Pharmacological management of unipolar affective disorder

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Abstract

Unipolar affective disorder, or depression, is the one of the leading causes of disability worldwide and its effective management is a high priority. Treatment is required whether or not the illness is seen as 'reactive' to circumstances or understandable. Guidelines for its management have been produced by the National Institute for Health and Clinical Excellence (NICE) and the British Association for Psychopharmacology (BAP). These recommend rating the severity of the illness and using this as a guide for treatment. For less severe depression, antidepressants are recommended only when a patient fails to respond to other interventions or there is a history of more severe depression. For moderate-to-severe depression, antidepressants such as citalopram or fluoxetine are recommended as first-line treatments. The management of treatment-resistant depression (failure to respond to two adequate courses of antidepressants) is complex. NICE includes recommendations to consider augmentation of an antidepressant with cognitive behavioural therapy or lithium, monotherapy with venlafaxine or phenelzine (the latter particularly for atypical depression), and the combination of mirtazapine plus a selective serotonin reuptake inhibitor. BAP guidelines also include consideration of atypical antipsychotic or tri-iodothyronine augmentation of antidepressants. Other strategies have limited data supporting them and are not recommended, or are for use only in specialist centres.

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Keywords antidepressants; depression; mood disorders; monoamine oxidase inhibitors; selective serotonin reuptake inhibitors (SSRIs); serotonin and noradrenaline reuptake inhibitors; tricyclic antidepressants

Unipolar affective disorder, or depression, is the commonest mental health problem seen by both psychiatrists and general practitioners, and is estimated to be the leading cause of disability.[1] Guidelines for the management of depression were published in the UK by the National Institute of Health and Clinical Excellence (NICE) in 2004.[2] These guidelines are currently under revision. More recently, guidelines have been published by the World Federation of Societies of Biological Psychiatry (WFSBP)[3] and the British Association of Psychopharmacology (BAP).[4] This review focuses on the recommendations made by NICE and how these are updated by the BAP. The guidelines described above are an accessible source of references regarding this topic.

When considering the pharmacological management of depression a number of issues need to be addressed; these are considered in turn.

When should antidepressants be used?

Historically, depression was divided into 'endogenous' and 'reactive' types, the former resulting from some underlying biological predisposition of the individual and the latter being secondary to some social stressor. However, there does not appear to be any relationship between response to antidepressant treatment and apparent cause of the depression. As a result, the distinction of endogenous and reactive depression is not felt to be clinically useful and, indeed, can be detrimental as the diagnosis of 'reactive' or 'understandable' depression can result in under-treatment.

NICE recommends that depression be diagnosed using the International Classification of Diseases tenth revision (ICD-10) criteria (Table 1), with severity rated as 'mild' when only four symptoms are present, 'moderate' when five or six symptoms are present, and 'severe' when the patient has seven or more symptoms. The BAP has, however, recommended use of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), which has a higher threshold for diagnosis (see Table 1), with severity assessed by a combination of number of symptoms and the degree of functional impairment.

In general there is agreement between NICE and BAP that, for patients with mild depression, antidepressants are not recommended routinely as first-line treatments. Rather, advice regarding anxiety and sleep management is recommended. Watchful waiting can also be employed; this entails arranging to review the patient again in 1–2 weeks and actively following them up if they do not attend. Guided self-help and supervised exercise programmes may also be helpful. Antidepressants are recommended only for patients who do not respond to the above strategies, or who have a history of more severe depression. For patients with moderate-to-severe depression, or less severe depression that has been unresponsive to other interventions over 2–3 months, antidepressants should be offered as first-line treatments.

Specific psychotherapies (e.g. cognitive behavioural therapy) are recommended for patients who refuse antidepressants or in whom it is essential to avoid side-effect problems.

Symptom checklist for diagnosis of a depressive episode

- Persistent low mood**
- Loss of interest or pleasure**
- Fatigue or low energy*
- Disturbed sleep
- Poor concentration or indecisiveness
- Poor or increased appetite
- Suicidal thoughts or acts
- Agitation or slowing of movement
- Guilt or self-blame
- (Low self-confidence)

ICD-10 requirements for a diagnosis of depression are 4 of the above 10 symptoms for mild depression, 5–6 for moderate depression, and 7 or more for severe depression. Patients must have one of the three symptoms marked with an asterisk. DSM-IV criteria are subtly different. Patients must have at least 5 of the first 9 symptoms (low self–confidence is not included). They must also have at least one of the symptoms marked with two asterisks.

