Management of treatment-resistant depression

A guide for GPs

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Inadequate response to antidepressants or psychological interventions is not uncommon among patients seen in clinical practice. This article reviews possible biological and psychosocial causes of poor response in people with depression and discusses options for management.

The impact of depression is vastly underestimated. It silently robs individuals not only of their ability to enjoy the simple daily pleasures of life, but moreover affects their capacity to engage with family and friends, and to contribute to their workplace and broader community.

At a national level, the Australian National Survey of Mental Health and Wellbeing reported that major depressive disorder (MDD; unipolar depression) affected at least 4% of Australians over a year and led to these people being unable, or less able, to carry out their usual activities for six days per month.[1] Internationally, the Global Burden of Disease Study reported major depression to be the fifth leading cause of disability.[2] Furthermore, depression is associated with a significantly increased mortality rate (at about 70% above usual rates) due to physical conditions such as cardio- and cerebrovascular disease, as well as high rates of suicide.[3]

KEY POINTS

- Initially ensure that patients with depression have received an adequate dose and duration of appropriate treatment, be that antidepressants and/or psychological treatment.
- Review 'treatment-resistant' patients for possible causes of a poor response to treatment.
- There are a number of well-studied treatment options for patients who do not respond to initial simple antidepressant treatments.
- As some of the options recommended in this article are not widely used in primary care, GPs should have a low threshold for referring such patients to a psychiatrist experienced in difficult-to-treat depression.

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Many depressed patients do not respond well to treatment

A guide to the treatment of depression has been recently published in *Medicine Today* and will not be replicated here.[4] Rather, this article will focus on an approach to the assessment and treatment of depressed patients who do not respond well to standard treatments; that is, those with treatment-resistant depression (TRD).

SUMMARY OF STEPS FOR CLINICAL ASSESSMENT OF A PATIENT WITH SUSPECTED TREATMENT-RESISTANT DEPRESSION

- Clarify whether the patient is truly treatment resistant
- Confirm whether major depressive disorder is the primary diagnosis
- Check whether the patient is on medications that may be contributing to depression
- Assess whether the patient has relevant comorbid conditions that need to be addressed
- Investigate whether the patient has unresolved psychosocial issues

The benefit of treatments for depression is measured either in terms of rates of response (i.e. those whose symptoms improve by at least 50%) or rates of remission (i.e. those with no or minimal remaining depressive symptoms). As those who respond may still have significant persisting levels of depression, there is an increasing focus on remission rates, as this is what matters to patients and their families.

The most comprehensive study of remission rates with a selective serotonin reuptake inhibitor (SSRI) antidepressant followed by a structured series of subsequent treatments has been the US Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial.[5] This large outpatient study found that only one-third of the 3671 enrolled subjects with depression remitted with the SSRI citalopram, with a further one-third responding after trials of up to three further treatment steps. In other words, one-third of acutely depressed patients did not remit, even after potentially receiving four treatment options. The study reflected the common experience in clinical practice of high rates of inadequate improvement with standard treatments for depression.

The impact of such persisting depression is profound. A US commercial-claims database reported that those who had failed to respond to at least two adequate courses of treatment had higher rates of overall healthcare resource use and more work-loss days.[6] A study of a Swedish national register found that those with TRD had higher mortality rates than other patients with depression, with an increased all-cause mortality rate of 1.35, and mortality rates due to suicide and accidents that were particularly high, at 1.97.[7] These statistics are not surprising, because patients who repeatedly fail to respond to courses of treatment become increasingly demoralised and despondent.

It should be emphasised here that some patients with depression who are apparently treatment resistant do ultimately remit – seemingly spontaneously – after months or years of unsuccessful treatment, reflecting the underlying episodic and recurrent nature of this condition.

Defining treatment-resistant depression

There have been various approaches to defining TRD, with most predicated on the number of adequate courses of antidepressants to which the patient has failed to respond. The most common definition is a failure to respond to at least two such antidepressant courses. One major limitation of these definitions is the lack of recognition of the place of appropriate psychological treatments in the treatment of depression.

