Pharmacological management of depressive disorders

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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

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

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 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 Psychiatry[4] 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

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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 psychoeducation. 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 or Psychopharmacology guidelines[1] and Maudsley Prescribing Guidelines in Psychiatry[4]

Drug	Group	Advantage	Disadvantage
Recommended as first-line treatment			
Sertraline (50–200 mg/day)	SSRI	Most favourable efficacy-to-tolerability profile	Nausea, sexual dysfunction
Escitalopram (10–20 mg/day)			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 (MT1, MT2) 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