Depression: current approaches to assessment and treatment

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Depressive disorder continues to represent a major burden on global health and the mainstay of treatment remains a range of psychological treatments, such as cognitive behavioural therapy (CBT), and antidepressant drug treatments. Unfortunately, treatment strategies across the board are only modestly effective. Concerns persist over which treatments to deploy in different circumstances, how to optimise their use and how to handle treatment failure.

Here we consider some aspects of current guidance and evidence, recent controversies and potential advances.

Severity of depression and treatment selection

Guidelines emphasise the role of symptom severity in directing treatment planning (see Figure 1), where robust evidence supports treatment of moderate to severe depression with antidepressant drugs (see Tables 1 and 2). However, their efficacy at the milder end of the severity spectrum remains uncertain.

Recent meta-analyses have attempted to assess effectiveness across the severity spectrum but suffer due to either methodological shortcomings or limited data availability. In a very recent review, we found that it is not yet possible to make definitive statements on the efficacy of antidepressants in milder forms of depression: too few studies have directly addressed the issue in adequately defined diagnostic groups of patients with mild disorder. Present guidance thus relies instead on inference from heterogeneous populations.

Assessing severity has also proved less than straightforward. In 2006, the Quality and Outcomes Framework (QOF) introduced incentives to general practices for measuring the severity of depression, endorsing the use of patient-completed questionnaires – the Patient Health Questionnaire (PHQ-9), the Hospital Anxiety and Depression Scale (HADS) or the Beck Depression Inventory-II (BDI-II).

However, it is clear that each of these rating scales measure severity differently in the same populations and that only low-quality evidence exists to suggest that measuring severity (as...
Figure 1. Depression – recommended management and treatment algorithm; IPT = interpersonal therapy
Strategies in mild depression

Practitioners face uncertainty in identifying milder forms of depression and in choosing treatments. NICE guidance advocates nonpharmacological therapy first line, with the caveat that long-standing symptoms, past episodes of depression or significant functional impairment suggest that antidepressants still warrant consideration. A primary-care survey of the prior histories of patients with subthreshold depressive symptoms suggests that many may fall into just such categories and that GPs appropriately treat them with antidepressants.9,10

On the other hand, the Improving Access to Psychological Therapies (IAPT) programme, which has been rolling out across England since 2006, gives some idea of the practical impact of psychological therapies in ‘real-world’ settings. Evaluation has been mixed, with the most recent report indicating that only around half of those referred actually enter treatment and only 20 per cent attend at least two therapy sessions. However, just over half of those (ie approximately 10 per cent of all referrals) who do engage in this way show some evidence of improvement (though outcome measurement was limited and, of course, the placebo response rate is unknown). There is a long way to go before confident assertions can be made in this complex clinical arena.

Are antidepressants overprescribed?

The volume of antidepressant prescriptions has been rising year-on-year around the world. Most recently, for example, the Organisation for Economic Co-operation and Development (OECD) reported that antidepressant use had doubled in the past 10 years among the 34 member nations.12 It is often

