depression (D).
- Repetitive transcranial magnetic stimulation (rTMS):
  - is not recommended as a first-line treatment for major depression (D),
  - could be considered in circumstances where other treatments are not possible or available and where rTMS is available within an experienced centre (D),
  - should be followed by continuation pharmacotherapy to prevent depressive relapse (D).
- Vagus nerve stimulation (VNS):
  - is not recommended as a first-line treatment for depression (D),
  - may be considered for patients with chronic depression that has not responded to other available treatments, being aware that there are no positive double-blind RCT data (see section 3.4) (C).
- Light therapy:
  - is an effective option for the acute treatment of seasonal autumn/winter major depression (seasonal affective disorder) (B); 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),
  - is more effective when given in the morning (B).

2.2.3 **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, S-adenosyl methionine (SAMe), folate or L-methylfolate 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) (see 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 generally be reserved for situations when first-line drug treatment has failed (D). Older monoamine oxidase inhibitors (MAOIs) should generally be reserved for patients where first-line antidepressant therapy has not been effective (D) and 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 clomipramine (B), venlafaxine (⩾ 150 mg) (B), escitalopram (20 mg) (B), sertraline (B), amitriptyline (C), or mirtazapine (C) in preference to other antidepressants.
- In psychotic depression combine an antidepressant with an antipsychotic initially in preference to treating with an antidepressant alone (A) or an antipsychotic alone (A).
- Other 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 (OCD) and SSRIs) (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),
- presence of atypical features (responds less well to imipramine than phenelzine) (B),
- in children and adolescents the side effect and benefit profile are different to those in adults, meaning that generally only SSRIs should be used (B), although in older adolescents TCAs may also be effective (C).

2.4 PRACTICAL ISSUES IN ACUTE MANAGEMENT

- Initially review patients every 1–2 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 and problems associated with stopping medication (S).
- At each review assess response, adherence with drug treatment, side effects and suicide 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).
- In older people, response to antidepressants may take longer (A).
- 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). Giving patients simple strategies for managing mild side effects (e.g. dry mouth) may be useful (D).
- 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); sildenafil (A) or tadafinil (B) for erectile dysfunction, and bupropion (B) for sexual dysfunction, in men; bupropion (A) or sildenafil (B) for sexual dysfunction in women; and 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 and the presence of symptoms suggesting unrecognised bipolarity, psychosis or atypical symptoms (S). The use of appropriate screening tools (e.g. MDQ or HCL for bipolarity) may be helpful (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 of 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 of 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

3.2.1 **Dose Increase (C)**

- The evidence supporting the efficacy of dose increase is limited, but it could be considered in individual patients 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 and TCAs) (C).

3.2.2 **Switching antidepressant (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)
  - switch 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); in the absence of other indications, consider preferentially antidepressants with some evidence of slightly higher efficacy (i.e. clomipramine, venlafaxine (⩾150mg), escitalopram (20 mg), sertraline, amitriptyline or mirtazapine (D).

3.2.3 **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 quetiapine (A), aripiprazole (A) or lithium (A) as first-line treatments, and risperidone (A), olanzapine (B), tri-iodothyronine (B) or mirtazapine (B) as second-line treatments, being aware that the evidence derives mainly from studies in which lithium and tri-iodothyronine were added to TCAs and the other drugs added to SSRI/SNRIs.
- other additions that could be considered are bupropion (B), buspirone (B), lamotrigine (C) and tryptophan (C); and in specialist centres with careful monitoring (S) modafinil (C), stimulants (C), oestrogen in perimenopausal women (C) and testosterone in men with low testosterone levels (C).
- In older people the evidence base is much smaller, but overall about 50% of patients respond to switching or augmentation. The best evidence is for lithium augmentation (B). There is also some evidence for venlafaxine and selegiline (C).
- In severely treatment resistant patients it may be appropriate to consider multiple combinations concurrently or to use other approaches with extremely limited evidence, but only in specialist centres with appropriate safeguards (D).

3.3 NEXT-STEP PSYCHOLOGICAL TREATMENT OPTIONS

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

3.4 NEXT-STEP PHYSICAL TREATMENT OPTIONS

- Electroconvulsive therapy (ECT):
  - should be considered as an option for patients who have not responded to other treatments (C).
- Transcranial direct current stimulation (tDCS):
  - has limited evidence of efficacy in patients resistant to other forms of treatment (B) and is not recommended in routine clinical practice except as part of a clinical trial and where prospective outcome evaluation is planned (S).
- Repetitive transcranial magnetic stimulation (rTMS):
  - has limited evidence of efficacy but could be considered for individuals who are intolerant of other treatments and who have failed to respond to initial treatment strategies. However, the availability of rTMS is limited, and evidence to support benefit in patients who are unresponsive to more than 3–4 antidepressant treatments is currently lacking (D).
- Vagus nerve stimulation (VNS):
  - has limited evidence of efficacy, and no positive double-blind RCTs, but could be considered in patients with chronic and/or recurrent depression who have failed to respond to four or more antidepressant treatments (C),
  - should only be undertaken in specialist centres with prospective outcome evaluation and where provision for long-term follow-up is available (S).
- Deep brain stimulation (DBS):
  - is only recommended in specialist centres as part of a research process or a clinical programme subject to independent oversight (S).
- Ablative neurosurgery:
  - could be considered for patients unresponsive to all other pharmacological and psychological treatments (D) but should only be provided 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 oversight (S).

3.5 NEXT-STEP OTHER TREATMENT OPTIONS

- Consider adding omega-3 fatty acids (B), SAMe (B), L-methylfolate (B) 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 five lifetime episodes and/or two episodes in the last few years) at least 2 years should be advised (A) and for most long-term treatment should be considered (C).
- There is consistent evidence that continued antidepressant treatment in older people halves relapse rates (A).
- 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).
- Mindfulness-based cognitive therapy (MBCT) added to usual treatment may be useful for preventing relapse in those with ⩾3 previous episodes (B).
- 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). Maintenance ECT (MECT) may be effective for some individuals, particularly older adults (C). MECT should be considered if a patient shows a good response to and tolerability of ECT but relapses rapidly after the course of treatment despite optimisation of pharmacotherapy (D). If used the benefits and adverse effects of MECT should be carefully and regularly monitored (S).

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, subject to the limitations described in section 3 (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 serotonin and noradrenaline reuptake inhibitors (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 (to a lesser extent) adolescents compared with adults and so a different cost–benefit balance applies,
  - decreased tolerability of the elderly to antidepressants,
  - high risk of depressive relapse in the elderly with comorbid medical illness.
- Note that the evidence base is very much smaller for treating depression in children and adolescents and in the elderly. We describe available evidence in the relevant section of these guidelines, but note that it may often be necessary to extrapolate from adult data.

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 potent 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).

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 guides treatment choice (II). DSM-5 major depression is a useful marker for the severity above which antidepressants provide significant 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 (Lewinsohn et al., 2000; Paykel and Priest, 1992). 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, comorbidity 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) are identifiable though do not appear to form distinct categories (e.g. Angst et al., 2007; Kendell, 1968). A similar argument about continua is applicable to the duration of depressive symptoms. Dysthymia refers to depressive symptoms which are subthreshold for, and not a consequence of, a major depressive episode and which last for 2 years or more. The diagnosis of dysthymia is difficult to make and its validity and impact on treatment choice are unclear. This distinction between dysthymia and chronic major depression is further blurred in DSM-5 (American Psychiatric Association, 2013) with the consolidation of the two conditions into persistent depressive disorder.

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(a)) although there is even more uncertainty about thresholds for duration than severity.

We think it is clinically useful to distinguish the diagnosis of depression from the decision to treat. In particular, it is still not clear when people will benefit from antidepressants. If a diagnosis of depression seems appropriate, we think there is an additional step to consider the severity, duration of depression and the number of previous episodes in order to decide whether treatment is indicated. Diagnosis is an important factor, but not enough on its own.

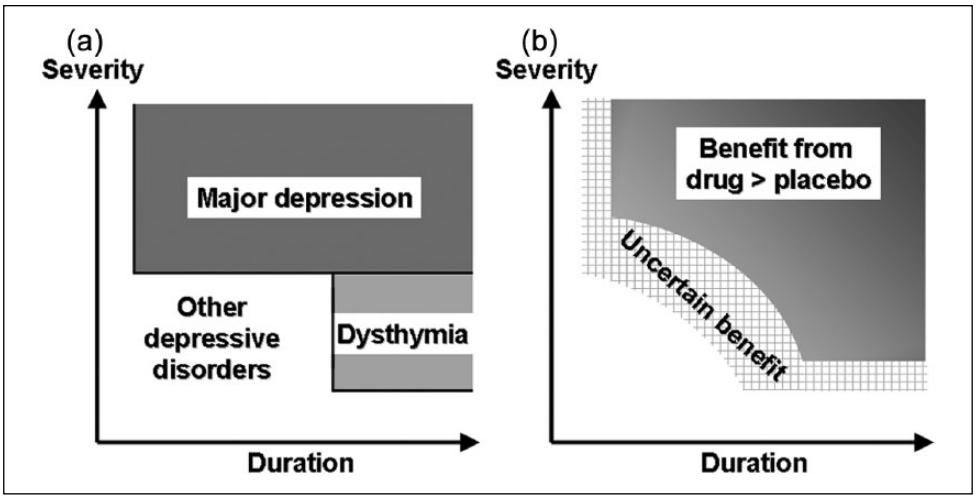

Figure 1. A dimensional approach to depressive disorders and response to treatment.
a) Relationship between dimensions and categories of depressive disorder (see Table 2 for criteria for a major depressive episode).
b) Benefit from antidepressant drug treatment over placebo increases with severity and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

Table 2. Classification of depressive states.

Classification used in Guideline	DSM-5[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 5 symptoms[c] (F32.0)
		Recurrent depressive disorder current episode severe (F33.2), moderate (F33.1) or mild with at least 5 symptoms[c] (F33.0)
Subthreshold depression (includes 'minor' depression)	Depressive disorder not otherwise specified (311)	Depressive episode, mild with 4 symptoms[c] (F32.0)
		Recurrent depressive disorder current episode mild with 4 symptoms[c] (F33.0)
		Mixed anxiety and depressive disorder (F41.2)
	Adjustment disorder with depressed mood/ mixed anxiety and depressed mood (309)	Adjustment disorder – depressive reaction/mixed anxiety and depressive reaction (F43.2)
		Other mood [affective] disorders (F38)
	Persistent Depressive Disorder (300.4)	Dysthymia (F34.1)

a. 5th Revision of the American Psychiatric Association's Diagnostic and Statistics Manual (American Psychiatric Association, 2013).
b. 10th Revision of the International Classification of Diseases (Bauer et al., 2007).
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.

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, 5th Edition (DSM-5; American Psychiatric Association, 2013) 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-5 or a depressive episode in ICD-10. Nevertheless, their respective thresholds differ in that DSM-5 requires a minimum of five symptoms and ICD-10 only four, so that DSM-5 identifies more severe depression than ICD-10 (Wittchen et al., 2001). We use DSM-5 criteria in preference to ICD-10 in these guidelines (Tables 2 and 3) given its predecessor DSM-IV's (American Psychiatric Association, 2000) 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 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. DSM-5 has also recognised the importance of chronic depressive symptoms independently of severity or number of symptoms, and thus the new category persistent depressive disorder requires fewer symptoms but a 2-year duration (Table 3).

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,

Table 3. Abridged DSM-5 criteria[a].

Major Depressive Episode:

A Over the last 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.

Episodes are classified as mild (few symptoms beyond minimum, mild functional impairment), moderate (minimum symptoms and functional impairment between mild and severe), severe (most symptoms present, marked or greater functional impairment).

Persistent Depressive Disorder:

Depressed mood for most of the day, for more days than not, for 2 years or longer.

Presence of 2 or more of the following for the same period:

1. Poor appetite or overeating
2. Insomnia or hypersomnia
3. Low energy or fatigue
4. Low self-esteem
5. Impaired concentration or indecisiveness
6. Hopelessness

Never without symptoms for 2 months.

[a]adapted from American Psychiatric Association (2013).

however, be recognised that the severity of depression commonly varies over time within individuals (Judd et al., 1998) 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 worldwide 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 (Ballenger et al., 2001; Simon et al., 2002; Weissman et al., 1996). In a meta-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 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., 2006). In a 12-year follow-up study of psychiatric patients, varying degrees of depressive symptoms were present for 59% of the time, with 15% of the time spent in major depression (Judd et al., 1998). 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 (Akiskal et al., 1995; Angst, 1985). Patients with early onset depression in adolescence appear to have an even greater risk eventual bipolar disorder (Kovacs, 1996).

There has been some discussion about whether the prevalence and incidence of depression is increasing. A recent paper has compared the results of the 1993, 2000 and 2007 UK psychiatric morbidity surveys that used a similar sampling strategy and

identical assessment. Their conclusion (Spiers et al., 2012) was that there might have been a slight increase in prevalence in women but there was no evidence of any change in men. Reports of more dramatic increases have tended to rely upon retrospective information and are probably less reliable (Kessler et al., 1994).

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. 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); it causes a greater decrement in health state than angina, arthritis, asthma and diabetes (Moussavi et al., 2007). In the latest Global Burden of Disease estimates, depression had risen from 15th to 11th rank between 1990 and 2010 (Murray et al., 2012). Prolonged depression has major consequences for psychosocial function, both because of the symptoms of depression and because it is associated with impaired cognitive function (DeBattista, 2005; O'Brien et al., 2004). Depressive disorders are also associated with increased mortality and, in particular, suicide, one of the leading causes of death in young people in the developed world. 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).

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 (Barrett et al., 1988; Blacker and Clare, 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 (Kessler et al, 2003; Weissman et al, 1996). Medical illness is also associated with increased rates of major depression (Moussavi et al., 2007; Sutor et al., 1998; Wells et al., 1988). It is also worth noting that there is considerable disability associated with depressive symptoms that fall just below the diagnostic threshold (Das-Munshi et al., 2008).

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.

Some 30–50% 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 including 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 on the part of the doctor (Davidson and Meltzer-Brody, 1999; Priest et al., 1996; Tylee et al., 1995). However, undetected patients have less severe disorders and are functioning better than detected patients (Ronalds et al, 1997; Schwenk et al., 1996; 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 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; Lin et al., 2001; Thompson et al., 2000).

Screening questions and self-report scales for the detection of depressive disorders are generally fairly sensitive but vary in specificity (Arroll et al., 2003; Gilbody et al., 2007b; Goldberg et al., 1988; Whooley et al., 1997; Wilkinson and Barczak, 1988). Several commonly used tools 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 two '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 (Ronalds et al, 1997; Simon et al, 1999a; Thompson et al., 2000; Tiemens et al., 1996), 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.

The Geriatric Depression Scale (Yesavage et al., 1982) is the most widely used depression screening scale for older people. A recent paper by Allgaier et al. (2013) found that the (much shorter) WHO-Five Well-being Index (WHO-5) and the 15-item version of the GDS had similarly high sensitivity and specificity.

Table 4. Screening for depressive disorders.

Questions:
Two-question test[a,b]:
1. During the last month, have you often been bothered by feeling down, depressed or hopeless?
2. During the last 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)[e]
A 9-item self-rating scale for the proportion of the time in the last 2 weeks that depressive symptoms have been present. It has an 80% sensitivity at detecting depression and a 92% specificity[f].
Quick Inventory of Depressive Symptomatology (QIDS)[g]
A 16-item self-report questionnaire covering each of the nine domains of DSM-5. Covers reversed biological features (e.g. hypersomnia, weight gain and increased appetite).
Geriatric Depression Scale (GDS)[h]
Developed specifically for the elderly; the 15-item version has 85% sensitivity and 88% specificity for major depression. The WHO-5 is a shorter alternative.
Hypomania Check List (HCL-16)[i]
A 16-item screening questionnaire for bipolarity; 83% sensitivity and 71% specificity.

[a]Whooley et al. (1997).
[b]Arroll et al. (2003).
[c]Zigmond and Snaith (1983).
[d]Wilkinson and Barczak (1988).
[e]Kroenke et al. (2001).
[f]Gilbody et al. (2007b).
[g]Rush et al. (2003).
[h]Allgaier et al. (2013).
[i]Forty et al. (2010).

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 any benefit from telephone case management in treating major depression (II) but guideline/algorithm-driven treatment combined with structured assessment and management 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: a multiprofessional approach, application of a structured management plan, scheduled patient follow-up and 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 (ES 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 a 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 5 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 (Bower et al., 2006; Gensichen 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 numbers 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, 2007). 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% vs. 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 (Adli et al., 2006; Trivedi et al., 2004) did show improved outcomes over treatment as usual, persisting at least to 1 year.

Collaborative care also appears to be an effective and highly acceptable approach for treating depression in older people (Bruce et al., 2004; Chew-Graham et al., 2007; Hunkeler et al., 2006), though one large study from Holland showed only small benefits for this approach (Van Marwijk et al., 2008). Effect sizes for depression scores were 0.30 at 12 months and 0.17 at 24 months in the Hunkeler et al. study, and 0.382 at 6 months in the van Marwijk et al. study. Equivalent effect sizes could not be calculated from the published data in the Chew-Graham et al. and Bruce et al. studies.

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 – and certain groups – such as children and adolescents – have specific treatment implications (Goodwin, 2003; National Institute for Clinical Excellence, 2009) 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 48–50% compared with 30–32% on placebo, NNT 5–7) (I). There is insufficient/inconsistent evidence that greater efficacy can be obtained by combining antidepressants from the start (II) and or using higher initial doses of SSRIs. Some 55–65% of depressed patients treated with antidepressants have clinically important continuing symptoms (I). Smaller drug–placebo differences (principally due to greater responses to placebo) are seen in primary care patients versus psychiatric outpatients (II) and children and adolescents versus adults (II). Systematic reviews of placebo-controlled antidepressant trials in the elderly suggest somewhat smaller effect sizes, particularly in trials restricted to participants aged 65 and over (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 benefits for antidepressants over placebo appear to increase with duration of depression (II); evidence is conflicting about whether it also increases with increasing severity in moderate to severe major depression (I). Clear thresholds for clinically important benefit are not known and are 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 severe depression and melancholia and higher in less severe, shorter duration episodes preceded by life events, and in children and adolescents (I–III).