Table 1

Dysthymia (chronic subsyndromal depressive symptoms) is not considered in the NICE depression guidelines; however, the BAP guidelines suggest that antidepressants are the first-line treatment if the risk/benefit ratio is acceptable, based on the likely side effects of the drug and the degree of disability suffered by the patient.

Choice of antidepressant

Generally, all antidepressants are of equal efficacy. As a result, the choice of antidepressant is based on factors other than potency. The relative side-effect burden of the various classes of antidepressants (Table 2), together with the presence of concurrent illnesses and additional medication, needs to be considered. If a patient has previously tolerated, and responded well to, a particular antidepressant, it is wise to consider this drug. In addition, if a close relative has responded well to a particular drug, there may be some value in considering this for the patient. Otherwise there are few indicators of which patient will respond to which drug.

Tricyclic antidepressants

Tricyclic antidepressants (TCAs), particularly the tertiary amine TCAs (Table 2), are often associated with a burden of side effects greater than that of many of the newer antidepressants such as the selective serotonin reuptake inhibitors (SSRIs). Even at low doses, patients can be troubled by anticholinergic side effects. These can be minimized by gradual dose increments until a therapeutic dose is achieved (125 mg amitriptyline equivalence per day or greater). The hypotensive and cardiac effects of TCAs limit their use in the elderly and the infirm, and lead to toxicity in overdose, which generally precludes their use in those at risk of suicide unless there is extremely close supervision. As a result, TCAs – with the exception of lofepramine, which is generally better tolerated and less toxic than other TCAs – are not appropriate first-line treatments in patients with mild or moderate depression, and should generally not be used in primary care. There is some evidence to suggest that the older TCAs, possibly specifically amitriptyline, are more potent than SSRIs, especially in inpatients. Consequently amitriptyline is recommended by the BAP for consideration in severely ill patients.

Selective serotonin reuptake inhibitors

SSRIs tend to be better tolerated than TCAs and so are recommended by NICE as first-line treatments in primary care. Choice between the SSRIs is particularly influenced by pharmacokinetics. Fluoxetine, and its major metabolite norfluoxetine, have long half-lives. As a result the drug reaches a steady state in the body only after around 5 weeks, even though a clinical effect may be seen earlier. An occasional forgotten dose has little effect on plasma concentrations. In addition, if the drug is stopped suddenly, plasma levels will fall gradually over around 5 weeks, preventing any discontinuation phenomena. However, this long period for withdrawal can be problematic if a patient needs to be switched to another drug. Paroxetine has a much shorter half-life and so a switch to an alternative antidepressant can generally be safely done after stopping the drug for just 1 week. However, paroxetine's short half-life also makes it more likely to cause discontinuation withdrawal symptoms (dizziness, nausea, paraesthesia, headaches) if stopped suddenly. Citalopram and sertraline have intermediate half-lives (with washout periods of around 2 weeks) and also have fewer interactions with other medications. NICE specifically recommended fluoxetine and citalopram because these were available in generic form at the time of publication of the guidelines. Escitalopram, the *s*-stereo isomer of citalopram, has evidence for greater potency than citalopram and possibly other SSRIs, and as a result is suggested for consideration in more severely ill patients in the BAP guidelines.

Side effects: SSRIs can cause side effects of increased anxiety and nausea. These symptoms tend to resolve over 3–4 days after drug initiation or dose increment. Increased anxiety can be a particular problem for patients who may already have significant anxiety symptoms as part of their illness. However, it is generally unnecessary to supplement the prescription of a SSRI with a benzodiazepine or other drug with anxiolytic properties. Rather, it is important to counsel patients that anxiety symptoms may initially worsen before improving. Increased anxiety and agitation when starting SSRIs may lead to an increased suicide risk, and so close monitoring is necessary in the early stages of treatment. In the long term, the most prevalent side effect of SSRIs is sexual dysfunction, with decreased drive and arousal plus difficulty reaching orgasm. This is associated with reduced compliance.

Monoamine oxidase inhibitors

Traditional monoamine oxidase inhibitors (MAOIs) (e.g. phenelzine, tranylcypromine) have little role as first- or second-line treatments, owing to their interactions with various drugs and foods. When used, they are often well tolerated, although side effects can be serious (e.g. pulmonary oedema). Tranylcypromine is also the only antidepressant with true addictive