More sophisticated approaches to TRD recognise that there are dimensions of treatment resistance. A number of structured clinical approaches to measuring the degree of treatment resistance have been developed, with the Maudsley staging method being one of those more commonly used.[8] In a recent article, a 'TRD staging' system was suggested based on different management approaches to those who fail to respond to two adequate courses of antidepressants or psychological treatments ('stage 1 TRD') as opposed to those who fail to respond to three or more such courses ('stage II TRD').[9] The authors proposed that those with higher levels of resistance may require more invasive or higher-risk treatments (such as deep brain stimulation). This approach to managing TRD is outlined below.

In response, others have argued that this approach proposes too low a threshold for higher-risk treatments. They have instead suggested the concept of 'multiple-therapy- resistant major depressive disorder', whereby nonstandard interventions would be considered only for MDD patients who fail to respond to multiple courses of psychotherapy, antidepressants, augmenting strategies and electroconvulsive therapy (ECT).[10] I agree that the proposed threshold for using invasive or higher-risk treatments is much too low, and would potentially lead to excessive use of such treatments.

Causes of treatment resistance

No biological differences have been consistently reported in patients who develop treatment resistance, although brain changes related to small vessel disease have been implicated in reduced responsiveness to antidepressant treatments in older patients (so-called vascular depression).[11] A recent large study in the Netherlands found that older age in general was a strong determinant of worse outcome in MDD, although the potential factors underlying this association (biological, psychosocial and socioeconomic) were not able to be elucidated.[12]

Clinical assessment

For simplicity, I will define TRD in this article as failure to respond to at least two adequate courses of antidepressant treatment – either pharmacological or psychological. The following steps (summarised in the Box) can be worked through to assess a patient in whom TRD is suspected:

- Clarify whether the patient is truly treatment resistant, i.e. that they have received and tolerated adequate courses of treatment. For antidepressants, this comprises adequately high doses for at least four to six weeks. On a detailed history, many patients with apparent TRD

have either not tolerated or have not received adequate treatment courses in terms of either dose or duration, i.e. they are pseudoresistant. Many patients do not take the recommended amount or duration of medications (e.g. not collecting repeat prescriptions). Furthermore, some courses of psychological treatment are not adequate in duration – patients may need more than the commonly used six sessions of cognitive behavioural therapy (CBT).

- Confirm whether MDD is the primary diagnosis; that is, exclude other psychiatric conditions such as bipolar disorder and schizophrenia or relevant physical disorders such as Parkinson's disease, hypothyroidism or frontal lobe dementia that may each either mimic the psychomotor agitation or slowing of MDD or be true 'organic' causes of depression.[13] Also ensure that the patient is truly suffering from MDD as distinct from being upset about a life event, and that their unhappiness is not an element of the mood variation that can be seen with personality disorder, particularly borderline personality disorder, without necessarily being depressed at all.
- Check whether the patient is on medications that may be contributing to depression, such as steroids, isotretinoin or interferon.
- Assess whether the patient has relevant comorbid conditions that need to be addressed, such as anxiety, substance use disorders or personality disorder.
- Investigate whether the patient has unresolved psychosocial issues such as ongoing relationship, employment or financial problems, unresolved grief or domestic violence.

For many patients, the most effective option is to address any of the relevant issues detailed above, in addition to pursuing appropriate physical treatments for depression. I would emphasise that these are not mutually incompatible choices.

Management options

For more detail of the treatment options listed below, and the evidence base supporting them, the relevant articles could be read.[14,15] It should also be noted that although the following clinical options each have a supporting evidence base, there have been no definitive head-to-head comparative studies to guide the clinician about which options are the most effective (such as switching versus augmentation). Further, as some of these options are not widely used in primary care, the GP should have a low threshold for referring such patients to a psychiatrist experienced in difficult-to-treat depression.

Optimise the adequacy of the current treatment

Before switching or augmenting treatment it is crucial to optimise current treatment as follows:

- Ensure that the patient has received and tolerated an adequate dose of an antidepressant and/or an adequate course of appropriate psychological treatment. Exclude poor adherence with antidepressants, which is common in practice.
- If the patient has tolerated an adequate course, gradually increase

the dose to higher levels within the range approved in the TGA product information.
- For patients who are highly sensitive to antidepressant side effects or do not respond to multiple adequate antidepressant courses, it may be worthwhile undertaking genetic testing of relevant hepatic enzymes such as the cytochrome P450 family, to exclude possible genetic poor metabolisers or ultra-rapid metabolisers.[16] The place of such genetic testing to assist in the choice of antidepressants in routine clinical care is currently considered controversial.[17]

Switch antidepressants

There is no evidence that switching to an antidepressant of a different class (e.g. moving from an SSRI to a serotonin-noradrenaline reuptake inhibitor [SNRI]) is more effective than moving to a different antidepressant within the same class (e.g. changing from one SSRI to another); however, it is my preference to change antidepressant classes. In my experience, although I usually prescribe SSRIs as the first treatment, SNRIs are often effective options after failure to respond to SSRIs.