The original 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 3 points (2 points for treatment-resistant depression), an effect size of 0.5 or a relative risk of 0.8 versus placebo for clinical efficacy. It should be noted that the updated NICE guidance (National Institute for Clinical Excellence, 2009) no longer adopted this rule, although it continues to be cited. Recent evidence (G Lewis, personal communication, 2015) suggests that patient evaluation of benefit is better explained by a percentage change in symptoms scores rather than absolute values, so that larger change scores are needed for more severe, compared with less severe, depression. This guideline takes the view that while statistical separation between drug and placebo in RCTs is informative about whether a treatment is effective, pragmatism and clinical judgement are needed to decide clinical usefulness based on the risk–benefit balance in specific situations rather than using 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 2.4.1).

There is strongest evidence for the efficacy of treating major depression of at least moderate severity (e.g. typically a 17-item HDRS >17 or Montgomery–Asberg Depression Rating Scale (MADRS) >20), the entry criterion for most 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. An issue highlighted since the last guideline is publication bias due to the non-publication of negative studies. An analysis of 74 placebo-controlled antidepressant RCTs registered with the US Food and Drugs Administration (FDA) and using approved drug dosages (Turner et al., 2008) showed that 31% of studies, predominantly the negative ones, were not published. Meta-analysis of all studies revealed a 32% smaller effect size compared with published studies (0.31 vs. 0.41). A meta-analysis of 56 published and unpublished approved-dose RCTs of SSRI and SNRIs

submitted for marketing approval in Sweden (Melander et al., 2008) showed a 16% difference in response rates between antidepressants and placebo (47% vs. 32%, NNT 7), a little smaller than previously reported response rates in a meta-analysis of 75 published short-term RCTs (50% vs. 30%, NNT 5) (Walsh et al., 2002). Both analyses showed wide variation between studies, with evidence from Walsh et al. (2002) that responses rates, especially to placebo, have been increasing over time. A meta-analysis of 15 published 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 rate 58% vs. 44%, NNT 7 recalculated from the paper). This suggests generally higher response rates to antidepressant and placebo in primary care and possibly less difference than in psychiatric outpatients.

It has been argued that the data from meta-analyses such as these suggest that antidepressants only have clinically meaningful effects in the most severely depressed patients (Kirsch et al., 2008). However, others have argued that, although the drug–placebo differences are indeed larger as the severity of depression increases, the definitions of clinically meaningful effects and of severe depression as used by Kirsch and colleagues are not widely agreed, and that observed effects of antidepressants are clinically meaningful for those with more moderate levels of depression (McAllister-Williams, 2008), a position also taken by NICE. It is important to place the effect sizes of antidepressants into context as being similar to those seen for treatments used in medicine as a whole (Leucht et al., 2012).

It is also 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), which compares with 30–32% response rate on placebo (Melander et al., 2008; Walsh et al., 2002) (i.e. NNT of 9–10). A meta-analysis found a similar sized, but non-significant, benefit to placebo over no treatment in depression (ES 0.27) from four very atypical studies (Hrobjartsson and Gotzsche, 2004).

There is current emphasis on remission as a goal of treatment as responders may still have significant residual symptoms, even if subthreshold for major depression. Residual symptoms are estimated to occur in about 30% of patients at the end of acute treatment, and are associated with greater functional disability, suicide risk and risk of relapse (Kennedy and Foy, 2005). Studies reporting remission rates typically find 35–50% remission with antidepressants and 25–35% with placebo in short-term treatment (Dawson et al., 2004; Gibbons et al., 2012; Smith et al., 2002; Thase et al., 2001), indicating that a half to two-thirds of depressed patients have continuing symptoms after acute treatment with antidepressants. Because of this there is interest in maximising efficacy at initial treatment. One strategy has been to consider combining antidepressants with complementary actions from the start of treatment. One small study found considerable benefit from combining mirtazapine with fluoxetine, venlafaxine or bupropion compared with fluoxetine alone (Blier et al., 2010). However, a larger study (CO-MED) found no difference in efficacy between escitalopram monotherapy, escitalopram plus bupropion or venlafaxine plus mirtazapine, but more adverse events with the venlafaxine–mirtazapine combination (Rush et al., 2011). Another possibility is to start with high-dose treatment, and a meta-analysis of nine RCTs comparing different fixed doses of SSRIs (Papakostas et al., 2010) has suggested that a high starting dose is more effective than the usual dose; however, the effect is small and at the price of greater discontinuation due to intolerance. At present, therefore, there is insufficient evidence to recommend either of these as a general strategy to increase efficacy. Other strategies to increase efficacy include combination with CBT (discussed in Evidence section 2.2.1), addressing patient preference and maximising expectation and placebo effects in treatment delivery (see Evidence section 2.4.1).

Elderly. A meta-analysis of 17 published 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 vs. 5) (Walsh and Sysko, 2005). More recent meta-analyses have been in keeping with this. Nelson et al. (2008) identified 10 trials of newer antidepressants and found considerable heterogeneity between them, but an overall NNT of about 10. Kok et al. (2012) reviewed a broader range of trials (including both older and newer antidepressants and with relatively generous entry criteria) and also found an overall superiority for active antidepressants against placebo. However, Tedeschini et al. (2011) found that although antidepressants were superior to placebo in the over-55s, the statistical significance of the difference was no longer apparent in the subset of studies with an age 65 entry criterion. They emphasised marked heterogeneity across studies and the relatively small number of 65+ studies available for inclusion. They also commented that physical comorbidity, executive dysfunction, chronicity of the depressive episode and undertreatment might all have influenced treatment outcome adversely in the 65+ studies. Since the publication of these meta-analyses two further positive placebo-controlled trials of antidepressants in people aged 65 and over have been published (Heun et al., 2012; Katona et al., 2012), and one study of quetiapine monotherapy (50–300 mg/day) found it to be more effective than placebo in short-term treatment of depression in this age group (Katila et al., 2013).

Two large studies of new-generation antidepressants (sertraline and mirtazapine) for depression in Alzheimer's disease failed to show significant amelioration of depressive symptoms compared with placebo (Banerjee et al., 2013; Rosenberg et al., 2010).

Children and adolescents. The use of antidepressants in children and adolescents has been controversial 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). However, there appear to be important differences between drug types. For TCAs a recent Cochrane review identified 14 trials versus placebo in those aged 6–18 (Hazell and Mirzaie, 2013). Overall, there was no effect on response rates and only a small effect on depressive symptoms (ES −0.32). However, when the analysis was confined to adolescents, the effect on symptoms was larger (ES −0.45), albeit that quality of studies was found to be low. Another Cochrane review

of a variety of newer-generation antidepressants identified 19 trials against placebo, and found remission rates of 45% versus 38% on placebo (Hetrick et al., 2012). There was also evidence of an increased risk of suicidal ideation or behaviours (4% vs. 2.5% on placebo). A previous meta-analysis focussed on response rates; it included unpublished studies and combined SSRIs (11 studies) with nefazodone, mirtazapine and venlafaxine (15 studies altogether). Response rates were 61% on antidepressants compared with 50% on placebo (NNT 10) (Bridge et al., 2007). A more recent meta-analysis of studies involving SSRIs only identified 13 studies (2530 children and adolescents). The pooled OR for response was 1.57, with a larger OR (2.39) for fluoxetine. The significance for individual antidepressants depends to some extent on method of analysis. In Hazell and Mirzaie (2013), the largest drug–placebo differences were also seen in trials of fluoxetine (relative risk of remission 1.47 vs. placebo). Effect sizes for continuous data (reduction in depressive symptoms) were significant for fluoxetine (0.43), citalopram (0.34), sertraline (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 showed a significant benefit in the former (10 studies, 62% vs. 49% response, NNT 7–8) with a lack of statistically significant benefit found in the latter (five studies, 65% vs. 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 challenge in using antidepressants for the treatment of children and adolescents is whether the benefits outweigh adverse events as first-line treatment and considering their place in the overall management (see Evidence section 2.3.2)

Medically ill. A systematic review of 18 published 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 STAR*D trial (Trivedi et al., 2006b). A study of predictors of response to citalopram in patients with coronary artery disease (Habra et al., 2010) highlights an interaction between physical disease burden and older age in reducing response to both placebo and antidepressants.

Threshold for treatment. Reliable assessment of the severity of depression is problematic. Definitions related to rating scale scores are problematic because of variation in instruments and assessment practices as well as lack of clinical utility. In this guideline we have adopted the DSM-V 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/DSM-5) major depression may be a rough marker for benefit from antidepressants over placebo. In post-hoc analyses, two studies (Paykel et al., 1988; Stewart et al., 1983) 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 for those with major depression. Similarly, two RCTs in primary care of enhanced treatment resulting in improved medication adherence showed benefits for the intervention over treatment as usual in those with major depression but not those with minor (subthreshold) depression (Katon et al., 1996; Peveler et al., 1999).

Three RCTs in patients with minor depression have shown little or no benefit for antidepressants over placebo (Barrett et al., 2001; Rapaport et al., 2011; Williams et al., 2000). 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 likely reason for the lack of separation of antidepressants from placebo seen in the other trials is the high remission rate on placebo (49–66%) (Barrett et al, 2001; Rapaport et al., 2011; Williams et al., 2000); in one of the studies milder depression severity predicted response to placebo but not to paroxetine (Sullivan et al., 2003).

A recent meta-analysis of published antidepressant RCTs in depression identified 17 dysthymia studies which they compared with 165 in major depression (Levkovitz et al., 2011). There was a significantly greater drug–placebo difference in dysthymia (52% vs. 29%, NNT 5) than major depression (54% vs. 38%, NNT 7), primarily due to the lower response to placebo in dysthymia.

The degree to which severity of major depression influences response to antidepressants compared with placebo within the moderate to severe range of major depression is unclear. As noted, some evidence supports a greater separation with greater severity (Angst et al., 1993; Fournier et al., 2010; Khan et al., 2005a; Kirsch et al., 2002, 2008; Ottevanger, 1991), but the two largest data sets reported to date with 56 (Melander et al., 2008) and 39 (Gibbons et al., 2012) RCTs, the latter using individual patient data, failed to find a significant effect of severity in this range (initial HDRS scores mostly lying between 19 and 27), although the effect was numerically larger at higher severity.

Greater duration of major depressive episode (over timescales of 1–2 years) is associated with a poorer response to placebo (Khan et al., 1991; Stewart et al., 1989, 1993), with possibly a lesser effect on response to antidepressants (Joyce et al., 2002; Khan et al., 1991; Trivedi et al., 2006b). Recent studies of duration of untreated illness in first-episode depression found much lower response rates if antidepressant treatment was delayed for more than 3–6 months (Bukh et al., 2013; Okuda et al., 2010) which may reflect the natural history of depressive episodes, with a higher chance of spontaneous resolution early in the disorder (see below). 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., 2006). 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 evidence described above that response to antidepressants decreases if the duration of untreated illness is longer than 3–6 months (Bukh et al., 2013; Okuda et al., 2010), there is balance to be made between overtreating self-limiting depressive episodes with antidepressants and undertreating depression that is going to persist. A threshold of about 2–3 months is currently best supported by the limited evidence, but it is important not to consider solely duration of symptoms in treatment decisions.

It would be helpful if it were possible to distinguish between depressive states that are relatively transient and likely to improve spontaneously or with low-intensity support, and those which are precursors of more severe, recurrent or chronic conditions where antidepressants are likely to be helpful (Kessing, 2007). Overall, the clinical presentation of the current depressive episode, and whether or not there was a preceding life-event, affects response to antidepressants relatively little (e.g. Angst et al, 1993; Brown, 2007; Ezquiaga et al., 1998; Fava et al., 1997; Tomaszewska et al., 1996; Vallejo et al., 1991), but possibly greater severity (but 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 (Brown et al., 1992), lesser severity (Stein et al., 2006; Sullivan et al, 2003), 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/active monitoring', or indeed how it should be carried out. It is therefore important to consider the current episode in the context of the overall history of depression, and the nature of previous episodes, when considering treatment options.

2.2 Alternatives to antidepressants for acute treatment

2.2.1 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. Waiting list control may act as a nocebo and inflate apparent treatment effects (II). Non-specific psychological treatment (i.e. 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 CBT (I), behavioural activation (BA) (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 PST (I), marital therapy (II), brief psychodynamic psychotherapy (II), counselling (I) and self-help techniques such as computerised CBT and guided self-help. Efficacy attributable to the specific technique is not clear in subthreshold and mild major depression or severe major depression in adults (I). Experienced therapists are needed for treating moderate to severe major depression if psychological therapies are employed (II).***

CBT, BA 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. There is very limited evidence regarding the effectiveness of psychological treatments in children under 13 years old. PST shows particular promise in older people (II). In primary care, following patient preference for psychological or antidepressant treatment improves treatment adherence and may positively influence overall outcome (II).

Combination psychological and antidepressant treatment appears no more effective than psychological therapy 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 but not all studies find that combining an SSRI and CBT is no more effective than an SSRI alone (I), although combination treatment may be more effective where initial response to an antidepressant is poor (I).

General considerations. 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. Publication bias is as real a problem with psychological therapy trials as for medication (Cuijpers et al., 2010). 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 evaluation comparable with that required for antidepressants. It is also notable that evaluation of possible side effects and harms of psychological therapies is often neglected; available data suggest that where measured, rates of adverse effects are 5–20% (Linden and Schermuly-Haupt, 2014). It is outside the remit of this review of evidence to consider the different varieties or variations of specific psychological techniques, such as "third wave" cognitive therapies. However, it is likely that new developments will see an increasing evidence base for matching applied cognitive behavioural techniques to specific clinical problems, such as rumination-focussed CBT for chronic depression and mindfulness-based CBT for highly recurrent depression.

Efficacy of psychological therapy. Accepting the limitations of trials of psychological therapy research, and in particular the control groups chosen, recent reviews/meta-analyses (summarised in Cuijpers et al., 2011) have concluded that in adults with depressive symptoms there is evidence of acute efficacy for the following psychological therapies: CBT (91 studies, ES 0.67), BA (10 studies, ES 0.87), IPT (16 studies, ES 0.63), PST (13 studies, ES 0.83), non-directive supportive therapy (14 studies, ES 0.57), self-control therapy (six studies, ES 0.45) and short-term psychodynamic psychotherapy (five studies, ES 0.69). There is only preliminary/modest evidence against waiting list/usual care/no treatment for marital therapy (two studies, ES 1.28) (Barbato and D'Avanzo, 2006). A more recent meta-analysis of BA versus

waiting list/drug placebo/relaxation/treatment as usual identified 26 studies, with an effect size of 0.74 (Ekers et al., 2014).

The size of the effect seen with specific psychological treatments is reduced if non-specific effects are taken into account. A meta-regression analysis (Haby et al., 2004) 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' (i.e. 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 vs. 0.27 vs. 1.61, respectively) (Cuijpers et al., 2007c). Furukawa et al. (2014) identified 49 RCTs (2730 participants) of CBT for depression comparing the use of waiting list, no treatment and psychological placebo controls using network meta-analysis. As with other analyses, effect sizes were higher when waiting list control (OR 6.26) was used rather than psychological placebo (OR 1.65). Interestingly, indirect comparison of the control groups found randomisation to no treatment was superior to waiting list control (OR 2.9), suggesting that being randomised to waiting list is a nocebo liable to worsen patient outcome, although the authors acknowledge the often poor quality of the underlying studies.

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 (ES 0.16−0.17) (Cuijpers et al., 2007a). This could be accounted for by non-specific effects of the interventions (see above). A more recent meta-analysis of 16 RCTs of psychological therapy (predominantly CBT and IPT) for dysthymia and chronic depression combined (Cuijpers et al., 2010) found a small effect (ES 0.23) on depression when compared with control groups.

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, BA 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, ES 0.15) (Cuijpers et al., 2007c).

A meta-analytic review of psychological therapies for depression in older adults indicates that the overall effect size is at least as great as for antidepressants, though as the authors suggest this conclusion needs to be treated with some caution since psychological therapy control groups are quite different from their placebo-treated equivalents in antidepressant studies (Pinquart et al., 2006,). Problem-solving therapy may be particularly suitable for older people whose depression is complicated by significant executive dysfunction (Alexopoulos et al., 2003; Gellis et al., 2007).

Although studies have generally found positive effects for CBT in children and adolescents, more recent reviews have generally confirmed smaller effect sizes than that found in early trials (ES 0.53) (Klein et al., 2007). One large and influential trial found CBT to be less effective than fluoxetine (March et al., 2004), although the combination of CBT plus fluoxetine was better than fluoxetine alone. However, another study found no additional benefit of adding CBT to good clinical care including fluoxetine (Goodyer et al., 2007), and another also found little evidence for an additional benefit of combined CBT and drug treatment over drug treatment (fluoxetine) alone (Dubicka et al., 2010). There is accumulating evidence for IPT in this age group, which suggest it is more effective than waiting list/clinical monitoring (Mufson and Sills, 2006; Tang et al., 2009).

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 psychological therapy with strongest evidence for significant reduction of subsequent relapse is CBT (see Evidence section 4.1).

Comparative efficacy of psychological therapies. In comparative studies of broadly defined depression there appears little difference in efficacy between CBT and other 'bona fide' psychological therapies (11 studies, non-significant ES 0.16 in favour of CBT) (Wampold et al., 2002), CBT and BA (12 studies, non-significant ES 0.08 in favour of CBT) (Ekers et al., 2007) or CBT and activity scheduling (AS) (10 studies, non-significant ES 0.01 in favour of AS) (Cuijpers et al., 2007b). A placebo-controlled RCT found no difference between CBT, BA and antidepressants in mild to moderate major depression but an advantage to antidepressants and BA 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). BA was found to be more effective than brief dynamic or interpersonal psychotherapy (three studies, ES 0.56) and supportive therapy (two studies, ES 0.75) in treating depressive symptoms (Ekers et al., 2007).

Cuijpers et al. (2011) reviewed all head-to-head studies in which a given psychological therapy was compared in at least five studies. Against all other therapies, IPT was significantly more effective (ES 0.21) and non-directive supportive therapy significantly less effective (−0.17), with no differences for the other therapies studied (CBT 0.03, BA 0.14, psychodynamic −0.07, PST 0.40, social skills training 0.05). A network meta-analysis identified 198 studies, including 15,118 adult patients with depression (Barth et al., 2013). Few differences were apparent between therapies, except that interpersonal therapy was significantly more effective than supportive therapy (ES 0.30). This meta-analysis also showed that effect sizes were significantly lower in smaller and lower-quality trials. Since then, a large (341 patients) study compared 16 sessions of CBT versus brief psychodynamic psychotherapy in depressed outpatients (with antidepressant medication added if indicated) (Driessen et al., 2013). There were no significant differences in outcome, although remission rates were low overall (24% CBT, 21% psychodynamic at endpoint, 35% vs. 27% at 1-year follow-up).

