

Pharmacological management of depressive disorders

Anthony J Cleare

Roman Duncko

Abstract

This article outlines current guidelines for the pharmacological treatment of depression. For acute treatment of moderate to severe depression in the absence of specific factors, the recommendation is treatment with a selective serotonin reuptake inhibitor or mirtazapine. Other options for acute antidepressant treatment are discussed, and advantages and disadvantages of specific drugs are outlined. Recommendations for next-step treatment for patients with an inadequate response include increasing the dose, switching to another antidepressant, augmentation with another agent or using a combination of antidepressants. Again, recommendations for specific drugs are outlined, and the common advantages and disadvantages of specific drugs are listed in a table format. The options for non-pharmacological treatments are briefly explored in regards to symptom severity and other clinical features, and a list of non-pharmacological treatment options is provided.

Keywords Acute treatment; antidepressant; augmentation; depression; guideline; next-step treatment; recommendation

Diagnosis

A correct diagnosis of a specific depressive disorder and its severity, chronicity and risk factors is crucial for successful management. Clinicians should have a good working knowledge of diagnostic criteria and be watchful for depressive symptoms in vulnerable groups, but there is no evidence of direct benefit from non-targeted screening.¹

Most cases can be managed in primary care. Management should include scheduled follow-up with monitoring of symptoms (ideally using standardized outcome measures) and

Anthony J Cleare BSc MBBS PhD FRCPsych is Professor of Psychopharmacology and Affective Disorders at the Institute of Psychiatry, Psychology and Neuroscience, King's College London, and Consultant Psychiatrist at the Maudsley Hospital, UK. Competing interests: Within the last three years (since July 2013) Prof Cleare has served on advisory boards for Livanova and Allergan, and received grant support from Lundbeck.

Roman Duncko MUDr PhD MRCPsych is Academic Clinical Lecturer at the Institute of Psychiatry, Psychology and Neuroscience, King's College London, and higher trainee in General Adult Psychiatry at the South London and Maudsley NHS Foundation Trust, UK. His research interests include neuroendocrinology and psychophysiology of depression and anxiety disorders, alternative negative emotions in OCD and depression. Competing interests: none declared.

Key points

- Correct diagnosis is crucial for the successful management of depression
- Antidepressant medication is recommended as a first-line treatment for moderate to severe or for chronic depression
- In the absence of specific factors, selective serotonin reuptake inhibitors or mirtazapine are recommended for the acute treatment of depression
- Increasing the dose, switching to another antidepressant, augmentation with another agent and a combination of antidepressants are recommended as 'next-step' treatments

functional recovery, but also focus on adherence to medications. Active case management interventions can be beneficial but are not in widespread use.

Patients should be referred to a psychiatric service if there is a high suicide risk, occurrence of psychotic symptoms or suspicion of bipolar disorder, if there has been insufficient response to treatment and/or if the primary care professional feels insufficiently experienced to manage the case.² In addition, all cases involving a child or adolescent presenting with depressive disorder should be referred to the relevant psychiatric services.³

Acute treatment and management

Antidepressant medication is a first-line treatment for moderate and severe depression and for any depression continuing for 2 years or longer. Antidepressants should also be considered in patients with currently mild depression who have a past history of moderate or severe depression, or where symptoms have persisted for more than 2–3 months. Antidepressants are not recommended as first-line treatment for mild depressive symptoms of shorter duration unless there is a previous history of recurrent moderate to severe depression.² Similarly, pharmacological management is not recommended for children or adolescents with depression unless they suffer from severe symptoms, there has been an insufficient response to alternative treatment and/or there is a past history of recurrent moderate to severe depression.³

Psychological therapies are an alternative first-line treatment for mild to moderate depression, and the combination of medication and psychological therapy is recommended in more complicated cases such as chronic, severe, highly recurrent or treatment-resistant depression.¹

Most antidepressant drugs have broadly similar efficacy, and the choice of specific drug should be based on several factors including the efficacy of drugs on specific symptoms, interaction with other drugs and safety in overdose.¹ In the absence of specific factors, the Maudsley Prescribing Guidelines in Psychiatry⁴ recommend a selective serotonin reuptake inhibitor (SSRI) or mirtazapine as first-line treatment because of better tolerability and safety; however, other drugs can be selected based on

history of previous response or specific effects on symptoms (see Table 1 for details on the benefits and disadvantages of specific drugs).