<table>
<thead>
<tr>
<th>Co-morbidity</th>
<th>Antidepressant*</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>No co-morbidity</td>
<td>sertraline</td>
<td>consider mirtazapine or short-term benzodiazepine if sedation</td>
</tr>
<tr>
<td></td>
<td>citalopram</td>
<td>required</td>
</tr>
<tr>
<td></td>
<td>fluoxetine</td>
<td></td>
</tr>
<tr>
<td>Older adults</td>
<td>citalopram</td>
<td>consider lower starting dose</td>
</tr>
<tr>
<td></td>
<td>mirtazapine</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>fluoxetine</td>
<td>sertraline is the drug of choice post-MI</td>
</tr>
<tr>
<td></td>
<td>sertraline</td>
<td>avoid tricyclics</td>
</tr>
<tr>
<td>Hepatic impairment</td>
<td>citalopram</td>
<td>dose reduction may be necessary</td>
</tr>
<tr>
<td></td>
<td>paroxetine</td>
<td>avoid fluoxetine and lofepramine</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>citalopram</td>
<td>dose reduction may be necessary</td>
</tr>
<tr>
<td></td>
<td>sertraline</td>
<td>avoid fluoxetine, lofepramine and venlafaxine</td>
</tr>
<tr>
<td>Severe renal or hepatic disease</td>
<td>seek specialist advice</td>
<td></td>
</tr>
<tr>
<td>Epilepsy</td>
<td>citalopram</td>
<td>avoid tricyclics – seizure risk related</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>fluoxetine</td>
<td>consider withdrawal in third trimester</td>
</tr>
<tr>
<td></td>
<td>(consider risk</td>
<td>avoid paroxetine</td>
</tr>
<tr>
<td></td>
<td>benefit ratio)</td>
<td>refer to NICE CG45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>consider specialist advice</td>
</tr>
<tr>
<td>Breast feeding</td>
<td>sertraline</td>
<td>refer to NICE CG45</td>
</tr>
<tr>
<td>Sexual dysfunction</td>
<td>mirtazapine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>reboxetine</td>
<td></td>
</tr>
<tr>
<td>Children and adolescents under 18 years</td>
<td>fluoxetine</td>
<td>consider specialist advice</td>
</tr>
</tbody>
</table>

* see Table 2 for minimum effective doses

Table 1. Choosing an antidepressant (from Cornhill Medicines Group, NHS Grampian, 2010)
assumed that rising prescription volumes must indicate antidepressant overprescription and lay media reports in particular suggest that practitioners are prescribing too readily.

However, raw prescription rates do not indicate how many people are being treated or why. It has been shown that diagnostic rates are not rising but rather that duration of treatment is increasing. Small changes in the quality of antidepressant treatment can have large effects on prescription rates: doubling the duration of antidepressant treatment doubles the prescription volume – without changing the number of patients being treated.

As the study indicates, most patients are receiving an inadequate duration of therapy (often less than one month rather than the recommended minimum of six); the gradual improvement in this state of affairs over the years is the principal source of rising prescription volumes. Thus if antidepressants are being used effectively the rise in prescription volume is unavoidable.

The use of antidepressants for indications beyond mood disorder also contributes to elevated prescription rates. In Scotland the use of amitriptyline increased over 20 per cent in the last few years and now accounts for nearly a third of all patients taking an antidepressant. Amitriptyline is now rarely used in the treatment of depression, however, but is commonly given in the management of neuropathic pain.

Recent changes in classification

NICE guidance on the management of depression now makes reference to the Diagnostic Statistical Manual (DSM) for the diagnosis of depression; the fifth version was launched in May 2013 among significant controversy, and there has been widespread concern about the widening of diagnostic categories. How has depression fared?

The DSM-5 criteria for a major depressive episode are outlined in Table 3. Neither the nine symptom criteria nor the two key symptoms have altered from those specified in DSM-IV. Similarly, the two-week time period, when symptoms are required to be present, remains the same.

What has changed is the removal of the ‘bereavement exclusion’. Previously, for a diagnosis of a major depressive episode to be made, individuals were required not to be bereft within two months. This exclusion has been removed, recognising that bereavement does not apply to a fixed period and acknowledging that loss is a stressor that may precipitate a major depressive episode. The symptoms are not due to the direct physiological effects of a substance or a general medical condition of a substance or a general medical condition.

Also of note is the removal of the diagnostic category ‘dysthymia’. Instead, this is now categorised as ‘persistent depressive disorder’, which incorporates the former ‘chronic major depressive disorder’.

It seems unlikely that these changes will have a significant impact on the treatment of depression.