Psychological therapy versus pharmacotherapy. In comparing specific psychotherapies and antidepressants, the influential *National Institute of Mental Health* (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 psychological therapy (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% vs. 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 psychological therapies 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). In contrast, a second 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 psychological therapy. In studies purporting to examine this (Derubeis et al., 1999, 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 (Derubeis et al, 2005; Scott, 1996; Shaw et al., 1999).

Thase et al. (1997) in a mega-analysis (combined individual data) of six studies found equal efficacy for combined drug and psychological therapy compared with IPT or CBT in patients with mild to moderate major depression (HDRS <20) but a poorer response to psychological therapy 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 treatments were not from comparative studies, nor were the studies directly comparable in terms of blinded assessment or adequate placebo condition, making interpretation insecure.

Combination of psychological therapy and medication. 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 ones 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 the combined IPT and sertraline over sertraline (Browne et al., 2002). For dysthymia and chronic depression combined, Cuijpers et al. (2010) found that psychological therapy was significantly less effective than pharmacotherapy (effect size −0.31), but this finding was wholly attributable to studies of dysthymic patients. Combined treatment was more effective than pharmacotherapy alone (effect size 0.23) and psychological therapy alone (d=0.45).

NICE (2009) reviewed the evidence and found nine studies comparing combined CBT plus antidepressants versus antidepressants alone and six studies of the combination versus CBT alone. The combination treatment had a lower risk of discontinuation compared with antidepressants (relative risk (RR) 0.81) and was more effective post-treatment (ES 0.38 on self-rated and 0.46 on clinician-rated depression scores), but longer-term data were limited. However, the effect sizes of the combination against CBT alone were smaller, and non-significant (ES 0.17 on self-rated depression scores post-treatment). However, Cuijpers et al. (2009) reviewed 18 studies (1838 patients) comparing combined treatment with antidepressants and a variety of psychological therapies versus psychological therapy alone (Cuijpers et al., 2009). Combined treatment was more effective (ES 0.35), but sub-analyses suggested that difference was significantly smaller in those studies using CBT. Differences did not persist to follow-up. A large (452 patients) pragmatic study compared individualised antidepressant plus cognitive therapy with antidepressant alone over 42 months (Hollon et al., 2014). Eventual recovery rates were higher for the combined treatment (72.6% vs. 62.5%, NNT 10), although subgroup analysis found the benefit of combined treatment was limited to patients with severe, non-chronic major depressive disorder (81.3% vs. 51.7%; NNT 3). Fewer patients dropped out of combined treatment versus antidepressant medication treatment alone (18.9% vs. 26.8%). However, remission rates did not differ significantly.

An RCT of depressed inpatients (mean HDRS 23.5) reported greater efficacy for IPT combined with antidepressants compared with antidepressants and clinical management (response 70% vs. 51%) (Schramm et al., 2007). A meta-analysis of psychological therapy specifically in inpatients identified 12 RCTs using mostly CBT or BA, and found an additional effect of psychological

therapy over and above usual care (effect size 0.29, NNT 6) (Cuijpers et al., 2011).

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; Goodyer et al., 2007; Melvin et al., 2006).

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.

Patient preference. Several primary care studies have investigated the effects of patients' stated preference and treatment choice on treatment adherence and outcomes. Most primary care patients express preference for psychological therapy over antidepressants (Mergl et al., 2011; Van Schaik et al., 2004). However, many patients do not follow their stated preference when they are actually given a choice of treatment. In one study comparing antidepressant with group CBT, guided self-help and placebo for mild to moderate depressive disorders, 59% of primary care patients expressed preference for psychological therapy and 22% expressed preference for antidepressant prior to treatment allocation (the remaining 18% being undecided). Yet, when a proportion of these patients were then given a choice, 54% actually chose antidepressant (including half of these who had expressed preference for psychological therapy and most of those who had been undecided) and only 36% chose group CBT (Hegerl et al., 2010; Mergl et al., 2011). Therefore, the effects of patients' stated preference and actual patient choice have to be considered separately. Patients who were allocated to a treatment arm where they were free to choose between antidepressant and psychological therapy were less likely to drop out, but achieved no better outcomes than patients who were randomly allocated to treatment (Hegerl et al., 2010). But, among those randomised to a particular treatment, those whose treatment matched their stated pre-allocation preference did better than those who received the non-preferred treatment (Mergl et al., 2011). Similar results were found in another primary care study of antidepressants and counselling with a patient preference arm (Chilvers et al., 2001). Other studies indicated that there may be a more rapid improvement if treatment is matched to treatment preference (Lin et al., 2005; Van Schaik et al., 2004). In summary, and based on this limited evidence, while giving patients with depression a free choice between antidepressants and psychological therapy may not necessarily lead to better outcomes, taking patients' stated preferences into account when making treatment decisions is likely to improve both adherence and outcomes.

In practice, patient preferences have to be balanced with availability and cost implications. One naturalistic study found antidepressants to be the most cost-effective strategy for the majority of patients (Miller et al., 2003).

Self-administered therapies. 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 their application, including the degree of guidance and treatment in control arms. A 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 efficacy relative to 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. Another issue is that while self-administered therapies involve less therapist time, they involve at least as much, and sometimes more, patient time. A meta-analysis of internet-based CBT, mostly against waiting list/treatment as usual/attention (i.e. active) placebo found only a small significant effect for studies of subjects with depressive symptoms (five studies, ES 0.27) compared with a large effect for those with anxiety symptoms (six studies, ES 0.96), but this may have partly been accounted for by the degree of monitoring and/or feedback support provided for the treatments (Spek et al., 2007).

Bibliotherapy based on CBT principles was evaluated in a meta-analysis which identified 11 studies (Anderson et al., 2005). There was a significant benefit against treatment as usual/waiting list (eight studies, ES 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 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).

Aerobic exercise. A Cochrane review (Cooney et al., 2013) identified 39 RCTs of aerobic exercise including 2326 participants. The overall effect size for reduction is depressive symptoms at end of treatment was −0.62, although trials varied considerably in quality, and including only high-quality trials the effect size dropped to −0.18 and was no longer statistically significant. Few studies reported longer-term outcomes; where they did the effect size was less than seen at end of treatment (−0.33). Weaker evidence exists for the benefit of exercise in children and adolescents (Larun et al., 2006).

The few studies directly comparing exercise with other treatments suggest it is as effective as antidepressants or psychological therapies, but there are inherent difficulties in blinding and other risks for bias in these studies, and many were in non-clinical populations, such that no firm conclusions on relative efficacy can yet be drawn, especially in more severely depressed people.

Regarding the method of delivery, the TREAD trial randomised 361 adults with depression to receive 'facilitated physical activity' – a combination face-to-face and telephone sessions encouraging physical activity, rather than supervised physical activity per se – as an adjunctive treatment for depression. There was no benefit over treatment as usual (Chalder et al., 2012). A small RCT of supervised exercise in major depression in adults found that 12 weeks of 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).

In summary, while there does appear to be benefit from exercise, it remains unclear the extent to which exercise may provide additional benefits to other therapies, the extent to which other aspects of exercise such as social interaction, engagement in enjoyable activity and a sense of achievement (i.e. components of BA) may be important, and the optimum type, intensity and duration of exercise required to produce a clinical effect.

2.2.2 Physical treatments. ***Summary: Electroconvulsive therapy is effective in the short-term management of depression (I). It may act more quickly than antidepressants (IV) although comparative trials are lacking. ECT is more effective than treatment with antidepressants (I), particularly in more severe depression (including psychotic depression) and treatment-resistant patients (III). However, relapse rates are high (II). Relapse rates are lower if a continuation therapy is used (I). There is evidence for the following as being protective against relapse after ECT: antidepressant continuation (I); nortriptyline and lithium (II); and maintenance ECT (I).***

Transcranial direct current stimulation (tDCS) may be effective in acute treatment (I) but studies are small, heterogeneity is high, trials are short, and subjects were not resistant to other forms of treatment. Blinding is difficult to achieve and where blinding has been adequate, treatment effects disappear.

Studies of repetitive transcranial magnetic stimulation (rTMS) in patients with minimal treatment resistance report positive results and good tolerability when compared with sham stimulation (I), but studies are heterogeneous and suffer from problems with blinding, with a high risk of bias. There are few replicated long-term follow-up data for rTMS and duration of response remains unclear.

Vagus nerve stimulation (VNS) has not been demonstrated as effective in a double-blind study. Open and observational data suggest that it may be more effective than treatment as usual in patients with chronic depression who have failed to respond to four or more antidepressant treatments (III). Longer-term follow-up studies confirm that response is usually maintained for at least 2 years and relapse/ recurrence rates are lower than those for drug treatment (II). VNS is unlikely to be appropriate for patients who have not attempted standard treatments but, while derived from largely open studies, has some evidence for benefit in treatment-refractory cases (III).

Bright light therapy as acute monotherapy is more effective than a variety of sham conditions for seasonal depression (I), and to a lesser degree non-seasonal depression (II). In seasonal depression, it is as effective as fluoxetine (II) and CBT (II) in acute treatment. There is no evidence of long-term benefits of light therapy, and little support for its use as an add-on therapy to antidepressant medication. Morning light is more effective than evening light (I). Citalopram and bupropion may prevent relapse after response to light therapy (III).

Sleep deprivation may produce a rapid, transient elevation in mood until the next sleep (II); there is no evidence to support its routine use clinically.

Electroconvulsive therapy. *Short-term efficacy*: Two large systematic reviews have demonstrated that ECT is more effective than sham ECT and drug treatment. The UK ECT Review Group (2003) included six studies with an overall effect size of 0.91 in favour of ECT compared with simulated ECT. Eighteen studies comparing ECT with pharmacotherapy were pooled to produce an effect size of 0.80 in favour of ECT, although some studies had small numbers. The US FDA found broadly similar results (Food and Drug Administration, 2011): a course of real ECT is more effective than sham ECT (five studies) with a difference in HDRS score of 7.1 points. Compared with antidepressant medication (eight studies) the difference was 5.0 points.

Long-term efficacy: The FDA review commented on the lack of long-term follow-up data; most studies examining outcomes from ECT rarely have follow-up beyond 4 weeks. Further, the relapse rate is high, with placebo relapse rates of 65–84% compared with 18–60% on antidepressant maintenance therapy. A recent meta-analysis found 32 studies with up to 2 years of follow-up (Jelovac et al., 2013). Across all RCTs, antidepressant medication halved the risk of relapse compared with placebo in the first 6 months (NNT 3). Even with continuation pharmacotherapy, 51% of patients relapsed by 12 months, most (38%) relapsing inside 6 months. The 6-month relapse rate was similar in patients treated with continuation ECT (37%). Continuation pharmacotherapy or maintenance ECT both extend the time to relapse (Kellner et al., 2006). The evidence base for efficacy of pharmacological continuation therapy in post-ECT relapse prevention exists mainly for tricyclic antidepressants (Jelovac et al., 2013). One RCT found that the combination of nortriptyline and lithium reduced relapse rate from 84% on placebo to 39% at 24 weeks (Sackeim et al., 2001a). Published evidence is limited or non-existent for commonly used newer antidepressants or popular augmentation strategies.

In older patients as well, there is evidence that continuation pharmacotherapy is protective against relapse (Navarro et al., 2008). A recent systematic review also concluded that maintenance ECT is as effective as continuation pharmacotherapy in severely depressed elderly patients, but acknowledged that many studies lacked methodological rigour (Van Schaik et al., 2012). One study found that the combination of optimised antidepressant medication plus group CBT was more effective at preventing post-ECT relapse than medication alone or medication plus ultra-brief-pulse continuation ECT at 6 months (sustained response rates of 77%, 44% and 40%, respectively) and 12 months (65%, 33% and 28%) (Brakemeier et al., 2014).

Electrode placement: With regards to electrode placement, meta-analysis of older studies suggests that bilateral ECT is slightly more effective than unilateral ECT (22 studies; effect size 0.32) (UK ECT Review Group, 2003). The FDA found that the difference between bilateral and unilateral ECT is about 4.0 points on the HDRS in favour of bilateral ECT (five studies). However, a recent randomised comparison of electrode placements reported broadly similar rates of response between bifrontal, bitemporal (bilateral) and right unilateral ECT, but a more rapid rate of improvement with bilateral ECT (Kellner et al., 2010).

Frequency: With regard to the optimum frequency of ECT, a recent review by Charlson et al. (2012) compared twice-weekly and thrice-weekly ECT (seven studies, *N*=214). There was no difference in efficacy between twice- and thrice-weekly treatment, but thrice-weekly ECT was more efficacious than once-weekly. The UK standard of twice-weekly ECT is therefore likely to be appropriate.

Electricity dose: High-stimulus dose is moderately more effective than low dose (seven studies; ES 0.58) (UK ECT Review Group, 2003). However, there remains insufficient evidence to draw firm conclusions about the risk/benefit ratio of high-dose versus low-dose ECT. NICE (who based their updated guidelines on the UK ECT Review Group's analysis) were unable to reach firm conclusions about effects of dose (and electrode position) on outcome from ECT, concluding that while high-dose unilateral ECT was slightly more effective than low-dose bilateral ECT, these differences were not clinically important (National Institute for Health and Clinical Excellence, 2009).

Cognitive effects: One of the most commonly reported adverse effects from ECT is memory impairment, typically affecting autobiographical memory during the period of treatment, and some patients may experience longer-term memory problems which can persist for up to 3–6 months. Factors associated with greater cognitive effects include: sine wave stimulation; bilateral electrode placement; older age; female gender; and lower premorbid intellectual function (Sackeim et al., 2007b). These findings were mirrored by the UK ECT Review Group, who also confirmed the relationship between higher doses and greater cognitive effects (UK ECT Review Group, 2003). In a comparison of electrode placements, Kellner et al. (2010) found that cognitive effects did not differ significantly between bifrontal, bitemporal (bilateral) and right unilateral ECT. A meta-analysis (Semkovska and McLoughlin, 2010) of 24 cognitive variables measured across 84 studies (2981 patients) found significant decreases in cognitive performance 0–3 days after ECT in 72% of variables (ES ranging from 1.1 to 0.21). However, only one variable remained impaired 4–15 days post ECT, and there were no impairments detectable after 15 days. Indeed, 57% of variables (including processing speed, working memory, anterograde memory and some aspects of executive function) showed improvement over pre-ECT levels (ES ranging from 0.35 to 0.75). This reinforces the difficulties in separating out the effects of ECT and depression on cognition, both acutely and in longer-term follow-up. The authors acknowledge the lack of good research on retrograde amnesia and/or autobiographical memory, but again point out the confounding effects of depression on these aspects of cognition, and the lack of standardised measures.

Despite the well-established adverse effects associated with ECT, clinicians need to be cognisant that the evidence base for treatments in patients who have failed to respond to more than 2–4 antidepressants remains weak, and ECT offers advantages for those that have not responded to medication (Heijnen et al., 2010). Importantly, in severely unwell patients (e.g. persistent suicidality, psychomotor retardation, psychotic symptoms and/or reduced fluid intake) where emergency treatment is required, ECT may be the treatment of choice due to the quicker speed of onset (Waite and Easton, 2013).

Transcranial direct current stimulation. Transcranial direct current stimulation was developed in response to observations that direct current applied to the cerebral cortex could affect blood flow (Bindman et al., 1964), and human trials of polarisation were underway by the late 1960s and early 1970s (for example: Arfai et al., 1970).

There have been at least eight RCTs comparing direct current stimulation with placebo in depression, many of which originate from the same small groups of researchers. There is heterogeneity in the electrode placement of the cathode and anode (most commonly the left dorsolateral prefrontal cortex) and the majority of trials are short (2–4 weeks) and involve patients who are not resistant to other forms of treatment. Not all RCTs report positive findings (for example: Loo et al., 2010, 2012).

A recent systematic review of RCTs of tDCS in depression reported active tDCS to be more efficacious than sham tDCS, with an effect size of 0.74 (Kalu et al., 2012). However, these findings were heavily influenced by the inclusion of a small number of studies where the methods and participants were poorly described and had small numbers of participants; excluding the low-quality studies removes the difference between the groups.

Repetitive transcranial magnetic stimulation. Repetitive transcranial magnetic stimulation involves the focussed stimulation of the superficial layers of the cerebral cortex using an external wand that delivers a rapidly changing magnetic field.

There are a number of systematic reviews and meta-analyses of RCTs of rTMS for depression. Lam et al. (2008) compared 24 studies (*N*=1092) of active rTMS versus sham in patients who had failed to respond to one previous treatment. Pooled response rates for response were 25% (rTMS) vs. 17% (sham) (NNT 12.5), and 9% (rTMS) vs. 6% (sham) for remission (NNT 33). Schutter (2010) reported an overall effect size of 0.63 (CI 0.03–1.24) in a review of nine studies (*N*=252) comparing rTMS with sham. The studies were heterogeneous, with wide variation in study size and stimulation site.

There remains significant uncertainty regarding optimum treatment parameters, efficacy in more treatment-refractory patient groups, and the duration of any treatment effects. In a review by Allan et al. (2011) the authors identified 1789 studies relating to rTMS in the treatment of mood disorders but only 25 studies had data for analysis. Only nine studies had follow-up data, with a mean follow-up period of 4.3 weeks. Heterogeneity was greater than that expected by chance, and the difficulties in blinding were highlighted. Overall response rates were 35.8% (active) vs. 15.0% (sham) (Allan et al., 2011).

Most studies are short and the risk of bias is high. Issues relating to blinding were highlighted in a review by Broadbent et al. (2011), who reported that few studies of rTMS reported blinding success (13/96; 13.5%). When delivered within published safety parameters, rTMS appears relatively safe with a low rate of serious adverse effects, although high-intensity and high-frequency stimulation can cause seizures in normal subjects.

In a 1-year follow-up study of individuals (*N*=257) who had received rTMS for depression, Dunner et al. reported that 62.5% continued to meet response criteria throughout the follow-up period (Dunner et al., 2014). Participants at baseline had depression of moderate severity (IDS-SR score 45) and had failed to respond to an average of 2.6 adequate antidepressant treatments in the current depressive episode. Out of 78 participants who had remitted at the end of treatment, 70.5% did not relapse over 12 months, although many did receive additional applications of

rTMS and most patients remained on continuation antidepressant medication.