There are few sufficiently powered head-to-head studies directly comparing different antidepressants, but there may be small benefits for escitalopram, sertraline, venlafaxine, mirtazapine, clomipramine and amitriptyline; in more severely ill patients, and in other situations where maximizing efficacy is of overriding importance, these are recommended in preference.¹ Combination treatment with antidepressant and antipsychotic medication (e.g. venlafaxine with quetiapine) is more effective than monotherapy for the treatment of depression with psychotic symptoms. Other factors affecting the choice of antidepressant include:

- patient preference (particularly for medication versus psychological therapy)
- psychiatric and medical co-morbidity, for example using serotonergic antidepressants for co-morbid obsessive-compulsive disorder or generalized anxiety disorder, and tricyclic antidepressants (TCAs) for chronic pain
- interactions with other medications
- previous response to a particular medication

- effects on specific depressive symptoms, such as appetite or sleep
- adverse effects.

The initial phase of acute management should include reviews every 1–2 weeks assessing the response, adherence to treatment, adverse effects and suicide risk. Mild or transient adverse effects (anxiety, nausea with SSRIs) can be managed by psycho-education. More severe or persistent adverse effects may require a dose reduction, change to an antidepressant with a different adverse effect profile, non-pharmacological management (e.g. diet for weight gain with mirtazapine) or introduction of another medication (short-term benzodiazepines for anxiety, sildenafil or bupropion for sexual dysfunction).¹

Improvement of symptoms is often first noted during the first 1–2 weeks, and treatment options should be reviewed if there are no signs of improvement after 4 weeks.

Next-step treatment for inadequate response

Before deciding about next-step pharmacological treatment (Table 2), it is important to evaluate and *address other factors* that are possibly contributing to the lack of response.¹ These

Examples of advantages and disadvantages of selected antidepressant drugs and their dose range for acute treatment of depression based on the British National Formulary,⁵ British Association of Psychopharmacology guidelines¹ and Maudsley Prescribing Guidelines in Psychiatry⁴

Drug	Group	Advantage	Disadvantage
Recommended as first-line treatment			
Sertraline (50–200 mg/day) Escitalopram (10–20 mg/day)	SSRI	Most favourable efficacy-to-tolerability profile	Nausea, sexual dysfunction As above + possible QT _c prolongation at higher doses
Mirtazapine (15–45 mg/day)	Noradrenergic and specific serotonergic antidepressant	Higher response rates than duloxetine, fluoxetine, fluvoxamine and paroxetine	Adverse effect profile includes sedation and weight gain
Further treatment options if suitable in relation to adverse effect profile, previous responses or patient's preference			
Venlafaxine (75–375 mg/day)	SNRI	More effective than SSRIs	Higher drop-out rates due to adverse effects
Clomipramine (30–250 mg/day) Imipramine (75–300 mg/day) Amitriptyline (75–200 mg/day)	TCAs	Same as or higher efficacy than SSRIs	Less tolerated than SSRIs, higher toxicity in overdose
Phenelzine (45–90 mg/day)	MAOI	More effective for 'atypical depression' (increased appetite/weight gain, increased sleep, severe fatigue) than TCAs	Risk of serious interaction with medications and food
Duloxetine (60 mg/day)	SNRI	More effective than SSRIs for co-morbid pain	Possible lower overall efficacy for depressive symptoms
Agomelatine (25–50 mg/day)	Melatonin (MT ₁ , MT ₂) agonist and 5-HT _{2c} antagonist	Efficacy comparable to SSRIs and venlafaxine	Risk of hepatotoxicity
Vortioxetine (10–20 mg/day)	Serotonin modulator and stimulator	Similar efficacy to SSRI/SNRI medications	Similar tolerability to SSRI/SNRI medications

5-HT, 5-hydroxytryptamine; MAOI, monoamine oxidase inhibitor; SNRI, serotonin–noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Table 1

Next-step drug treatments based on the British Association of Psychopharmacology guidelines¹ and Maudsley Prescribing Guidelines in Psychiatry⁴