For SNRI nonresponders, useful options include the older antidepressants, such as tricyclic antidepressants (nortriptyline is the best tolerated, and clomipramine may be the most effective but is often poorly tolerated) and the older monoamine oxidase inhibitors (MAOIs) such as phenelzine and tranylcypromine. Despite a substantial evidence base for these older MAOIs, they are underutilised in practice, particularly by younger psychiatrists who have little confidence and experience in using them.[18] Another useful option to consider is off-label prescription of the nicotine anticraving agent bupropion. Bupropion is not approved as an antidepressant in Australia, but has been widely used as such and is highly regarded by clinicians in the US. Further, bupropion has a distinct mechanism of action in its reuptake inhibition of noradrenaline and dopamine. Some treatment-resistant patients may respond to newer antidepressants such as vortioxetine, although the evidence base for this is very limited.

Add or switch to a relevant psychological intervention

Adding or switching to a relevant psychological intervention such as CBT is often effective in improving symptom severity.[19] A recent meta-analysis has confirmed the experience of clinical practice in demonstrating that the addition of psychological treatments (such as CBT in particular) to antidepressants increases the likelihood of improved outcome.[20]

Augment the antidepressant with a nonantidepressant agent

The best evidence for augmentation of antidepressants is for the off-label use of atypical antipsychotics (such as quetiapine, aripiprazole, risperidone and olanzapine) and lithium. In my experience, lithium augmentation is frequently a robust effective strategy and is underused in contemporary practice. (Note that renal and thyroid function should be checked before initiating lithium treatment.) There is also some evidence for augmentation with triiodothyronine (T3), although I have not found this strategy particularly successful in my clinical practice. Off-label use of lamotrigine to augment antidepressants in MDD is widely used in clinical practice; however, there is no evidence base to support this – unlike in bipolar depression – and it is an agent with potential severe adverse effects (such as Stevens-Johnson syndrome).

Combine antidepressant classes

Combining antidepressant classes (such as venlafaxine and mirtazapine) is not uncommon in practice despite the evidence base for this being equivocal and the rate of burdensome adverse effects of combinations high.[21,22] The strategies of switching antidepressants or augmenting with nonantidepressant agents are therefore preferable to combining antidepressants.

Electroconvulsive therapy

ECT is the best-studied neurostimulation treatment. It is often highly effective, particularly for the patient with marked psychomotor retardation or agitation, or psychotic features.

Transcranial magnetic stimulation

Although transcranial magnetic stimulation (TMS) is increasingly available, it is not MBS listed. The clinical profile suggesting that a response to TMS is likely appears to differ from the clinical profile of patients who are likely to respond to ECT, with younger nonpsychotically depressed patients perhaps being the more relevant subjects for this option.

Novel and experimental treatments

Psychosurgical approaches are rarely used in contemporary practice. There is some equivocal evidence for deep brain stimulation, but in practice such neurosurgical interventions are only available in Victoria because of legal proscription in other states.[23] Ketamine (intravenous, intranasal or subcutaneous) is a potentially promising treatment but at present there is minimal evidence for its sustained efficacy and safety over weeks or months and there are risks of abuse.[24]

Conclusion

It is not uncommon in clinical practice to see patients whose depressive symptoms do not remit following initial treatment with SSRI antidepressants or psychological therapies. However, many depressed patients ultimately respond after appropriate clinical review of potential reasons for 'nonresponse' and/or commencement of other well-validated treatment options. As some of the options recommended in this article are not widely used in primary care, GPs should have a low threshold for referring such patients to a psychiatrist experienced in difficult-to-treat depression. MT

COMPETING INTERESTS: None.

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