Vagus nerve stimulation. While open studies of VNS have consistently reported response rates of 40–50%, the only RCT failed to demonstrate efficacy for active VNS after 10 weeks (15% vs. 10%) (Rush et al., 2005a), although the duration of the trial may have been too short to observe treatment effects. A large, 12-month study compared 205 patients with VNS (plus treatment as usual) with 124 matched patients who only received treatment as usual. Response rates after 12 months were 27% for VNS+treatment as usual and 13% for treatment as usual ($p<0.011$). This equates to a NNT of 7 for response. In a systematic review of VNS for major depression, Martin and Martín-Sánchez (2012) entered nine uncontrolled studies into a meta-analysis. Although they commented that: "...insufficient data are available to describe VNS as effective in the treatment of depression...", the effect size for VNS was 1.29 and the size of effect was greater with higher levels of depressive symptoms (Martin and Martín-Sánchez, 2012). The authors questioned whether placebo effects could have explained the benefits of VNS, but against this the placebo response rate is generally diminished and transient in refractory patients, whereas with VNS effects are generally sustained (Brunoni et al., 2009) and the response rate in VNS-treated patients is of a similar magnitude to that obtained with pharmacological and psychological therapies in the STAR*D trial (Rush et al., 2006a,b).

Maintenance of response is high, with approximately 65% of responders maintaining their gains at 2 years (Sackeim et al., 2007a). Similar maintenance of response has been reported in European studies of VNS, with 53% of patients achieving response status after 2 years of treatment (Bajbouj et al., 2010). These figures compare favourably with the outcomes from treatment as usual where the response rate after 24 months was 18.4%, and where only 38% responders at 12 months were responders at 24 months (Dunner et al., 2006).

Adverse effects from VNS for depression are broadly comparable with those seen in its use for epilepsy. Tolerability of VNS is good, with most patients experiencing reductions in adverse effects during the 12 months after implantation; the main exception being voice alteration (Rush et al., 2005b).

Bright light therapy. Evaluation of studies of light therapy is problematic because of wide methodological variation, often very short-duration trials (mostly 1 week) and lack of long-term data. Furthermore, adequate blinding is a common problem in many studies evaluating light therapy for both seasonal and non-seasonal depression (Even et al., 2008). 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, ES 0.84) and dawn simulation (five studies, ES 0.73) were effective. In non-seasonal depression, bright light used as sole therapy was effective (three studies, ES 0.53) but not when used as an adjunct to antidepressants (five studies, ES 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 described here. There was a small non-significant benefit to light therapy (18 studies, ES 0.22), but the effect was larger and significant if confined to morning light therapy (11 studies, ES 0.43). In two studies without any adjunctive treatment there was a non-significant benefit to light therapy (ES 0.64) with a smaller non-significant benefit if it was adjunctive to antidepressant medication (14 studies, random ES 0.24). Sleep deprivation and shorter studies (i.e. 7 days) tended to be associated with a larger effect of light therapy.

In RCTs subsequent to these meta-analyses, light therapy in seasonal affective disorder was found to have equal efficacy to fluoxetine (remission 50% vs. 54%; response 67% vs. 67%) in a medium-sized 8-week study (Lam et al., 2006) and to CBT and combined treatment in two very small 6-week studies (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 (Epperson et al., 2004; Martiny, 2004; McEnany and Lee, 2005), but efficacy in the elderly is unclear (Loving et al., 2005; Tsai et al., 2004). In one study an advantage of 5-weeks' adjunctive light therapy was lost after continuing for a further 4 weeks on sertraline monotherapy (Martiny et al., 2006); another study found that light therapy hastened response to citalopram over 2 weeks (Benedetti et al., 2003).

In a comprehensive review of RCTs, NICE (2009) noted many methodological issues with studies of light therapy; focussing on the higher-quality studies, it concluded that there was a large effect size of bright light against waiting list control, but only a small effect against attentional controls. The very few studies comparing light with active control treatments had shown no difference in efficacy.

Taken together, studies do suggest probable short-term benefit for light therapy in seasonal affective disorder (where there is limited evidence for efficacy of antidepressant medication, see Evidence section 2.3.1) 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.

Sleep deprivation. A review of sleep deprivation studies (Giedke and Schwarzler, 2002) concluded that about 60% of patients had improved significantly 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.

2.2.3 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 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).

St John's Wort. 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 (relative risk 1.15, response rate 54% vs. 46%, NNT 12–13), with a much larger effect in small studies of more poorly defined depression (response rate 50% vs. 8%, NNT 2–3). However, since then a further five placebo-controlled trials in major depression of moderate severity have been published (Bjerkenstedt et al., 2005; Fava et al., 2005; Gastpar et al., 2006; Kasper et al., 2006; Uebelhack et al., 2004). Combining these studies with those from Linde et al. (2005) yields a significant pooled benefit over placebo (17 studies, relative risk 1.53, response rate 53% vs. 35%, NNT 5–6). Results are heterogeneous 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, the data suggest short- to medium-term efficacy for standardised extracts of hypericum (in doses between 600 mg and 1800 mg) in major depression with efficacy at least equal 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). Linde et al. (2008) conducted a meta-analysis of 29 trials in major depression, 18 of which were comparisons with placebo and 17 comparisons with synthetic antidepressants. Drop-outs due to adverse effects were less frequent with hypericum than with both TCAs (2.4% vs. 9.8%) and SSRIs (3.6% vs. 6.8%). 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. Omega-3 fatty acids are polyunsaturated fatty acids (PUFAs) that are involved in neuronal, vascular and immune functioning. Eicosapentaenoic 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 (Appleton et al., 2006; Freeman et al., 2006) (ES 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.

The use of S-adenosyl-l-methionine (SAMe) is described in Evidence section 3.2.3, and of folate, L-methylfolate and creatine in Evidence section 3.5.

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 where possible; for example, in cases 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 and previous history of overdose (drugs with lower lethality are to be preferred).

2.3.1 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 or clomipramine may be marginally more effective than other TCAs/SSRIs, and older MAOIs may be less effective than imipramine (I). Venlafaxine, escitalopram and sertraline 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). Indirect comparisons using network meta-analyses have also found marginal efficacy benefits for mirtazapine over other newer-generation antidepressants (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 depression 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). For persistent depressive disorder, indirect comparison using network meta-analyses found benefit of moclobemide and amisulpride versus fluoxetine (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 identified (II).

Comparative efficacy of antidepressants. Although many 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 ongoing 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); issues of selective analysis and company sponsorship; treatment setting; analysis by 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.

The early Danish University Antidepressant Group studies (1986, 1990) found superior efficacy of clomipramine 150 mg/day versus citalopram (40 mg/day) and paroxetine (30 mg/day), although there are some problems with these studies, including the suggestion that the inpatient status and effects on sleep favoured clomipramine (Montgomery et al., 2007). 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 SNRIs (such as venlafaxine, duloxetine and milnacipran) compared with SSRIs. Two meta-analyses of venlafaxine compared with SSRIs with different study inclusion criteria came to different conclusions about relative efficacy, or at least the size and certainty of any effect. Nemeroff et al. (2008) found a small advantage to venlafaxine (34 studies, remission difference 5.9%, NNT 17), only significant against fluoxetine when SSRIs were considered separately. In contrast, Weinmann et al. (2008) 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. A more recent meta-analysis compared both venlafaxine (54 studies) and duloxetine (14 RCTS) with SSRIs and each other (Schueler et al., 2011). Venlafaxine was more effective than SSRIs for response (OR 1.20) but not remission (1.12), at the expense of higher drop-outs due to side effects (OR 1.38). However, the dose of venlafaxine needs to be considered given the possible evidence for a dose–response relationship (Rudolph et al., 1998) and for dual action only at higher doses (above 150 mg) (Debonnel et al., 2007). Duloxetine was not more effective than SSRIs, but had higher discontinuation due to side effects than venlafaxine (OR 1.79). A pooled analysis of two comparative RCTs comparing venlafaxine and duloxetine found no significant difference in efficacy, although response rates were numerically higher for venlafaxine and duloxetine did not meet predefined non-inferiority criteria (Perahia et al., 2008). A meta-analysis of milnacipran compared with SSRIs found no significant difference in response rates (six studies, 60% vs. 57.5% response) (Papakostas and Fava, 2007). It is therefore not possible at present to generalise about relative SNRI, or SNRI vs. SSRI, efficacy.

A 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% vs. 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., 2007b). 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% vs. 62% (NNT 24), although in secondary analysis in severely depressed patients the difference was greater (68% vs. 58%, NNT 10). A Cochrane meta-analysis also found that citalopram was less likely to lead to response (OR 0.67) and remission (OR 0.53) than escitalopram (Cipriani et al., 2009a). Whether these findings will hold up as further studies are done with escitalopram used as a comparator rather than experimental drug remains to be seen.

Cipriani and colleagues published a widely cited study in which RCTs comparing two or more of 12 new-generation antidepressants were pooled using network meta-analyses (Cipriani et al., 2009b). Mirtazapine, escitalopram, venlafaxine and sertraline had higher response rates (50% reduction in clinical ratings) than duloxetine, fluoxetine, fluvoxamine, paroxetine and reboxetine, while reboxetine was significantly less efficacious than all other antidepressants. Calculated ORs using fluoxetine as a standard comparator were sertraline 0.80, escitalopram 0.76, venlafaxine 0.78, mirtazapine 0.73 and reboxetine 1.48 (lower values favour comparator). In addition, escitalopram and sertraline showed fewer discontinuations than did duloxetine, fluvoxamine, paroxetine, reboxetine and venlafaxine, leading to the conclusion from these data that sertraline and escitalopram have the most favourable efficacy to tolerability profile among these drugs. A subsequent meta-analysis assessed 234 studies, of which 118 were head-to-head comparisons (Gartlehner et al., 2011).

From head-to-head studies, they found greater response rates for escitalopram compared with citalopram (OR 1.49), sertraline compared with fluoxetine (OR 1.42) and venlafaxine compared with fluoxetine (1.47).

Since the last guidelines were published, a meta-analysis of all data for the noradrenaline reuptake inhibitor reboxetine, including unpublished studies, has suggested that it is not an effective antidepressant (Eyding et al., 2010). Remission rates were no better than placebo (OR 1.17) and worse than for SSRIs (fluoxetine, paroxetine and citalopram; OR 0.80). Withdrawals due to adverse events were also higher than for fluoxetine (OR 1.79). However, another meta-analysis found no difference in efficacy between reboxetine and SSRIs (Papakostas et al., 2008). More recently, a RCT comparing reboxetine and citalopram found that the difference in efficacy between reboxetine and SSRIs disappeared when differential non-adherence was accounted for (Wiles et al., 2014). Nevertheless, the uncertainty about efficacy and the poorer overall tolerability suggests that routine use of reboxetine should be avoided, but does not preclude a trial of the drug in patients unresponsive to primarily serotonergic antidepressants.

In summary, conclusions about the relative efficacy of antidepressants vary depending on: whether drugs are considered individually or grouped by class/pharmacology; whether dosing is taken into account for drugs with dose–response relationships; whether one uses head-to-head studies, meta-analyses or indirect comparison via network meta-analysis; and which treatments are used as comparators. Head-to-head comparisons suggest there are likely to be small advantages for clomipramine, venlafaxine, escitalopram and sertraline; other evidence additionally supports small advantages for amitriptyline and mirtazapine. While the magnitude of these differences is likely to be small overall, with large NNTs, in individual patients where maximal efficacy is required (e.g. severely ill or treatment-resistant patients) the differences may be more relevant.

Atypical depression. 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 can improve in response to environmental stimulation) and at least one associated symptom (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 (ES 0.27) with no difference between phenelzine/moclobemide and SSRIs (three studies, ES 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 nortriptyline 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.

Seasonal depression. 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).

Melancholic depression. 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; Heiligenstein et al., 1994; Joyce et al., 2003; Navarro et al., 2001; Parker, 2002; Parker et al., 2001; Tollefson and Holman, 1993), and we conclude it is insufficient to guide first-line choice of antidepressant.

Psychotic depression. Wijkstra et al. (2010) found in a three-arm double-blind RCT that response rates were higher for the combination of venlafaxine and quetiapine (66%) than for venlafaxine (33%) alone. However, superiority for the combination was not demonstrated in comparison with imipramine alone (52% response rate). A meta-analysis (Farahani and Correll, 2012) found five trials in which acute treatment with an antidepressant–antipsychotic combination treatment was compared with antidepressant monotherapy (N=337) and four trials comparing it to antipsychotic monotherapy (N=447). The combination treatment was superior on efficacy measures against both monotherapies (NNT 7 vs. antidepressant monotherapy and NNT 5 vs. antipsychotic monotherapy). Discontinuation rates and reported side-effect rates were similar, except for more somnolence with antidepressant–antipsychotic co-treatment versus antidepressants. Longer-term studies of combination treatment are lacking. Nevertheless, the evidence is now sufficient to recommend what is most clinicians' current practice, namely the use of an antidepressant–antipsychotic combination for the acute treatment of psychotic depression. Also, there is some evidence that TCAs might be more effective than newer antidepressants (Wijkstra et al., 2006).

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). A more recent study reported a correlation between mifepristone plasma concentration and clinical response (Blasey et al., 2011). However, although patients with trough mifepristone plasma concentrations greater than 1660 ng/mL were significantly more likely to have a rapid and sustained reduction in psychotic symptoms than those who received placebo, the study failed to demonstrate efficacy on its primary end point.

Persistent depressive disorder. Kriston et al. (2014) undertook a network meta-analysis of interventions for patients meeting criteria for persistent depressive disorder in DSM-5. In total, 28 drug trials, 15 trials of psychological therapies and five of

combination therapies were identified (>8000 participants for efficacy analyses). Response rates were significantly higher than placebo for fluoxetine (OR 2.9), paroxetine (3.8), sertraline (4.5), moclobemide (7.0), imipramine (4.5), ritanserin (2.4), amisulpride (5.6) and acetyl-l-carnitine (5.7). Pairwise comparisons showed advantages of moclobemide (OR 2.4) and amisulpride (OR 1.9) over fluoxetine. Interpersonal psychotherapy with medication outperformed medication alone in chronic major depression but not in dysthymia. Evidence on CBASP plus medication was inconclusive. Interpersonal psychotherapy was less effective than medication (0.48) and CBASP (0.45).

Symptom profile. 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 suggested a lack of clinically important differential effects. However, the large GENDEP study randomised 800 individuals to a noradrenergic antidepressant (nortriptyline) or a serotonergic one (escitalopram) (Uher et al., 2009c). Using symptom dimensions as opposed to total depression scale scores, escitalopram was more effective on mood and cognitive dimensions and nortriptyline on neurovegetative symptoms (including sleep disturbance, appetite loss and libido). This was taken to suggest that drugs acting on both serotonin and noradrenaline reuptake were more likely to be of benefit in those with more neurovegetative symptoms as part of their depressive syndrome.

Comorbid psychiatric disorder. While psychiatric comorbidity predicts a generally poorer response to antidepressant treatments (e.g. Trivedi et al., 2006b), 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). Depression combined with anxiety (anxious depression) has been found to respond less well to citalopram in the first step of the STAR*D study (Fava et al., 2008). However, a large RCT found no difference in outcomes of treatment with escitalopram or nortriptyline between anxious and non-anxious depression or depression with and without comorbid anxiety disorders when baseline depression severity is controlled for (Uher et al., 2011). A meta-analysis of 10 RCTS of anxious depression found that response rates were slightly greater following SSRI than bupropion treatment for both depression (65.4% vs. 59.4%; NNT 17) and anxiety (61.5% vs. 54.5%; NNT 14) (Papakostas et al., 2008). Thus, if anxiety does impair outcomes of antidepressant treatment, there are few indications that one type of antidepressant is notably more effective than another, and the NNTs of those differences found are of small clinical relevance in most circumstances (Akkaya et al., 2006; Sir et al., 2005). An exception may be 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).

Gender. The apparently straightforward question as to whether gender influences response to different types of antidepressants is complicated by age, menopausal status and tolerability considerations (e.g. Kornstein et al., 2000). The literature on this is inconsistent. While some small to medium studies do suggest that younger women in particular may respond preferentially to SSRIs over noradrenaline reuptake inhibitors (TCAs, maprotiline, duloxetine, reboxetine) (Baca et al., 2004; Berlanga and Flores-Ramos, 2006; Joyce et al., 2002; Kornstein et al., 2000; Martenyi et al., 2001) and women responded better to citalopram in STAR*D than did men (Young et al., 2009), other studies have found no such effect (Khan et al., 2005b; Kornstein et al., 2006; Quitkin et al., 2001, 2002; Thiels et al., 2005; Uher et al., 2009a; Wohlfarth et al., 2004). Some of the observed effects may be accounted for by poorer tolerability of TCAs in younger women (Baca et al., 2004; Joyce et al., 2002; Kornstein et al., 2000). 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. Khan et al., 2005b; Kornstein et al., 2000), but the lack of gender difference seen in several large studies of SSRIs, including a study of sertraline treatment in over 5000 patients (Thiels et al., 2005; Trivedi et al., 2006b; Uher et al., 2009a) argues against a clinically relevant effect. Results are inconsistent as to whether men respond better than women to TCAs (Quitkin et al., 2001, 2002; Wohlfarth et al., 2004). One retrospective analysis of 1746 patients reported that women responded better to MAOIs than men (Quitkin et al., 2002).

Pain. Pain symptoms are common in depression (Ohayon and Schatzberg, 2003) and have been associated with poorer response to treatment and an increase in suicide rate in some studies (Bair et al., 2004; Karp et al., 2005; DeVeaugh-Geiss et al., 2010), but the effect was nullified by controlling for baseline depression severity, socioeconomic status and demographic factors, suggesting that pain in itself is not a causal factor (Leuchter et al., 2010). 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; Lee et al., 2007; Perahia et al., 2006).

Biological and other markers of response. A variety of biological predictors of response to specific antidepressants have been proposed, including plasma amino acid concentration and synthesis (Ji et al., 2011; Moller et al., 1986; Porter et al., 2005), dexamethasone suppression test (Benkelfat et al., 1987; Rihmer et al., 1985) or other endocrine markers (Juruena et al., 2009), cerebrospinal fluid monoamine metabolites (Timmerman et al., 1987), inflammation (Cattaneo et al., 2013), neuroimaging markers (Wise et al., 2014), EEG measures (Iosifescu, 2011) and a variety of molecular genetic markers (Taylor et al., 2010). None has yet provided results that have been sufficiently replicated

in independent samples, or that are suitably practical or reliable enough to be useful clinically.