Drug	Advantage	Disadvantage
Switch to another antidepressant		
Another SSRI	See Table 1	
Venlafaxine		
Mirtazapine		
Vortioxetine		
Agomelatine		
Consider TCA or MAOI		
Augmentation or combination		
First line		
Quetiapine (150–300 mg/day)	Well tolerated, good evidence	Sedation, weight gain
Aripiprazole (2.5–10 mg/day)	Well tolerated, good evidence	Akathisia, agitation
Risperidone (0.5–2 mg/day)	Well tolerated	Hyperprolactinemia, extrapyramidal symptoms
Lithium (600–1200 mg/day for plasma concentration 0.4–1.0 mmol/litre)	Good evidence	Acute toxicity with narrow therapeutic window, requires plasma level monitoring; thyroid and renal effects
Second line		
Olanzapine (2.5–10 mg/day)	Well tolerated	Sedation, weight gain
Tri-iodothyronine (20–50 microgram/day)	Well tolerated	Requires thyroid function monitoring
Bupropion (up to 400 mg/day)	Well tolerated	Off licence in UK
Mirtazapine (30–45 mg/day)	See Table 1	
Mianserin (30 mg/day)	Well tolerated	Risk of blood dyscrasias
Bupirone (up to 60 mg/day)	Some evidence	Less well tolerated
Others		
Lamotrigine (200–400 mg/day)	Widely used	Risk of rash, requires slow titration
Modafinil (100–400 mg/day)	Rapid effect	Can worsen anxiety
Ketamine (0.5 mg/kg intravenously over 40 minutes)	Rapid effect	Not widely available, possible negative cognitive effects, duration of effect unknown, bladder toxicity

MAOI, monoamine oxidase inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Table 2

Non-pharmacological treatments of depression based on the British Association of Psychopharmacology guidelines¹ and NICE guideline on depression in adults⁴

Treatment	Advantages	Disadvantages
Psychological therapy	Efficacy of cognitive behavioural therapy, interpersonal therapy and behavioural activation is comparable to antidepressants for mild/moderate depression	Requires active engagement of patients, availability can be variable with local services
ECT	Good efficacy, including for severe and treatment-resistant depression, quicker onset than antidepressants	High relapse rates, cognitive adverse effects (usually temporary)
Repetitive transcranial magnetic stimulation	Reasonable evidence, no major adverse effects	Not widely used, less effective than ECT
Vagus nerve stimulation	Efficacy comparable to pharmacotherapy and psychotherapy in open studies	Invasive procedure, not widely used, lack of evidence from randomized controlled trials
Bright light therapy	Reasonable efficacy for seasonal affective disorder	Limited evidence for non-seasonal depression
Supervised aerobic exercise	Can be effective as adjunct to antidepressants	Not recommended as an alternative to antidepressants

ECT, electroconvulsive therapy.

Table 3

include assessing adequacy of dose and treatment adherence, and reviewing the diagnosis, including possible psychiatric or medical co-morbidity, but also considering chronic social difficulties involved in maintaining the symptoms. If the review after 4 weeks of adequate treatment shows some improvement, it is recommended to continue treatment for another 2–4 weeks, but proceed with the next-step treatment if there is insufficient improvement at 6–8 weeks.

Next-step drug treatment can consist of *increasing the dose* in the absence of significant adverse effects and if there has been some improvement, particularly with drugs with established dose–response relationships such as venlafaxine, escitalopram and TCAs, and bearing in mind the lack of good evidence for this strategy with other SSRIs.

Another next-step treatment option is *switching to another antidepressant*. This can be initially within the same antidepressant class (SSRIs), but after more than one failure, switching to a different class is recommended. The strongest evidence of improvement is for switching from an SSRI to venlafaxine, but there are also reports of improved remission rates after switching from SSRIs to bupropion, mirtazapine or vortioxetine and agomelatine. In the absence of potentially toxic interactions (i.e. fluoxetine to TCAs or monoamine oxidase inhibitors (MAOIs) to serotonergic drugs) switching or cross-tapering directly without a washout period is recommended.¹

Further options for next-step treatment are *using add-on therapies* (antidepressant augmentation) or *combining antidepressants*. Augmentation treatments with the strongest evidence are quetiapine, aripiprazole, risperidone (all used in lower doses than for antipsychotic effects) or lithium. The second-line recommendation includes augmentation with olanzapine or triiodothyronine, or combination with bupropion, mirtazapine or buspirone. Further recommended options include adding lamotrigine, modafinil or intermittent ketamine infusions.