Treatment failure and resistance

Failure to respond to antidepressants is common in depressive disorder, with perhaps only one-third achieving full remission after initial treatment with an SSRI and one-half showing

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>Minimum effective dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>citalopram</td>
<td>20mg daily</td>
</tr>
<tr>
<td>fluoxetine</td>
<td>20mg daily</td>
</tr>
<tr>
<td>paroxetine</td>
<td>20mg daily</td>
</tr>
<tr>
<td>sertraline</td>
<td>50mg daily</td>
</tr>
<tr>
<td>mirtazapine</td>
<td>30mg daily</td>
</tr>
<tr>
<td>reboxetine</td>
<td>8mg daily</td>
</tr>
<tr>
<td>venlafaxine</td>
<td>75mg daily</td>
</tr>
</tbody>
</table>

Table 2. Minimum effective doses (from the Maudsley Prescribing Guidelines)

5 (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least 1 of the symptoms is either 1 or 2. Symptoms should be present most of the day or nearly every day.

1. depressed mood
2. markedly diminished interest or pleasure in all, or almost all, activities
3. significant weight loss when not dieting or weight gain (eg a change of more than 5% of body weight in a month), or decrease or increase 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 or guilt about being sick)
8. diminished ability to think or concentrate, or indecisiveness (either by subjective account or as observed by others)
9. recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning

The symptoms are not due to the direct physiological effects of a substance or a general medical condition.

Table 3. DSM-5 criteria for major depressive disorder (adapted from the American Psychiatric Association)
Ensuring treatment adequacy is, however, a key element in optimising outcomes even at the earliest stages. It is obviously important to ensure that the diagnosis is correct, taking account of co-morbid conditions (including substance misuse) and to ensure that treatments are being used as directed. As noted, duration of treatment is a key factor, with many patients receiving courses of antidepressants that are too short to be effective. Equally, though, it should be recognised that failure to show any response after four to six weeks predicts treatment failure in the longer term, so regular early review and assessment is necessary to plan ‘next-step’ treatment at the right time.

There is little evidence that increasing the dose of an SSRI enhances outcomes in depression (though venlafaxine and tricyclics may show such dose-dependent effects).

The value of CBT in poorly responsive patients as an adjunct to treatment with antidepressant drugs was recently demonstrated in a large multicentre trial in primary care. Patients who had not responded to six weeks of antidepressant treatment were assessed at six months having been randomised to either treatment as usual (TAU), or TAU plus CBT. Half of the patients receiving TAU plus CBT had responded, while only one-fifth of those receiving TAU met response criteria.

**Onset of action**

The ideal antidepressant drug of the future would not only result in higher response rates than current medication – it would also act faster. Though antidepressants display pharmacological and psychological effects within hours, they have a noticeable delay in the onset of their therapeutic action (typically two to four weeks). This delay is important, not only because patients continue to suffer but because they may also decide to alter or stop taking their treatment as a result.

We know that faster onset of action is achievable – electroconvulsive therapy can act more quickly in depression than any antidepressant drug – but the treatment is invasive, associated with significant side-effects and requires hospitalisation.

Yet drugs with rapidly acting antidepressant properties may have been with us for some time: recent studies indicate that the dissociative anaesthetic ketamine and the muscarinic receptor antagonist scopolamine (hyoscine) not only share antidepressant action but can act within hours rather than weeks.

Neither drug has proven to be a practical treatment to date – they both have significant side-effects and their antidepressant activity may not be sustained – but investigation of their common molecular effects (each acting on excitatory amino acid systems and synaptogenesis) may prove to be the blueprint for novel agents with mechanisms of action quite unlike those of traditional antidepressants.

**Conclusion**

Depression is common and heterogeneous and uncertainties persist regarding the choice of effective treatments, particularly for milder presentations. Concerns about increases in prescribing volumes of antidepressants are unwarranted since this has mainly been a result of improvements in prescribing practices. Where depression is unresponsive to treatment, augmenting antidepressant therapy with CBT has been demonstrated to be an effective strategy.

Recent changes to the classification of depression in DSM-5 are unlikely to change treatment choices.

**References**


**Declaration of interests**

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