2.3.2 Tolerability/safety considerations. ***Summary: Older TCAs and the newer SNRIs are less well tolerated than SSRIs as assessed by treatment discontinuation in RCTs, though the differences are small (I). There are significant differences in the pattern of adverse effects between antidepressants (I–II), with the main group differences being: TCAs and noradrenaline reuptake inhibitors – antimuscarinic side effects, dizziness and sweating; SSRIs/SNRIs – gastrointestinal, stimulatory and sexual side effects; 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 are associated with a small (<1%) increase in non-fatal suicidal ideation/behaviour in adolescents/younger adults 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).

Some antidepressants can increase the QTc interval (I) and, if possible, avoidance of their co-prescription with other drugs that may lengthen the QTc is advised (IV). Prescribers should be aware of potential drug interactions including liver enzyme inhibition/induction and SIADH (S)

General issues. 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 to interpret given the different side-effect profiles. A review of antidepressant meta-analyses that assessed 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 drop-outs 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 meta-analysis of 29 studies in the elderly found a similar result (Mottram et al., 2006), and there is generally an increased rate of drop-outs in the elderly compared with younger adults (Anderson, 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, drop-outs (Gartlehner et al., 2005). However, subsequent meta-analyses have found slightly greater rates of discontinuation due to adverse effects on venlafaxine compared with SSRIs (De Silva et al., 2012; Nemeroff et al., 2008; Schueler et al., 2011; Weinmann et al., 2008).

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 agomelatine, bupropion, reboxetine, mirtazapine, nefazodone (n.b. nefazodone discontinued in several countries in early 2000s due to concerns of hepatotoxicity) moclobemide and vortioxetine (Clayton et al., 2003; Gregorian et al., 2002; Kennedy et al., 2008; Langworth et al., 2006; Montejo et al., 2001, 2010; Thase et al., 2005).

It has been suggested that in some patients SSRI treatment may be associated with emotional blunting such that both positive and negative emotions are experienced less intensely. However, it is not easy to distinguish this possibility from the effects of depression itself. If SSRIs do produce emotional blunting, alternative, less serotonergic medications, may be helpful (Corruble et al., 2013; Price et al., 2012).

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 drop-outs 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 (Anderson, 2001; Leinonen et al., 1999; 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), though there are concerns about its dose-dependent prolongation of the QTc interval (discussed later).

Studies with duloxetine have reported both equal and poorer tolerability compared with SSRIs (Hudson et al., 2005; Khan et al., 2007; Lee et al., 2007; Perahia et al., 2006; Wade et al., 2007),with the largest and most recent meta-analysis reporting a higher discontinuation rate due to adverse events for duloxetine (Schueler et al., 2011). However, duloxetine has been reported to cause 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., 2008). Overall the data indicate that SNRIs have slightly poorer overall tolerability, as assessed by discontinuation rates due to side effects, than SSRIs.

Since the last guidelines, two new antidepressants have been released. Agomelatine is an MT1/MT2 agonist and 5HT2C antagonist (Servier Laboratories Limited, 2012). It can cause liver function test (LFT) elevation and there have been reports of hepatotoxicity but with no fatal outcomes. LFT elevation tends to occur in the first few months of starting treatment and enzyme levels usually return to normal after the drug is stopped. Agomelatine is contraindicated in patients with hepatic impairment. It is recommended that LFTs are checked when initiating agomelatine and at 3 weeks, 6 weeks, 3 months and 6 months after starting treatment and whenever clinically indicated (Servier Laboratories Limited, 2012). LFTs should be checked at the same time intervals if the dose is increased. Treatment should be stopped if transaminase levels exceed three times the upper limit of normal or if a patient develops symptoms or signs suggestive of hepatic injury. A review of clinical trial data indicated that the frequency of transaminase elevation (>3 times the upper limit of

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

Drug	Action	Side effect								Inhibition of hepatic enzymes	Lethality in overdose
		Anti-cholinergic[a]	Sedation	Insomnia/ agitation	Postural hypotension	Nausea/ gastro intestinal	Sexual dysfunction	Weight gain	Specific adverse effects		
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	–	–	+	–	++	++	–		–	?low
bupropion[b]	?DRI+NRI	–	–	+	–	–	–	–	increased seizure potential	–	? moderate
Receptor antagonists											
trazodone	5-HT_2 + α_1 > SRI	–	++	–	++	–	–	+	priapism	?	low
nefazodone	5-HT_2 > SRI	+	+	–	+	+	–	++		++	low
mianserin	5-HT_2 + α_1 + α_2	+	++	–	–	–	–	–		?	low
mirtazapine	5-HT_2 + 5-HT_3 + α_2	–	++	–	–	–	–	++		–	low

(Continued)

Table 5. (Continued)

Drug	Action	Side effect								Inhibition of hepatic enzymes	Lethality in overdose
		Anti-cholinergic[a]	Sedation	Insomnia/ agitation	Postural hypotension	Nausea/ gastro intestinal	Sexual dysfunction	Weight gain	Specific adverse effects		
Monoamine oxidase inhibitors											
phenelzine, tranylcypromine, isocarboxazid	Irreversible	+	+	++	++	+	++	++	hypertensive crisis with sympatheto-mimetics, oedema	?	high
moclobemide	RIMA	–	–	+	–	+	–	–		–	low
Other											
agomelatine	M + 5-HT_{2C}	–	+	+	–	+	–	–	Requires LFT monitoring	–	?
vortioxetine	SRI + 5-HT_3 + 5-HT_7 + 5-HT_{1B} + 5-HT_{1A}	–	–	–	–	++	+/–	–		–	?

NRI: noradrenaline reuptake inhibitor; SRI: serotonin reuptake inhibitor; DRI: dopamine reuptake inhibitor; 5-HT_{1A}: 5-HT_{1A} agonist; 5-HT_{1B}: 5-HT_{1B} partial agonist; 5-HT_2/5-HT_{2C}: 5-HT_2/5-HT_{2C} antagonist; 5-HT_3: 5-HT_3 antagonist; 5-HT_7: 5-HT_7 antagonist; α_1/α_2: α_1 antagonist/α_2 antagonist; M: melatonin agonist; RIMA: Reversible inhibitor of monoamine oxidase-A.

++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.

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 ideally in the original SPCs, or in a suitable reference book such as the British National Formulary (Joint Formulary Committee, 2014).

the normal range) is 1.4% with 25 mg daily and 2.5% with 50 mg daily (Servier Laboratories Limited, 2012).

Other than its hepatic effects, agomelatine appears to be well tolerated. The summary of product characteristics (SPC) states that hyponatraemia has not been reported and that agomelatine has a neutral effect on heart rate, blood pressure and body weight. There is no evidence of a withdrawal/ syndrome on abrupt cessation (Goodwin, 2009), and as such there is no need for tapering on stopping the drug (Servier Laboratories, 2012). Agomelatine showed a lower rate of treatment-emergent sexual dysfunction than venlafaxine with an equivalent remission rate (Kennedy et al., 2008). A low rate of sexual dysfunction was also noted in an 8-week healthy volunteer study in which the rate of sexual dysfunction with agomelatine was similar to that seen with placebo but lower than that seen with paroxetine (Montejo et al., 2010). This design avoided the confounding effect of depression on sexual function. Agomelatine is not associated with weight increase.

A meta-analysis of efficacy studies identified 20 trials with 7460 participants in the published literature, four from the European Medicines Agency file, and five from the manufacturer (Taylor et al., 2014). Agomelatine was significantly more effective than placebo with an effect size of 0.24 and relative risk of response 1.25. Compared with other antidepressants, agomelatine showed equal efficacy. Published studies were more likely than unpublished studies to have results that suggested advantages for agomelatine. A Cochrane review (Guaiana et al., 2013) came to similar conclusions, with agomelatine showing similar efficacy to SSRIs and venlafaxine; its tolerability was superior to venlafaxine and generally the same as SSRIs. However, another meta-analysis using placebo-controlled studies found a mean benefit for agomelatine of only 1.5 points on the HDRS, and a non-significant effect on relapse prevention, casting some doubt on the clinical significance of these effects (Koesters et al., 2013). There is no evidence of efficacy in the elderly and the manufacturers state the drug should not be used in the over-75s.

Vortioxetine is a serotonin transporter (SERT) blocker with a strong affinity for several serotonergic receptors (Alvarez et al., 2014). It is an antagonist of the 5-HT3 and 5-HT7 receptors, a partial agonist of 5-HT1B, and an agonist of the 5-HT1A receptor. Overall, its combined action on SERT and four subtypes of serotonergic receptors increases the extracellular concentration of serotonin, dopamine and noradrenaline.

Vortioxetine is indicated for the treatment of major depressive episodes in adults (European Medicines Agency, 2014). The starting and recommended dose is 10 mg vortioxetine once daily in adults less than 65 years of age. Depending on individual patient response, the dose may be increased to a maximum of 20 mg vortioxetine once daily or decreased to a minimum of 5 mg vortioxetine once daily. The SPC notes that patients treated with vortioxetine can abruptly stop taking the medicinal product without the need for a gradual reduction in dose. Regarding efficacy, 12 clinical trials have been carried out, nine of which had positive results versus placebo. When active comparators were included in the study design, no significant differences were found except in one study in which the efficacy of vortioxetine was superior to the comparator (agomelatine) in depressed patients who had failed to respond adequately to SSRI/SNRI treatment. Tolerability studies indicate that the drug does not appear to cause any clinically significant effects on blood biochemistry, vital signs or electrocardiography. The lack of weight gain and the lack of significant effect on QTc, if confirmed in routine clinical use, would be clinically important. At a dose of 10 mg vortioxetine daily the incidence rate of sexual dysfunction is low and similar to placebo. At higher doses the usual picture of SSRI-induced sexual dysfunction emerges. Vortioxetine produces positive effects on tests of cognitive function; whether it is more beneficial than SSRI treatment in this respect remains to be directly demonstrated.

The effect of antidepressants on cognition is of interest. Both "hot" (emotion laden) and "cold" (emotion independent) cognitive dysfunction is found in depression (Roiser and Sahakian, 2013; Roiser et al., 2012). Katona et al. (2012) reported a study in elderly major depressive disorder where vortioxetine (5 mg/day) showed superiority to placebo in cognition tests of speed of processing, verbal learning and memory. McIntyre et al. (2014) reported the effects of vortioxetine 10 and 20 mg/d vs. placebo on cognitive function and depression in adults with recurrent moderate to severe major depressive disorder. They found that vortioxetine significantly improved objective and subjective measures of cognitive function in adults with recurrent major depressive disorder and suggest that these effects were largely independent of its effect on improving depressive symptoms.

Suicidality. 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 (Fergusson et al., 2005; Gunnell et al., 2005) with 477 and 702 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 754 and 684 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).

An analysis of 61 placebo-controlled trials of paroxetine in adults showed that for all disorders combined there were no significant differences in the incidence of overall suicidality (i.e. suicidal behaviour plus suicidal ideation) between paroxetine and placebo (Carpenter et al., 2011). A higher incidence of suicidal behaviour was seen with paroxetine compared with placebo in all indications in those aged 18–24 years (2.19% vs. 0.92%). In contrast, no increase in suicidality was seen in older age groups. A higher incidence of suicidality was seen with paroxetine versus placebo in an analysis restricted to major depression, though this was largely explained by the higher incidence in young adults.

In order 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 6 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 the same pattern was also seen with psychological treatments and in primary care (Simon and Savarino, 2007). Ecological data have also failed to find any link between SSRI use and higher completed suicide rates in adults and children/adolescents (Gibbons et al., 2005, 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 show 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). Several naturalistic studies have shown that overall suicide rates have decreased as antidepressant prescriptions have increased (e.g. Gusmão et al., 2013), although these studies are not able to make causal links.

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. Suicidality requires careful monitoring during antidepressant therapy, particularly early on in treatment in younger adults.

Toxicity in overdose. Antidepressant drugs are involved in 10–20% of drug poisoning deaths in England and Wales (Cheeta et al., 2004; Morgan 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. An alternative measure of toxicity is the case fatality rate, which is calculated by dividing the mortality rate by the non-fatal self-poisoning rate (Hawton et al., 2010). The case fatality rate is less prone to selective prescribing than the fatal toxicity index. A recent study, based on UK prescriptions data and deaths (2003–2006 data), plus local data on non-fatal overdoses, showed that within this sample the fatal toxicity and case fatality indices provided very similar results (Hawton et al., 2010).

A number of studies have examined the fatal toxicity index in England and Wales between 1993 and 2002 (Buckley and McManus, 2002; Cheeta et al., 2004; Hawton et al., 2010; Morgan et al., 2004). In cases where only antidepressants were mentioned, TCAs and MAOIs had the highest toxicity, with about a 10- to 27-fold increase over SSRIs. Within the TCA-related group there was a wide range of toxicity; the rank order differs somewhat between analyses, but there is a consensus that desipramine (now withdrawn in the UK) and dosulepin (dothiepin) have particularly high toxicity, lofepramine relatively low toxicity and clomipramine intermediate. Venlafaxine and mirtazapine have toxicities substantially less than TCAs as a group but higher than that of SSRIs as a group (Hawton et al., 2010). Systematic data are not available for duloxetine or agomelatine (SPC) but spontaneous reports of adverse drug reactions suggest that both drugs have low toxicity in overdose. Of the SSRIs, citalopram is associated with a greater tendency for cardiac toxicity than other SSRIs in overdose (Isbister et al., 2004). In the study by Hawton et al. (2010) the relative fatal toxicity of citalopram was approximately twice that seen with SSRIs as a group, though it was still less than half of that seen with mirtazapine and venlafaxine and approximately a tenth of that seen with TCAs as a group (see Table 6). 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; and 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 wholly, attributable to patient characteristics, and possible mechanisms include cardiotoxicity, seizures, serotonin syndrome/muscle toxicity and central nervous system 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).

QTc prolongation. The QTc interval is the heart rate-corrected QT interval measured on electrocardiogram (ECG) that represents the time between the onset of electrical depolarisation of the ventricles and the end of repolarisation. The degree of QTc prolongation caused by a drug is a surrogate marker for its ability to cause torsade de pointes, a polymorphic ventricular arrhythmia that can progress to ventricular fibrillation and sudden death (Haddad and Anderson, 2002). In 2011 the Medicines and Healthcare Products Regulatory Agency (MHRA) issued a warning about the QTc prolonging effect of citalopram and escitalopram and set new maximum daily dose restrictions and contraindications (Medicines and Healthcare Products Regulatory Agency, 2011). For citalopram, the new reduced maximum doses introduced in 2011 were 40 mg for adults, 20 mg for patients older than 65 years and 20 mg for those with hepatic impairment. For escitalopram, the maximum daily dose for patients older than 65 years was reduced to 10 mg/day but for younger adults the maximum dose remained 20 mg/day. The MHRA recommendations were prompted by various data including double-blind placebo-controlled ECG studies that showed both citalopram and escitalopram were associated with a dose-dependent increase in the QTc interval from baseline. These data are supported by a more recent pharmacovigilance study that used records from a US healthcare system to investigate the effect of various antidepressants on the QTc interval (Castro et al., 2013). In this study, escitalopram, citalopram and amitriptyline

Table 6. Relative toxicity index of antidepressants (data from Hawton et al., 2010).

	Both genders	
	Rate ratio (95% CI)	Relative toxicity index[a]
TCAs		
Amitriptyline	8.6 (7.8–9.5)	1.0
Clomipramine	12.5 (8.9–17.0)	1.4
Dosulepin	23.3 (21.4–25.2)	2.7
Doxepin	22.5 (14.1–34.0)	2.6
Imipramine	12.8 (8.3–18.9)	1.5
Nortriptyline	11.0 (3.6–25.5)	1.3
Trimipramine	14.2 (7.8–24.3)	1.7
All seven TCAs	13.8 (13.0–14.7)	1.6
SNRI: Venlafaxine	2.5 (2.0–3.1)	0.29
NaSSA: Mirtazapine	1.9 (1.1–2.9)	0.22
SSRIs		
Citalopram	1.1 (0.8–1.4)	0.12
Fluoxetine	0.3 (0.2–0.5)	0.03
Fluvoxamine	0	0
Paroxetine	0.3 (0.1–0.5)	0.03
Sertraline	0.4 (0.2–0.S)	0.05
All five SSRIs	0.5 (0.4–0.7)	0.06

[a]index of toxicity relative to amitriptyline.

had a dose-dependent effect on QTc prolongation. In contrast, bupropion was associated with QTc shortening while seven other antidepressants (fluoxetine, paroxetine, sertraline, nortriptyline, duloxetine, venlafaxine and mirtazapine) had no significant effect (Castro et al., 2013).

The MHRA (2011) guidance specified that citalopram and escitalopram should not be prescribed to patients with congenital long QT syndrome, known pre-existing QT interval prolongation, or in combination with other medicines that prolong the QT interval. The last point is particularly relevant given the frequent co-prescription of SSRIs with antipsychotics; antipsychotics vary in their ability to prolong the QTc interval, but most have the potential to cause some degree of QTc prolongation (Haddad and Anderson, 2002; Leucht et al., 2013). If the combination is clinically indicated then it is recommended that a baseline ECG is reviewed first. In clinical practice the situation may be more complicated. Zivin et al. (2013) have reviewed outcomes in a cohort of US veterans who received a prescription for citalopram (N=618,450) or sertraline (N=365,898). Citalopram daily doses >40 mg were associated with lower risks of ventricular arrhythmia (adjusted hazard ratio=0.68) and all-cause mortality (adjusted hazard ratio=0.94) compared with daily doses of 1–20 mg, with no increased risk of cardiac mortality found. Citalopram daily doses of 21–40 mg were also associated with lower risks of ventricular arrhythmia (adjusted hazard ratio=0.80) compared with the lower dosage. Given that higher doses of sertraline were similarly associated with a lower risk of ventricular arrhythmia, it does suggest the possibility that depression itself is a risk factor for adverse cardiac events and that its successful treatment is associated with improved mortality rates. Another recent paper (Thase et al., 2013) reviewed cardiovascular effects of escitalopram (5–20 mg/day) versus placebo in over 3000 patients. The mean difference from placebo in the QTc was considered clinically insignificant (3.5 ms for all escitalopram doses, 1.3 ms for 10 mg and 1.7 ms for escitalopram 20 mg). Only one out of 2407 escitalopram patients had a QTc interval >500 ms and a change from baseline >60 ms. Rates of cardiac adverse events were similar between patients treated for 8–12 weeks with placebo (2.2%) or escitalopram (1.9%) and for 24 weeks with placebo (2.7%) or escitalopram (2.3%). As a result, concerns about QTc alone should not prevent effective use of citalopram and escitalopram in patients for whom these drugs are indicated. If using them in doses above MHRA-recommended levels, in patients at risk or in combination with other drugs that may have an effect on QTc such as antipsychotics, then it is recommended that a baseline ECG is reviewed before a change in dose or starting the combination, soon after it is started and subsequently after any significant dose increase, or change in drugs. It is also worth remembering that other antidepressants (e.g. TCAs) may increase the QTc interval and that this issue is not unique to citalopram/escitalopram.