Relapse prevention and treatment

The goal of treatment should be full remission of symptoms, given the higher rates of relapse associated with persisting residual symptoms. Because of the increased risk of relapse during the 6 months after recovering from depression, the recommendation is to continue the effective treatment for 6–9 months after the symptoms have improved in all patients. For patients with a higher risk of relapse, it is recommended to continue treatment for 1–2 years or even longer given that recurrence rates are 2–3-

fold lower on long-term maintenance therapy for as long as it is continued.¹

If depressive symptoms deteriorate while the patient is on continuation treatment, review the dose and adherence, as well as possible psychiatric and medical co-morbidity and adverse social factors. Where a patient has stopped antidepressant treatment, this should be restarted at the appropriate dose. Patients experiencing a recent relapse despite continued treatment may benefit from support and monitoring even without changing the medication as relapses are often self-limiting. Patients with persisting relapse may require an increased dose of antidepressant or to proceed with next-step treatments in accordance with the guidance above.¹

Stopping treatment

Abrupt stopping of treatment can result in discontinuation symptoms. Management of these usually mild symptoms should include explanation and reassurance but may require commencement and slower tapering of the used antidepressant or a switch to fluoxetine.⁴

Other treatment options

A detailed discussion is beyond the scope of this article, but the main options are summarized in Table 3. ◆

KEY REFERENCES

- 1 Cleare A, Pariante CM, Young AH, et al. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2008 British Association for Psychopharmacology guidelines. *J Psychopharmacol* 2015; **29**: 459–525.
- 2 National Institute for Health and Clinical Excellence. Depression in adults: recognition and management. Clinical Guideline No. 90. 2009, <http://www.nice.org.uk/CG90> (accessed 17 May 2016).
- 3 National Institute for Health and Clinical Excellence. Depression in children and young people: identification and management. Clinical Guideline No. 28. 2005. Retrieved from, <http://www.nice.org.uk/CG28> (accessed 17 May 2016).
- 4 Taylor D, Paton C, Kapur S. *The Maudsley prescribing guidelines in psychiatry*. John Wiley, 2015.
- 5 Joint Formulary Committee. British National Formulary (online). <http://www.medicinescomplete.com> (accessed 17 May 2016).

TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online [here](#).

Question 1

A 32-year-old woman presented to her GP with a 1-month history of symptoms of moderate depression. There were no signs of increased risk to self or others, no history of previous episodes of

depression and no co-morbid medical or psychiatric conditions. Physical examination was normal apart from a body mass index of 28 kg/m². The patient expressed a preference for pharmacological treatment.

What is the most appropriate next step in her management?

- A. Give advice on a healthy lifestyle and review in 2 months
- B. Prescribe mirtazapine
- C. Prescribe sertraline
- D. Prescribe venlafaxine
- E. Refer for psychotherapy

Question 2

A 50-year-old woman attended for review of treatment for severe depressive symptoms present during the previous year. She had been treated with escitalopram 5 mg/day for the previous 4 weeks and had not experienced any major adverse effects, but there was only minimal improvement in her symptoms. She had had no other medical or psychiatric conditions. Electrocardiography was normal.

What is the most appropriate next step in her management?

- A. Start quetiapine as add-on treatment
- B. Increase the dose of escitalopram
- C. Stop medication and refer for psychotherapy

- D. Switch to mirtazapine
- E. Switch to sertraline

Question 3

A 60-year-old man presented initially to his GP with reduced appetite with weight loss and insomnia. This had followed the death of his wife. His symptoms had persisted for a year. He had attended for counselling to address bereavement with no significant improvement and was not keen on further psychological treatment. He had had previous depressive episodes but had not sought help for these. He had mild osteoarthritis treated with ibuprofen and vitamins.

What is the most appropriate next step in his management?

- A. No need for antidepressant treatment but review in 2 months
- B. Refer for psychotherapy
- C. Start amitriptyline
- D. Start mirtazapine
- E. Start a selective serotonin receptor inhibitor