Drug interactions. The older MAOIs and TCAs are the antidepressants with the greatest potential for drug interactions due to their broad receptor profiles and in addition the ability of MAOIs to cause irreversible inhibition of monoamine oxidase. MAOIs can interact with a wide range of medications and foodstuffs. Hypertensive crisis can occur with indirect sympathomimetic agents and foods containing tyramine. The interaction of MAOIs with serotonergic agents, including other antidepressants, can cause serotonin toxicity (Flockhart, 2012). Both forms of interaction can be fatal (see Joint Formulary Committee (2014) for precautions regarding MAOI use). The risk of drug and dietary interactions is lower with moclobemide than with the older MAOIs by virtue of moclobemide being a RIMA. However, serotonin toxicity can still occur. Generally, serotonin toxicity occurs when two or more drugs that increase serotonergic transmission, particularly by different mechanisms, are co-prescribed. Symptoms occur on a spectrum of severity ranging from mild to fatal, and this is predictable from the pharmacology of the drugs involved. Most severe cases of serotonin toxicity that involve antidepressants involve MAOIs. Most modern antidepressants have selective receptor profiles and so less potential for pharmacodynamic interactions than the older TCAs and MAOIs.

Antidepressants differ in their effects on the cytochrome system. A pharmacokinetic drug interaction can occur if an antidepressant that inhibits a cytochrome enzyme is co-prescribed with a drug that is a substrate of the same isoenzyme, particularly if the co-prescribed drug has a narrow therapeutic index. Among modern agents, citalopram, escitalopram, venlafaxine, mirtazapine and reboxetine cause minimal inhibition of cytochrome isoenzymes and have a low risk of pharmacokinetic interactions. Fluvoxamine strongly inhibits CYP1A2 and CYP2C19 and fluoxetine and paroxetine strongly inhibit CYP2D6. Duloxetine and bupropion are moderate inhibitors of CYP2D6, as is sertraline (Spina et al., 2008). Where there are concerns about the potential for such interactions, we recommend consulting specialist advice.

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 and the individual drug SPCs. Some other considerations are addressed in Evidence section 5.

2.3.3 Other factors related to antidepressant choice. ***Summary: Giving patients a choice of treatment does not improve outcomes, but considering patients' preferences improves treatment adherence and may improve outcomes (II). Useful pharmacogenetic predictors of response to 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. Four studies incorporating a patient preference arm comparing antidepressants (Peveler et al., 2005) or antidepressants with psychological interventions (Chilvers et al., 2001; Hegerl et al., 2010; 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% vs. 35%, NNT 6) and patients exercising preference had earlier improvement in another (Lin et al., 2005). One study showed that patients often do not follow through with their stated preference when they are making treatment choices (Hegerl et al., 2010; Mergl et al., 2011). Matching between stated pre-treatment preferences and allocated treatment was associated with better outcomes in some studies (Chilvers et al., 2001; Mergl et al., 2011).

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 and these have not found consistent differences between different drugs (Peveler et al., 2005; Serrano-Blanco et al., 2006; Simon et al., 1999b).

Pharmacogenetics has the potential to produce a highly accurate test that only needs to be carried out once in individual's lifetime and could be used to personalise treatment selection, if replicable clinically significant genetic predictors of antidepressant response are identified (Uher et al., 2012). To date, no such predictor has been identified. Initial efforts have focussed on candidate genes believed to be important in antidepressant action. Serotonin transporter length polymorphism has shown some weak consistent effects across studies, but a meta-analysis concluded that these are likely due to publication bias (Taylor et al., 2010). Other pharmacodynamic candidate genes, including monoamine receptors, neurotrophic factors and genes involved in glucocorticoid signalling, have also been non-replicated when they were systematically investigated in large samples (McMahon et al., 2006; Uher, et al., 2009b, 2011). Functional variants in genes encoding drug-metabolising enzymes (e.g. cytochromes CYP2D6, CYP2C19) have been found to predict plasma levels of antidepressant drugs, but have no useful relationship to treatment outcome (Huezo-Diaz et al., 2012; Peters et al., 2008). More recent studies have searched the entire human genome for variants that might predict response to antidepressants. Two negative meta-analyses of over 3000 individuals with genome-wide data and prospectively recorded response to antidepressants suggest that common genetic variants with clinically significant effects on antidepressant efficacy are unlikely to exist (GENDEP investigators; MARS investigators; STAR*D investigators, 2013; Tansey et al., 2012). Based on this evidence, it is unlikely that a genetic test could improve treatment of depression in the near future.

Studies have now moved on to investigate using gene expression measurement (blood mRNA); results from the GENDEP sample have been somewhat more promising, suggesting that higher expression of inflammatory genes is associated with lack of response (Cattaneo et al., 2013; Powell et al., 2013). Further research will establish the reliability and clinical utility of any such findings.

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 (O'Reilly et al., 1994; Pare and Mack, 1971), 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 management

2.4.1 Optimising outcome. In Evidence section 1.4 we considered the method of service delivery; here we focus on individual prescribing practice. While outlining the important factors in the knowledge base needed by prescribers, we reiterate the views of expounded by a prominent UK psychopharmacologist in the British Journal of Psychiatry that "successful prescribing in psychiatry requires a collaborative and reflective clinical relationship characterised by continuity as well as warmth, kindness and hope." (Cowen, 2011).

Summary: Accurate diagnosis is important to optimise choice of therapies (IV). 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), although this risk seems largely confined to those under 25 years old (II). Improved adherence with antidepressants can be achieved by interventions which 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 doses (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 2 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). Complex or treatment-resistant cases may benefit from referral to specialist centres (IV).

Accuracy of diagnostic assessment. Making an accurate longitudinal diagnosis in order to distinguish accurately between unipolar and bipolar depression is important. The BRIDGE study reported rates of bipolarity among those presenting with an ongoing episode of major depressive disorder, and found that 16% met formal DSM-IV criteria for bipolar disorder, but many more had some sub-syndromal features of bipolar disorder (up to 47% on some definitions) (Angst et al., 2012).

The International Society for Bipolar Disorders (ISBD) Task Force Report on Antidepressant Use in Bipolar Disorders concluded that the evidence that patients with bipolar depression benefit from antidepressants is poor (Pacchiarotti et al., 2013). However, it is acknowledged that individual bipolar patients may benefit from antidepressants. They also suggest that SSRIs and bupropion have lower rates of manic switch than tricyclic and tetracyclic antidepressants and SNRIs. Because the frequency and severity of antidepressant-associated mood elevations is greater in bipolar I than bipolar II disorder, antidepressants should be prescribed only as an adjunct to mood-stabilising medications in bipolar I patients.

There are few studies to guide the management of patients with sub-syndromal bipolar symptoms. In STAR*D, a poor antidepressant response was not associated with many sub-syndromal bipolar features, including: family history of bipolar disorder; presence of at least one of six "manic-like" symptoms in the last 6 months; a history of early onset, short-duration or highly recurrent depression; or a composite measure of sub-syndromal bipolar features (Perlis et al., 2011). However, some features were associated with a poorer response, including pre-treatment irritability or agitation, atypical depression features or at least one "psychotic-like" symptom in the last 6 months. Further analysis suggested that many sub-syndromal features were independent of each other rather than representing a common syndrome. Supporting this, a polygenic score that indexes genetic risk for bipolar disorder was not associated with treatment outcome in two large samples including STAR*D (Tansey et al., 2014). These data do not address the issue of whether alternative treatment strategies (such as mood stabilisers) may be more effective in those with sub-syndromal bipolar symptoms. In addition, longitudinal data suggest that those who respond poorly to antidepressants have a higher likelihood of later being diagnosed with bipolar disorder. In two large Taiwanese cohorts followed-up for 8 years, the rates of a change in clinical diagnosis from unipolar to bipolar disorder were 25.6–26.6% in those who were initially categorised as "difficult to treat" based on antidepressant response, compared with 6.8–8.9% in those who were categorised as "easy to treat" (Li et al., 2012). There remains much clinical uncertainty in this area.

DSM-5 now includes a mixed features specifier which seeks to quantify manic symptoms present in patients with depression and depressive symptoms in (hypo)manic patients and will thus better describe "bipolar spectrum" patients. The mixed symptom feature specifier applies to major depressive disorder as well as bipolar disorder, and will potentially provide information about responses to antidepressants in major depressive disorder patients with some manic symptoms.

In addition to the failure to recognise bipolarity, other factors associated with a poor response to treatment include a failure to accurately characterise the presence of psychotic or atypical features within the presentation, or of anxiety disorder comorbidity. As noted in the previous section, the presence of these features may have a significant impact on the efficacy and choice of therapies. Finally, DSM-5 now includes an anxious distress specifier, acknowledging the potential modifying role of anxiety on response to treatment.

Frequency of monitoring. 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 was a greater number of follow-up visits (Posternak and Zimmerman, 2007), 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 and Savarino, 2007; Simon et al., 2006b), 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, Jr. et al., 1991). Whether there is benefit from using standardised symptom ratings as opposed to a clinical global impression of depression severity/improvement has not to our knowledge been directly tested, but the former have been integral to interventions improving outcome and have formed the basis of guidance about when to implement treatment changes (critical decision points).

Adherence. Although patients report that educational materials are somewhat helpful (Robinson et al., 1997), 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 recent systematic review identified 12 studies of delivering adherence interventions via pharmacists, with most studies showing a benefit although no formal meta-analysis was undertaken (Al-Jumah and Qureshi, 2012).

A meta-analysis of 22 studies found no difference in either the efficacy or the number of drop-outs 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 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.

Older people may if anything adhere more closely to antidepressant treatment than their younger counterparts, though cognitive impairment, absence of a carer and lack of information about drug treatment and possible side effects may decrease treatment adherence (Maidment et al., 2002). A small RCT of a psychoeducational intervention to increase treatment concordance suggests

that this approach may improve treatment outcome (Higgins et al., 2004).

Dosing. 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 drop-outs (six studies, NNH 11) (Furukawa et al., 2002a). 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 (Revicki et al., 1998; Simon et al., 1995). The case may be different in more severely ill patients, 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., 2002a). 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 drop-outs in RCTs (Anderson, 2000), so that lower doses of antidepressants are usually recommended (e.g. Joint Formulary Committee, 2014). 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.

Onset of antidepressant action. 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 of antidepressant action per se. 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 (Posternak and Zimmerman, 2005b; Stassen et al., 1996; Taylor et al., 2006) and substantial improvement in the first 2 weeks (typically ⩾25–30% reduction) strongly predicts final response (Aberg-Wistedt et al., 2000; Nierenberg et al., 2000; Stassen et al., 1996; 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. In 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, 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.

Plasma level monitoring. Therapeutic drug monitoring is an established procedure for lithium and some anticonvulsants but is rarely used for antidepressants. It potentially has a use 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). Pragmatically, in treatment non-responders plasma levels may help with detecting non-adherence and/or identifying fast-metabolisers, and plasma levels may also help when using especially high doses or complex combinations of drugs with potential pharmacokinetic interactions. Although the correlation between dose and plasma level is often poor, there are now data detailing the expected plasma level ranges for many antidepressants based on large patient samples (Reis et al., 2009).

Specialist services. Management of more complex or treatment-resistant cases of depression can benefit from referral to practitioners with special expertise in affective disorders or tertiary centres of excellence, a practice recommended by NICE (Shepherd et al., 2009). One uncontrolled study of inpatient treatment on a tertiary unit for affective disorders found response rates of 69% in a group of previously highly treatment-resistant patients (Wooderson et al., 2011).

2.4.2 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 drop-outs (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); adding sildenafil (I) or tadafinil (II) for erectile dysfunction, or bupropion 150 mg twice daily for sexual dysfunction (II), in men; and adding bupropion (I) or sildenafil (II) in women. 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 2.3.2), 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). Sexual side effects can be persistent and may be especially relevant for those needing to take medication for the longer term. Using a drug with a lower propensity for sexual side effects or using the interventions described below may be helpful.

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 benzodiazepines. While not testing this indication directly, a Cochrane review (Furukawa et al., 2002b) aggregating nine studies with a total of 679 patients found that those taking a combination of antidepressant and benzodiazepine were less likely to drop out than those taking an antidepressant alone (RR 0.63) and more likely to show improvement in their depression at 1 week (RR 1.63) and 4 weeks (RR 1.38; response rates 63% vs. 38%) (Furukawa et al., 2001). Although the groups were equally likely to experience side effects, those taking adjunctive benzodiazepines were less likely to drop out for this reason (RR 0.53). Balanced against these potential benefits, the main 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 23 RCTs involving 1886 people (Taylor et al., 2013). Both sildenafil (three studies) and tadafinil (one study) use improved sexual functioning in men with antidepressant related erectile dysfunction. There is less evidence for use of sildenafil in women, although one RCT did find positive benefits (Nurnberg et al., 2008). The addition of bupropion 150 mg twice daily (three studies) was effective whereas 150 mg once daily (two studies) was not in improving sexual dysfunction in both men and women. No other augmentation strategies have sufficient evidence of efficacy versus placebo. One study found that switching from sertraline to nefazodone was better than restarting sertraline, but nefazodone is no longer available. While switching to an antidepressant with lower potential for sexual dysfunction would have clear face validity, there are no other randomised comparisons of this strategy.

A study combining data from two RCTs of modafinil augmentation in patients with partial response to SSRIs with persisting fatigue and sleepiness found an improvement of depression and sleepiness over placebo with separation from week 1, 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.

The link between SSRIs and bleeding is discussed below in section 5.2. NICE recommends that SSRIs should not be offered as first line to those taking non-steroidal anti-inflammatory drugs (NSAIDs) or anticoagulant medication, and if SSRIs are ultimately required, they should be given with a *proton pump inhibitor* (PPI).

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' (failure to reach a predefined threshold, varying from 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, 2000). A signal detection analysis of three studies with different antidepressants found that 'non-improvement' (more accurately, failure to reach threshold for '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). In 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 (Mandelli et al., 2007; Sackeim et al., 2006). In all

patients showing no response to treatment after 3–4 weeks of optimised-dose treatment, consideration should be given to moving to next-step treatments (NICE, 2009).

A recent large RCT (n=566) compared an "early switch" strategy – switching from escitalopram to duloxetine at 4 weeks in non-responders – to a "conventional switch" strategy – switching to duloxetine at 8 weeks in non-responders (Romera et al., 2012). Remission rates at 16 weeks were higher in the early switch arm (43.3% vs. 35.6%), although time to remission did not differ.

If a patient has not responded it is also 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 (Mazure et al., 2000; Ronalds et al., 1997), or poor social support (Fekadu et al., 2012), may indicate therapeutic targets for intervention in addition to antidepressants.

Early attempts to "stage" treatment resistance relied largely on the number and type of failed treatments (e.g. Thase and Rush, 1997). More recently, a multidimensional model of treatment resistance has been developed that includes severity and duration in addition to treatment failures; this is a better prospective predictor of short-term (Fekadu et al., 2009a) and long-term (Fekadu et al., 2009b) outcome to treatment.

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 specific switch strategy with some evidence for enhanced efficacy is from an SSRI to venlafaxine (I), although there may be slightly higher remission rates for between-class than within-class switches from SSRIs overall (I). Vortioxetine is more effective than agomelatine in SSRI/SNRI non-responders (II). Switching to an antidepressant with some evidence of slightly higher efficacy may be preferable (IV). For many antidepressants abrupt switching appears safe and well tolerated (II), but for some drugs (e.g. MAOIs to SRIs and fluoxetine to TCA) there are dangerous pharmacodynamic or pharmacokinetic interactions (III).

The best evidence of efficacy in augmentation of antidepressants is for quetiapine, aripiprazole, risperidone and lithium (I). Evidence is less robust for olanzapine, tri-iodothyronine, bupropion, mirtazapine and buspirone (II). There are few direct comparisons between different augmentation strategies, but quetiapine is at least as effective as lithium (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 developing but preliminary evidence of efficacy for augmentation with modafinil, S-adenosyl methionine (SAMe), testosterone (in men with low testosterone levels) and oestrogen (in perimenopausal women) (II). Tryptophan augmentation may be effective (III) although is not always widely available. Data supporting methylphenidate and lamotrigine are weak (II). Augmentation with lithium and atypical antipsychotics is associated with significant side effects (I–II). Management of the more unusual or complex medication regimens may best be undertaken in liaison with specialist services or clinicians with a special interest (III).

In older people the evidence base is much smaller, but overall about 50% of patients respond to switching or augmentation. The best evidence is for lithium augmentation (II). There is also some evidence for venlafaxine and selegiline.

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 (1) increase the dose, (2) switch antidepressant or (3) augment/combine with a second agent. A serious problem is the lack of medium and longer-term efficacy and safety data.

3.2.1 Dose increase. 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). Three large randomised double-blind studies found that raising the dose of sertraline and fluoxetine has no benefit over staying on the original dose (Dornseif et al., 1989, Licht and Qvitzau, 2002; Schweizer et al., 2001). Indeed, the Licht and Qvitzan study reported that raising the dose of sertraline in non-responders at 6 weeks from 100 mg to 200 mg a day under randomised double-blind conditions had a significantly poorer outcome than staying on the lower dose. As higher doses are associated with a greater risk of adverse events and discontinuation effects, raising the dose of these drugs may increase the risk without the benefit of better efficacy. On the other hand, indirect evidence from differential dose studies in non-resistant patients suggests a possible slightly greater efficacy for higher-dose TCAs; 200–300mg imipramine dose equivalent versus standard doses (Adli et al., 2005), venlafaxine (225–375 mg vs. 75 mg, Rudolph et al., 1998) and escitalopram (20 mg vs. 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. A Swedish laboratory has prepared a reference guide to expected plasma levels and dose of common antidepressants (Reis et al., 2009).

3.2.2 Switching antidepressant. 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 (Carpenter et al., 2002; Ferreri et al., 2001). 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 with different methodology, including STAR*D (Rush et al., 2006b), 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% vs. 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% remission rate (McGrath et al., 2006a), although this was not dissimilar to the other antidepressant strategy used for the same level of treatment resistance. A meta-analysis of four randomised clinical trials found that there was a significantly higher remission rate in SSRI non-responders switched to a different antidepressant class (bupropion, venlafaxine and mirtazapine), but the difference was small (28% vs. 23.5%) and the NNT (about 22) unlikely to be clinically important (Papakostas et al., 2008). Since then, another study treated patients, retrospectively assessed as antidepressant treatment resistant, for 4 weeks with either open-label citalopram (⩾40 mg) or desipramine (⩾150 mg) before randomising each arm to either a continuation of that antidepressant or switching to the other for a further 4 weeks (Souery et al., 2011). There was no difference in response during the first 4 weeks, but after the second 4-week treatments phase remitter rates were higher among non-switched patients when pooled together. However, the pre-switch treatment duration was short for a treatment-resistant group, numbers were small in the second phase, and those switched had lower overall antidepressant dosing with longer periods of sub-therapeutic dosing during titration periods. After inadequate response to initial antidepressant therapy (SSRI/SNRI), vortioxetine (10–20 mg/day) was more effective than agomelatine (25–50 mg/day) after 8 weeks (remission 41% vs. 30%, response 62% vs. 47%) (Montgomery et al., 2014).

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 (Ruhe et al., 2006; Wohlreich et al., 2005), 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 SPCs and/or appropriate reference books are consulted such as the British National Formulary (Joint Formulary Committee, 2014) or the Maudsley Prescribing Guidelines (Taylor et al., 2015).

3.2.3 Augmentation and combination treatments. Adding a second agent tends to be called 'augmentation' when the drug is not primarily an antidepressant and 'combination' when two antidepressants are used.

Antipsychotics. The efficacy of certain atypical antipsychotics as augmenting agents has now been firmly established by the developing evidence base, though most studies to date have only looked at short-term efficacy. Two studies of typical antipsychotics did not find any benefit (Anderson, 2003) but a meta-analysis of 16 RCTs (published and conference presentations) of atypical antipsychotic augmentation in patients failing to respond to an antidepressants including olanzapine (five studies), quetiapine (five studies) aripiprazole (three studies) and risperidone (four studies), mostly added to fluoxetine or venlafaxine, showed a benefit for the combination (pooled response 44.2% vs. 29.9%, NNT 9) (Nelson and Papakostas, 2009) with no significant heterogeneity. Discontinuation rates due to adverse effects were 4-fold higher in the augmented versus placebo groups (NNH 17). A caution in interpreting these results is that some studies were not comparisons of augmentation against continuing the original antidepressant.

A more recent meta-analysis identified 14 studies where atypical antipsychotic augmentation of was compared with placebo (Spielmans et al., 2013). Remission and response rates were higher for quetiapine (three studies, remission 36% vs. 23% NNT 9, response 56% vs. 45% NNT 10), aripiprazole (three studies, remission 26% vs. 15% NNT 9, response 37% vs. 22% NNT 7) and risperidone (two studies, remission 24% vs. 11% NNT 9, response 42% vs. 27% NNT 8) than for the olanzapine–fluoxetine combination, with the latter not separating from placebo for response (five studies, remission 23% vs. 16% NNT 19, response 39% vs. 32% NNT 17 [NS]).

In two large published studies olanzapine + fluoxetine tended to be better than fluoxetine, but this combination 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% vs. 30%, NNT 10) and olanzapine (response 40% vs. 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 of aripiprazole augmentation, patients historically not responding to 1–3 previous antidepressants received 8 weeks' open prospective treatment with an SSRI or venlafaxine (Berman et al., 2007). In patients with a prospectively determined inadequate response at 8 weeks, and who continued on the same treatment, aripiprazole was more effective than placebo augmentation (response 34% vs. 24%, NNT 10) and had good tolerability.

Quetiapine is the only atypical antipsychotic licensed for use as an augmentation therapy in the UK. In a study of 446 patients with inadequate response to their current antidepressant, quetiapine XR 300 mg/day augmentation of a mixture of largely SSRI,

SNRI, bupropion or amitriptyline was more effective than placebo augmentation at 6 weeks (El-Khalili et al., 2010). In a large, open head-to-head comparison against lithium augmentation, both quetiapine XR monotherapy (300 mg/day) and quetiapine XR augmentation (300 mg/day) were not inferior on the primary outcome, while the quetiapine augmentation arm showed superiority against lithium augmentation on some secondary outcomes (see below under comparative studies of augmentation regimens). Of note was that quetiapine showed statistically larger falls on the MADRS as early as 4 days, and more benefit on sleep disturbance at end point. However, quetiapine augmentation was associated with more problematic weight gain (8% vs. 3%) and more glucose and lipid abnormalities than lithium.

One problem with the studies of atypicals is the relatively mild degree of treatment resistance, most studies focussing on patients showing inadequate response to one or two antidepressants.

Although there are few comparisons over the full dose ranges, effective doses of atypical antipsychotics when used for augmentation are generally lower than when used to treat psychosis. For quetiapine, one study found that 300 mg did not show greater rates of sustained remission than 150 mg (Vieta et al., 2013), but in another 300 mg was more effective than placebo whereas 150 mg was not (El-Khalili et al., 2010). Recommended dose ranges for aripiprazole are 2.5–10 mg, for olanzapine 2.5–10 mg and risperidone 0.5–2 mg/day (Taylor et al., 2015). There are no direct comparisons between the atypical antipsychotics. Differences in side effects and other actions may be helpful in choosing the most appropriate option on an individual basis. For example, aripiprazole has more activating effects whereas quetiapine has more sedating and anxiolytic effects, and these profiles may better suit individual patients. Furthermore, clinical experience suggests that one atypical antipsychotic may prove effective where another has failed; it is unclear the degree to which modes of action are shared or different between the individual drugs.

Lithium. While modest, there is also reasonably sound evidence supporting lithium augmentation of monoamine reuptake inhibitors; a meta-analysis of 10 small studies in treatment-resistant depression found a response rate of 41% vs. 14 % (NNT 5) (Crossley and Bauer, 2007), with most studies using lithium in the dose range 600—1200 mg. Lithium augmentation as the second stage in a four-step treatment programme in inpatients resulted in a 59% response rate (Birkenhager et al., 2006), but the results were disappointing in the STAR*D study when lithium was added as a third-stage treatment, with only 16% remitting and a 23% rate of discontinuation due to side effects (Nierenberg et al., 2006). Patient characteristics with high comorbidity and greater degree of treatment resistance together with unknown adequacy of lithium treatment (only ascertained in 57% of patients, with a median concentration of 0.6 mmol/L) could have contributed 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% vs. 7%) (Kok et al., 2007). A recent systematic review (Bauer et al., 2014) identified more than 30 open-label studies and 10 placebo-controlled trials of lithium augmentation. The main limitations of these studies have been the relatively small numbers of study participants and the fact that most studies included augmentation of TCAs, rather than newer drugs. Evidence from continuation-phase studies is sparse but suggests that lithium augmentation should be maintained in the lithium–antidepressant combination for at least 1 year to prevent early relapses. Concerning outcome prediction, single studies have reported associations of better outcome rates with more severe depressive symptomatology, significant weight loss, psychomotor retardation, a history of more than three major depressive episodes and a family history of major depression. Further clinical research on the role of lithium potentiation of the current generation of antidepressants is warranted. Of note is that lithium augmentation of SSRIs or venlafaxine is more effective when plasma levels above 0.6 mmol/L are achieved (Bauer et al., 2013).

Thyroid hormone. A meta-analysis of augmentation of TCAs with tri-iodothyronine (T3), 25–37.5 μg, in four small RCTs of treatment-resistant depression found significant benefit with regard to improvement in HDRS score (ES 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 a 2-week study in patients predominantly on SSRIs (Joffe et al., 2006). The STAR*D study found a non-significantly higher remission rate on T3 (25–50 μg) than lithium (23% vs. 16%, NNT 14) with significantly fewer patients discontinuing due to side effects (10% vs. 23%, NNH 8), although it should be noted that lithium levels were not consistently monitored in this study (Nierenberg et al., 2006).

Antidepressant combinations. 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 (1) an SSRI with mirtazapine, reboxetine, bupropion or a TCA, (2) mirtazapine with a TCA or venlafaxine and (3) 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 (Ferreri et al., 2001; Maes et al., 1999; Medhus et al., 1994), 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% vs. 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., 2002). In another RCT mirtazapine plus paroxetine was more effective than either drug alone both as first and second-step treatment (Blier et al., 2009). 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, 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 and pharmacokinetic interactions also complicate interpretation (Taylor, 1995). 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% vs. 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% vs. 27% remission 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% vs. 12%) but led to significantly greater symptom reduction and fewer side effect-related drop-outs (McGrath et al., 2006a). The CO-MED study mentioned earlier (Rush et al., 2011) was not specifically undertaken in a specifically treatment-resistant population, although it was a largely chronically unwell group of patients. There was no advantage of either an escitalopram–bupropion or venlafaxine–mirtazapine combination versus escitalopram–placebo at 12 weeks or 7 months.

Anticonvulsants. 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% vs. 40%, NNT 3) (Barbosa et al., 2003), and a randomised open comparison with lithium found a non-significantly better response to lamotrigine (53% vs. 41%, NNT 9) (Schindler and Anghelescu, 2007). A more recent RCT of lamotrigine added to paroxetine found no advantage for lamotrigine over placebo (Barbee et al., 2011). 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 and pindolol. Buspirone augmentation of SSRIs was not effective in two studies (Appelberg et al., 2001; Landen et al., 1998), 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).

Stimulants. 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% vs. 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). A meta-analysis of the short-term use of modafinil augmentation found four RCTS (n=568) in major depressive disorder, concluding modest benefits in increasing remission rates (OR 1.61) and reducing fatigue and depression (ES 0.35) (Goss et al., 2013). The effects have only been studied in the short term; there remain insufficient data on longer-term use of stimulants.

Other. Other strategies with preliminary evidence for efficacy in treatment-resistant patients are tryptophan addition (although tryptophan is not easily obtainable in many countries), especially to MAOIs (Anderson, 2003) and oestrogen in perimenopausal women (Morgan et al., 2005). In men with depression not responding to antidepressants and who had borderline or low testosterone, a small RCT (n=22) of testosterone gel replacement found an active–placebo difference of 6 points on the HDRS after 8 weeks of treatment (Pope et al., 2003). A meta-analysis of the use of testosterone to treat depression identified seven studies with a heterogeneous study population, but concluded that testosterone replacement is more effective than placebo (response rates 54% vs. 33%), with benefits most apparent in those with low testosterone levels (Zarrouf et al., 2009).

There is also research interest in the ability of a non-anaesthetic dose of the NMDA receptor antagonist, ketamine, to produce a rapid resolution of symptoms in patients with treatment-resistant depression (both bipolar and unipolar) in about 50% of participants. Short-term efficacy has been demonstrated against placebo and against an active comparator midazolam (NNT of 3 vs. midazolam, Murrough et al., 2013a). Two meta-analyses have been published. The first identified nine non-ECT studies including 192 patients with major depressive disorder (Fond et al., 2014), with an effect size for short-term reduction in depressive symptoms of −0.91. Four ECT trials were identified, including 118 patients predominantly with major depressive disorder; receiving ketamine as part of ECT anaesthesia reduced depressive symptoms post ECT (effect size −0.56). McGirr et al. (2015) identified seven RCTs employing an intravenous infusion and one RCT employing intranasal ketamine (149 with major depressive disorder, 34 with bipolar disorder). Remission rates were higher with ketamine relative to comparator (saline or midazolam) at 24 h (OR 7.1, NNT 5), 3 days (OR 3.9, NNT 6), and 7 days (OR 4.0, NNT 6), as were response rates (24 h: OR 9.1, NNT 3; 3 days OR 6.8, NNT 3; 7 days: OR 4.9, NNT 4). However, where studies have performed sequential follow-up, the antidepressant effect usually subsides over the following several days; thus far there is no established means of maintaining the response with oral glutamatergic medications (Aan Het Rot et al., 2012). Repeated intravenous administration of ketamine may be possible (Murrough et al., 2013b) but there are concerns regarding toxicity in chronic use, particularly bladder inflammation. Other more serious adverse effects include transient blood pressure elevation that may require treatment and transient psychotomimetic effects, but no persistent psychosis or affective switches. Few data are yet available as to the possibility of intranasal or oral use of ketamine, and the optimal dosing is not yet established.

A meta-analysis of placebo-controlled augmentation studies for antidepressant non-responsive depression (Turner et al., 2014) identified one small RCT (n=73) of SAMe. SAMe (800–1600 mg/day) was added to SSRI/SNRI medication for 6 weeks

(Papakostas et al., 2010). Response rates (36% vs. 18%; NNT 6) and remission rates (26% vs. 12%; NNT 7) were higher for patients treated with adjunctive SAMe than placebo. Discontinuation and adverse event rates did not differ. An earlier meta-analysis is no longer available, but reports identifying 47 studies investigating SAMe in depression, the majority involving small numbers of patients, and of highly variable quality; it purported to find a benefit of SAMe versus placebo in terms of reduced depressive symptoms (Hardy et al., 2001).

Manipulation of the glucocorticoid system may be of benefit in treatment-resistant depression; somewhat confusingly, both antiglucocorticoid treatment and steroid agonists may have some efficacy (DeBattista, 2006), though generally it is the former that have been studied. 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% vs. 33%, NNT 4) (Jahn et al., 2004). However, a larger study in a naturalistic NHS cohort of refractory patients (n=165 patients; McAllister-Williams et al., 2013), while yet to report fully, found no effect of metyrapone addition to serotonergic antidepressants (Watson et al., 2014). 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), but more data with this treatment are needed. Studies in psychotic depression using mifepristone have been described earlier (see section 2.3.1 above).

There are many other interventions that may be used in specialist centres, and which are regularly revised in publications such as the Annual Maudsley Prescribing Guidelines (Taylor et al., 2015). Table 7 lists some of these additional options not described elsewhere in these guidelines. Also of particular note is the increasing interest in anti-inflammatory strategies as an adjuvant to antidepressants. A recent meta-analysis has found better response and remission rates in patients treated with celecoxib added to a variety of antidepressants (Na et al., 2014), while there is unreplicated evidence from a small trial of benefit of specific anti-inflammatory treatment with the Tumour Necrosis Factor antagonist infliximab in those with raised pro-inflammatory markers (Raison et al., 2013).

Comparative studies of augmentation regimens. Few direct comparisons of augmentation strategies have been undertaken. Bauer and colleagues (2013) randomised patients to 6 weeks of open-label lithium augmentation (target 0.6–1.2 mmol/L; n=229), quetiapine XR augmentation (300 mg/day, n=231) or quetiapine XR monotherapy (300 mg/day, n=228). Both quetiapine arms were shown to be non-inferior to lithium augmentation. Of note was the demonstration that achievement of lithium doses in the target range (0.6–1.2 mmol/L) was more effective than those outside of this range (3 points difference on the MADRS at end point) and that around half of those receiving lithium had sub-optimal plasma levels. A meta-analysis of all EU-licensed drugs that had been studied as augmentation therapies in major depressive disorder found seven studies allowing comparative quantification of response and remission rates (Turner et al., 2014). Treatments identified were add-on antidepressants, quetiapine XR, lithium and SAMe. The main finding was that all classes of add-on interventions were similar in terms of rates of response and remission. The only statistically significant difference was of higher rates of response to SAMe than lithium, remission not having been assessed in the relevant studies. The poor underlying quality of individual trials was highlighted, and the role of SAMe is not yet established (see above).

Table 7. Other rare options for augmentation used in specialist centres only: see Maudsley Prescribing Guidelines for further details (Taylor et al., 2015).

Treatment	Dosing
Amantadine	up to 300 mg/day
Carbergoline	2 mg/day
D-cycloserine	1000 mg/day
Dexamethasone	3–4 mg/day for 4 days
Hyoscine	4 mcg/kg IV
Ketoconazole	400–800 mg/day
Mecamylamine	up to 10 mg/day
Nemifitide	40–240 mg/day subcutaneously
Omega-3-triglycerides	EPA 1–2 g/day
Pramipexole	0.125–5 mg/day
Riluzole	100–200 mg/day
Stimulants: amfetamine; methylphenidate	variable
Tianeptine	25–50 mg/day
Zinc	25 mg/day
Ziprasidone	up to 160 mg/day

Note: these options should be reserved for clinicians with special expertise in affective disorders and after reference to original research articles. The level of evidential support is highly variable and often extremely limited.

Studies in the elderly. In older people the evidence base is much smaller, but overall about 50% of patients respond to switching or augmentation. The best evidence is for lithium augmentation. Based on the very limited available trials, there is also some evidence supporting venlafaxine as more effective than paroxetine and selegiline as more effective than placebo in those elderly patients who have failed to respond to at least two prior antidepressants (Cooper et al., 2011).

3.3 Next-step psychological treatment

Summary: There is some evidence that augmenting with, or switching to, CBT may be effective in antidepressant non- or partial responders (I). In adolescents there may be additional benefit in adding CBT if a switch of medication to another SSRI due to non-response is indicated (I).

As discussed in section 2.2.1, 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. Recently the CoBalT study specifically compared outcomes in 469 primary care patients with at least mild depression (BDI score ⩾14 after 6 weeks of adequate antidepressant treatment) randomised to add-on CBT or TAU (Wiles et al., 2013). The response rate (50% reduction in BDI) at 6 months was 46% in the intervention group and 22% with TAU (odds ratio 3.3, calculated NNT 4). Remission rates were 28% and 15%, respectively (OR 2.3, calculated NNT 7) and the effect size for BDI

reduction was 0.53. The study was not blinded and there was no active control, but does suggest that CBT is of additional benefit in antidepressant non-responders.

It is unclear how CBT compares with other next-step treatments. 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% vs. 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 of follow-up after both treatments had stopped (Kennedy et al., 2003).

In a study of 334 adolescents with depression who had not responded to an SSRI, where all were switched to a second SSRI, the rates of response were higher when this switch was combined with CBT (54.8% vs. 40.5%, NNT 7) (Brent et al., 2008).

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 may be an efficacious treatment (III); however, published data on stereotactic ablative procedures are not controlled, though many hundreds of patients have been evaluated in case series. Early experimental data for DBS have shown promising results from open-label studies of stimulation of the subgenual cingulate, medial forebrain bundle and ventral anterior capsule or ventral striatum. However, two as yet unpublished multicentre RCTs evaluating the efficacy of subgenual cingulate cortex or ventral striatum/ventral capsule DBS were recently discontinued due to reported inefficacy.

The evidence for the general efficacy of physical treatments has been reviewed in Evidence section 2.2.2; here we address their use in depressed patients with treatment resistance where not covered earlier.

Data are mixed as to whether treatment resistance is associated with reduced efficacy of ECT (De Vreede et al., 2005; Husain et al., 2004b; Prudic et al., 1996; Van den Broek et al., 2004), 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., 2006). 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, 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 2.2.2, 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 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 number of cases (reviewed in Morishita et al., 2014). The brain areas which have been targeted in more than one patient include the subgenual cingulate, ventral anterior cingulate, nucleus accumbens, substantia innominata and medial forebrain bundle. In all reports, discontinuation of DBS (whether planned or accidental) produced a rapid return of severe symptoms and in a few cases led to suicide. However, Morishita et al. (2014) note only three controlled trials, two of which were reportedly discontinued due to "inefficacy based on futility analyses".

There are no RCTs nor 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). The largest case series was for stereotactic subcaudate tractotomy (>1300 patients) from which a number of prospective and retrospective studies were published (Bridges et al., 1994). Other targets with good quality data include the anterior cingulate and the anterior capsule.

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, but folate supplementation does not appear an effective treatment strategy (II). SAMe may be an effective adjunction to SSRI/SNRI medication (II) and L-methylfolate to SSRIs (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 of 11 and eight trials conducted, respectively, on patients with major depressive disorder and patients with depressive symptomatology but no diagnosis of major depressive disorder demonstrated significant clinical benefit of omega-3 PUFA treatment compared with placebo (ES 0.56 and 0.22, respectively) (Grosso et al., 2014).

A meta-analysis found that low folate status is associated with depressive symptoms (11 studies, OR 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). However, a recent larger study of 475 non-folate-deficient adults given 5 mg folate or placebo for 12 weeks found no benefits of folate at end point or 25 week follow-up (Bedson et al., 2014). Methyl-folate may be better supported: a pooled analysis from two placebo-controlled trials (n=148 and n=75) of different doses of L-methylfolate used as augmentation in SSRI non-responsive or partially responsive patients found that 15 mg/day for 30 days led to higher response rates (32% vs. 15%, NNT 6) whereas 7.5 mg/day was ineffective (Papakostas et al., 2012).

The evidence supporting the use of SAMe has been described earlier. One small study (n=52 females) of creatine (5 g/day) added on to SSRI treatment at the beginning of treatment (Lyoo et al., 2012) was associated with a greater reduction in depressive symptoms (ES 1.13 at 8 weeks end point). A small study of 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).

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 which, 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 include 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 that 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 with 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 (Kessing and Andersen, 2005; Solomon et al., 2000), residual depressive symptoms (Dombrovski et al., 2007; Kanai et al., 2003; Paykel et al., 1995), 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; McGrath et al., 2006b; Mueller et al., 1999), social stress/poor social adjustment (Kanai et al, 2003; Reimherr et al., 2001) and life events (Ghaziuddin et al., 1990; Paykel and Tanner, 1976). 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; Reynolds 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 (McGrath et al., 2006b; Nierenberg et al., 2004), and early response may in

fact be associated with lower relapse rates (Dew et al., 2001; Linden et al., 1997; Nierenberg et al., 2004). The risk of relapse decreases as the duration of remission increases (Franchini et al., 2000b; Solomon et al, 2000).

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% vs. 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 (Akerblad et al., 2006; Dawson et al., 1998). 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). A more recent meta-analysis of second-generation antidepressants found a pooled relapse on antidepressants of 22% compared with 42% on placebo up to 12 months (Hansen et al., 2008). The protective effect is also seen in older patients (Kok et al., 2011). It should be noted that these meta-analyses tend to pool studies investigating different antidepressants. Although there is no strong evidence of heterogeneity between the individual agents, the difference in acute efficacy should be borne in mind when interpreting the results clinically (Cipriani et al., 2009b). Furthermore, it should not be assumed that a drug which demonstrates acute efficacy will also remain protective in the longer term. Some regulatory agencies require evidence of long-term efficacy in order to grant a marketing authorisation.

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 (Akerblad et al., 2006; Katon et al., 2001). A retrospective study found that SSRIs were associated with slightly more relapse than TCAs or venlafaxine (14% vs. 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 (Bump et al., 2001; Franchini et al., 2000a; Lonnqvist et al., 1995; Montgomery et al., 1998; Walters et al., 1999) 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 after any episode of depression, with persisting benefit from continuing longer 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 a dose response relationship 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). In Geddes et al. (2003), the dose used for relapse prevention in these studies was usually the same as that used for acute therapy. There is little evidence surrounding when or how to discontinue medications.

Meta-analyses of lithium used as prophylaxis found a non-significant advantage for lithium over placebo in unipolar depression (three studies, relapse 40% vs. 63%, NNT 4–5) (Burgess et al., 2001) and no difference compared with antidepressants (six studies, depressive relapse 42% vs. 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. Johnstone et al., 1990; Prien et al., 1984) but more recent studies in treatment-resistant patients responding to lithium augmentation (Bauer et al., 2000) or ECT (Sackeim et al, 2001a) finding 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%/year vs. 1.48%/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: after

1–2 years only 10% of patients on antidepressants remained 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 TCAs 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% vs. 76%, NNT 2–3); patients compliant with continuation antidepressants had a 42% relapse rate (Hollon et al., 2005). Further, 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% vs. 72% in those with five or more previous episodes, NNT 4, but 63% vs. 59% in fewer previous episodes); however, the relapse rate on treatment as usual and in those with fewer episodes appears very high. Mindfulness Based Cognitive Therapy (MBCT) 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) (Ma and Teasdale, 2004; Teasdale et al., 2000). Two meta-analyses of four studies/160 patients (Chiesa and Seretti, 2011) and six studies/593 patients (Piet and Hougard, 2011) confirmed this finding; however, a more recent controlled study did not replicate the effect, although MBCT was more effective in the subgroup of participants with severe childhood trauma (Williams et al., 2014). 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 had not 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% vs. 25%, NNT 5), with numerical but not statistical benefit sustained to 12 months (13% vs. 29%, NNT 7) (Schramm et al., 2007). Relapse-prevention studies with continuation IPT as monotherapy after acute combination treatment with an antidepressant suggest 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% vs. 50%, NNT 4) (Frank et al., 2007). Over 3 years continuation IPT in combination with nortriptyline showed a trend to be better than nortriptyline alone after acute combination treatment (relapse 20% vs. 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 an RCT (37% vs. 32% relapse) (Kellner et al., 2006), which is better than the 65–84% relapse rate seen with patients maintained on placebo (see section 2.2.2). 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., 2006), 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, 2002a, 2006; Franchini et al., 2000b; Schmidt et al., 2002). 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), longer duration of treatment up to about 9 weeks when it appears to plateau (II), 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 and agomelatine 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 reviews by Haddad and Anderson, 2007; Howland, 2010). 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 and 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). Further, antidepressant discontinuation has been associated with an increased risk of suicide (Valuck et al., 2009). 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 paraesthesia, disequilibrium symptoms and tinnitus. 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; Tint et al., 2008). The incidence varies between drugs, and paroxetine and venlafaxine have been associated with high rates whereas fluoxetine and agomelatine appear to have low rates (Goodwin, 2009; Haddad and Anderson, 2007; Tint et al., 2008). The high incidence with venlafaxine and paroxetine, at least in part, relates to their relatively short half-lives (approximately 5 hours for venlafaxine and 11 hours for its active metabolite; 15–20 hours for paroxetine), while the relative lack of discontinuation with fluoxetine is presumably due to its long half-life (48–72 hours and its active metabolite 7–15 days). Agomelatine's low propensity for discontinuation, paradoxically, may relate to its very short half-life (around 1.5 hours) and once-daily dosing. In general, 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). The risk of antidepressant discontinuation may also be associated with the C(-1019)G polymorphism of the serotonin 1A receptor gene (Murata et al., 2010).

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 has been successful (Haddad and Anderson, 2007). Reintroduction 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. An important reason for discontinuation is pregnancy (Petersen et al., 2011) – note that antidepressant discontinuation symptoms have been observed in newborns exposed in utero (Galbally et al., 2009; Hale et al., 2010). 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 a year (Greden, 1993); however, a case-note review of nearly 400 patients followed-up for an average of nearly 3 years suggest that the risk of relapse into a new episode of illness is higher following rapid (1–7 day) versus gradual (14 days or more) discontinuation of antidepressants (Baldessarini et al., 2010).

5 Special considerations

5.1 Age

Special considerations regarding age have been reviewed as far as possible in the relevant sections, in particular Sections 2 and 3 where efficacy of antidepressants and alternative treatments are discussed. There is only limited evidence about next-step treatments in children and adolescents and in the elderly and prevention of relapse in children and adolescents. The elderly may also be particularly prone to specific adverse effects, for example hyponatraemia associated with SSRIs (Jacob and Spinler, 2006).

5.2 Comorbid medical illness

Summary: Antidepressants have small to moderate effects in people with comorbid medical illness (I). Choice of antidepressant should be guided by side-effect profile and potential for interaction with medication for other conditions, as there is no evidence of a differential effect of antidepressants across different medical conditions (I). SSRIs should be considered first line as they are generally better tolerated than TCAs (I). SSRIs modestly increase the risk of upper gastrointestinal bleeding particularly when co-administered with aspirin/NSAIDs (I); in those at high risk of bleeding, use of a non-SSRI or co-prescription of a PPI may be beneficial (II). TCAs may be associated with an increased risk of myocardial infarction (MI) (II). SSRIs, mirtazapine and bupropion do not generally increase the risk of cardiovascular events following MI (I–II).

Recent meta-analyses of RCTs have confirmed that antidepressants have a small to moderate effect in people with comorbid medical illness in the short to medium term (<18 weeks), with NNTs of 6–7 (Rayner et al., 2010). Severity of comorbid medical illness and presence of pain symptoms are associated with poorer response to treatment and higher risk of relapse, and may account for the higher NNT in this group (Bair et al., 2004; DiMatteo et al., 2000; Iosifescu et al., 2004a, 2004b; Trivedi et al., 2012). Greater complexity in diagnosing and assessing depression in people with comorbid medical illness (Von Ammon, 1995) may contribute to the reduced efficacy, by increasing heterogeneity of depression among participants in clinical trials. There is some indirect evidence that TCAs may have a greater effect than SSRIs in this group (Rayner et al., 2010), but when direct comparisons only are considered effect sizes are very similar in TCAs and SSRIs (National Institute for Health and Clinical Excellence, 2009).

NICE guidance for the treatment of depression in adults with chronic physical health problems (CG91) recommends that antidepressants should be reserved for people with (i) moderate to severe depression, (ii) mild depression that complicates the

management of the physical health problem, (iii) subthreshold depressive symptoms that persist for more than 2 years or (iv) subthreshold depressive symptoms or mild depression that persists despite less intensive treatments, such as low-intensity psychological treatments. SSRIs are recommended as first-line treatments due to greater safety and tolerability, with sertraline and citalopram being recommended due to their lower propensity to interact with other drugs. Collaborative care may also be used to overcome the barriers to treatment in people with comorbid medical illness, functional impairment and (i) moderate to severe depression or (ii) persistent subthreshold or mild depression (Step 3 in the stepped care model). Collaborative care, which consists of appointment of a case manager, development of a care plan, organisation of scheduled follow-up and multidisciplinary input, has a strong evidence base. Collaborative care reduces anxiety and depression (Archer et al., 2012), and is cost effective in adults with comorbid medical illnesses such as diabetes (Katon et al., 2008), coronary heart disease (Katon et al., 2012) and cancer (Strong et al., 2008).

Use of antidepressants in subthreshold or mild depression is not recommended due to the poor risk–benefit ratio; low-intensity psychosocial and psychological interventions are more appropriate in the first instance, ideally as part of a stepped care model where low-intensity treatments are tried first and treatment is escalated if symptoms persist or deteriorate. Evidence for the efficacy of psychological therapies in people with comorbid medical illness is mixed, however. Overall, the effects for psychological therapies is small, with most evidence for CBT from trials in coronary heart disease (Baumeister et al., 2011; Bower and Gilbody, 2005; Dickens et al., 2013; Welton et al., 2009; Whalley et al., 2011) and exercise in trials in chronic obstructive pulmonary disease (Coventry et al., 2013). The evidence supporting the use of stepped care is very limited (Bower and Gilbody, 2005), though experience from IAPT services indicate stepped care improves patient flow through services (NICE, 2009).

SSRIs are known to decrease platelet aggregability and activity, and prolong bleeding time with fluoxetine, paroxetine and sertraline the most frequently implicated (Halperin and Reber, 2007); as a result, non-SRI antidepressants should be favoured in patients with bleeding disorders. A recent meta-analysis looked at upper gastrointestinal (GI) bleeding with SSRI use, and found 15 case-control studies (393,268 participants) and four cohort studies (Anglin et al., 2014). There was an increased risk of upper GI bleeding with SSRI medications – OR 1.66 in the case-control and 1.68 in the cohort studies. This was lower than previous estimates, and translated to a NNH for upper GI bleeding of 3177 in a low-risk population and 881 in a high-risk population. As previously, a heightened risk where an SSRI and NSAID were co-prescribed was found (OR 4.25). The risk is not confined to GI bleeding; for example, reports have also suggested an increase in blood transfusion rates after orthopaedic surgery (Schutte et al., 2014). Studies suggest that PPIs decrease the risk of GI bleeds with SSRIs alone or in combination with NSAIDs; thus, Targownik et al. (2009) found that PPI co-prescription reduced the risk of SSRI-associated upper GI bleeding by 60% (OR 0.39). NICE (2009) recommends that SSRIs should not be offered as first line to those taking NSAIDs or anticoagulant medication, and if SSRIs are ultimately required, they should be given with a PPI.

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 2.3.2 for discussion). TCAs have been associated with an approximate doubling in the risk of 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; Sauer et al., 2003) 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., 2005) found no adverse effects on cardiovascular events or safety, with some possible benefit in two (Strik et al., 2000; Taylor et al., 2005). 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. Recent evidence that citalopram and escitalopram cause dose-dependent prolongation of the QT interval has been discussed above (see section 2.3.2). As well as the advice above that where possible these drugs should avoided in people with pre-existing QT prolongation and in combination with other medicines that prolong the QT interval (MHRA, 2001), in cardiac disease ECGs and correction of electrolyte imbalance should be considered before starting treatment.

Psychostimulants (methylphenidate, dexamphetamine, methylamphetamine and pemoline) may be useful for the treatment of depression in certain patients with comorbid medical illness, where (i) a rapid effect is required and (ii) problems with misuse, dependency or withdrawal reactions are not anticipated, for example, in situations of short life expectancy such as in patients with advanced cancer (Candy et al., 2008). Trials have generally been small and of low quality, though there is evidence from three trials (Elizur et al., 1979; Wagner and Rabkin, 2000) (two in patients with comorbid medical illness) that psychostimulants reduce depression (SMD=−0.87) and fatigue (SMD=−1.80) in the short term (⩽4weeks,) and are well tolerated. Effects in the medium term (5–12 weeks) were non-significant and tolerance was reduced. Effects of modafinil on depression, fatigue and hypersomnia were not significant, though there were few trials only.

There have been relatively few clinical trials of specific treatments for depression in older people with comorbid medical illness. A systematic review of the use methylphenidate in this context (Hardy, 2009) concluded that further trials were needed.

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. As a general principle, choosing an antidepressant which is less likely to interfere with the metabolism of other drugs is advisable in patients on multiple medications (see Table 5).

6. Summary and future recommendations

We have summarised above the current evidence base for the guidance we suggest, building upon previous editions of the BAP guidelines in the process. Although there have been a

number of developments that we highlight, we have been struck by the similarities of the present guidelines to those from 2008. Although there are two new antidepressant treatments (agomelatine and vortioxetine) which incorporate some novel mechanisms of action, their efficacy is thought at least partly to rely on activity within the serotonergic system, a factor in common with most of the already available antidepressants. There have been few major advances in the field, though the evidence supporting the use of atypical antipsychotic medication in non-responsive patients is now substantial. In addition, the ability of ketamine rapidly to alleviate depression in treatment-resistant patients is of theoretical interest and may lead to new classes of agents being developed.

The significant changes since the last guidelines were published in 2008 include the availability of these two new antidepressant treatment options, together with improved evidence supporting certain augmentation strategies (both drug and non-drug), management of potential long-term side effects, updated guidance for prescribing in elderly and adolescent populations and updated guidance for optimal prescribing.

However, as is clear from the evidence review, there are many areas in which the evidence base for clear recommendations remains weak. We highlight the uncertainty about treatment in those who have mixed affective features as part of their illness and thus may form part of the "soft" bipolar spectrum, and recommend further research into the extent to which these patients may benefit from mood stabilisers instead of, or in addition to, antidepressants. In a similar vein, we note that some recent treatments have been approved for treatment of "major depressive episodes", and urge that new treatments are evaluated in those whose depressive episodes occur in the context of a diagnosis of bipolar disorder, including bipolar spectrum or bipolar II disorder. Treatment resistance remains poorly understood, and as well as further research on the available next-step options, including head-to-head comparisons of the main drug and non-drug alternatives, we urge further studies of emerging novel targets for treatment, such as inflammatory, glutamatergic and other mechanisms.

But perhaps most important at the present time is the tragedy that many patients continue not to receive any treatment, or to receive inadequate treatment, for their depression. For many this is an avoidable cause of suffering, disability, morbidity and mortality; we hope that these guidelines will help clinicians and service planners in improving and optimising the antidepressant treatment that patients receive.

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Declaration of Conflicting Interests

All attendees completed conflict of interest statements that are held at the British Association for Psychopharmacology office according to BAP policy.

Declarations of the lead authors (Profs Cleare, Pariante and Young) within the last three years are as follows:

No author had patent/s or invention/s from which they may derive personal benefit in the area of psychopharmacology; or had ownership or part ownership of a company with interests in the area of psychopharmacology; or accepted a personal retainer from any company with an interest in psychopharmacology; or acted as an expert witness, either friendly or hostile, to any company with an interest in psychopharmacology; or had membership of the speakers' bureau for any company; or accepted travel or hospitality NOT related to a speaking engagement.

Prof Young (Lundbeck, Roche, Janssen, Sunovion) and Prof Pariante (Servier, Lilly) have acted as a consultant to companies with an interest in psychopharmacology. Prof Young (Lundbeck, Roche, Janssen, Sunovion) and Prof Cleare (Astra Zeneca, Pfizer) have accepted paid speaking engagements in industry supported symposia. Prof Pariante (Janssen) and Prof Cleare (Lundbeck) have held research grants from companies with an interest in psychopharmacology. Prof Young has indirectly been involved in many industry studies as an associate director for the National Institute for Health Research (NIHR) Clinical research Network.

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