New drugs, old problems

REVISITING... PHARMACOLOGICAL MANAGEMENT OF TREATMENT-RESISTANT DEPRESSION

Philip J. Cowen

Abstract

Effective pharmacological management of depression resistant to antidepressant medication is best carried out in the context of a supportive and collaborative relationship, following a mutually agreed care plan. Simpler pharmacological approaches such as switching antidepressant classes are tried first, then augmentation is used if needed. New classes of antidepressants have made antidepressant combination a popular augmentation strategy, but lithium addition has most supporting evidence. The use of atypical antipsychotics as augmenting agents is increasing. For patients unresponsive to these strategies, monoamine oxidase inhibitors and electroconvulsive therapy remain important. Large randomised pragmatic trials are needed to help clinicians and patients make better treatment choices.

Definition

The definition of treatment-resistant depression is somewhat arbitrary, but in pharmacological terms there is the presumption that the depressive syndrome has not responded to a trial of at least one antidepressant medication. It has been estimated that about 20–30% of patients with major depression fail to respond to treatment with a single antidepressant drug given in adequate dosage for an appropriate period. About half such patients will respond when switched to another antidepressant medication (see Fava, 2000). It is therefore helpful to identify different degrees of treatment resistance depending on the nature of the interventions that have been unsuccessfully deployed (Fig. 1).

Assessment

Patients with depression are often referred to psychiatrists after a considerable period of treatment with different pharmacological and psychological approaches. It is important to confirm the diagnosis of major depression and exclude general medical disorders. Psychiatric comorbidity such as substance misuse and personality disorder can worsen the outcome of depressive disorder. Other factors

Box 1 Developments in the pharmacological management of treatment-resistant depression

- Patients presenting to psychiatrists have usually already received at least two adequate trials of antidepressant medication without response
- More antidepressant medications are now available
- Treatment focus is on achieving clinical remission
- The evidence base of treatment remains poor
- Treatment algorithms and guidelines have been developed

Philip Cowen is Professor of Psychopharmacology at the Warneford Hospital (University Department of Psychiatry, Warneford Hospital, Oxford OX3 7JX. Tel.: 01865 226394; fax: 01865 251076; e-mail: phil.cowen@psych.ac.uk). He is also an honorary consultant psychiatrist at the Warneford and a Medical Research Council clinical scientist. His main interest is in the neurobiology of mood disorders and their treatment.
associated with lack of recovery from major depression include more severe depressive states, chronic social difficulties and continuing life events (see Anderson et al., 2000).

It is important to enquire about the possibility of manic or hypomanic episodes, whether or not these appear to have been precipitated by antidepressant medication. Hypomanic symptoms can be difficult to detect from a clinical history, but even episodes of brief duration can have implications for treatment response (see below). Bipolar II disorder is not uncommon in patients who present with treatment-refractory depression, and, from the point of view of medication response, depressed individuals with a premorbid ‘hyperthymic’ personality (unusually energetic, cheerful and motivated) may resemble patients with a bipolar II disorder (Hurowitz & Liebowitz, 1993).

The assessment should attempt to determine how long the depression has been present, its nature and course, and the treatments that have been used. Often, patients will have improved to some extent and this may influence whether or not major changes in pharmacological management are needed. It is also helpful to gain an idea of age at onset of the first depressive episode and the usual premorbid level of functioning. It is useful to develop with the patient a model for understanding the origin of the depression and possible maintaining factors under the usual headings of genetic risk (family history), temperament, childhood experiences, levels of social support and more recent stresses and losses. It is important to interview an informant, particularly if that person is a carer and therefore sharing the burdens imposed by the depressive illness.

**General measures**

All patients need psychotherapy in the general sense of supportive listening, education and reassurance. Patients with chronic depression are often under standably demoralised, pessimistic and despairing. The treatment plan should therefore be developed as a collaborative exercise between the patient and the clinical team, and a stepped approach adopted (see Thase et al., 2001). Patients appreciate a practitioner who makes it clear that pharmacological treatment will be used with care and skill and full, informed consent. Emergent adverse effects should be taken seriously and not minimised or attributed to underlying mental state.

Many patients with resistant depression are not at work and it is important to get a clear idea of how they are spending their time. Activity scheduling can be helpful, particularly if it is possible to find occupations that provide enjoyment or at least distraction from constant depressive ruminations.

The role of structured psychotherapies in the treatment of resistant depression is being developed (Thase et al., 2001). Cognitive techniques can be useful in helping patients to focus on achievement and interrupt negative thinking patterns.

**Medication issues**

The pharmacological treatment of patients who have failed to respond to antidepressant medication involves a number of different strategies:

1. optimisation of current treatment;
2. switching to another antidepressant;
3. combination treatment with antidepressants;
4. other augmentation treatments;
5. electroconvulsive therapy (ECT).

The Texas Medication Algorithm Project combines these strategies into a stepped approach, which is
described in simplified form in Fig. 1. Although the use of this algorithm is associated with better results than treatment as usual (Trivedi et al, 2004), many of the treatment suggestions are not backed by randomised trials. However, there is a good deal of evidence in the form of open studies and case series. The need for large-scale randomised trials of pharmacological treatment in resistant depression is increasingly recognised, and results from studies currently being conducted, such as the Sequenced Treatment Alternatives to Relieve Depression (STAR*D; Rush et al, 2004), which is sponsored by the US National Institute of Mental Health, are keenly awaited.

Generally, switching antidepressant medication is seen as the best initial step following failure with a first antidepressant medication. Augmentation strategies such as antidepressant combinations and lithium augmentation are recommended for patients who have not responded to two or more trials of single medications. However, application of this stepped approach should be flexible. For example, some patients may gain limited but definite benefit from an initial treatment and this will almost certainly be lost when the first preparation is withdrawn. A situation like this might recommend an earlier use of an augmentation strategy (Table 1). Finally, if an individual has, for example, depressive psychosis with active suicidal ideation it may be appropriate to consider the use of ECT before several lengthy trials of medication.

As noted in Box 1, where possible the aim of treatment should be to achieve remission, which in practice means that patients should be virtually asymptomatic. This is associated with lower rates of relapse to major depression. However, many pharmacological studies in treatment-resistant depression use a 50% reduction in a depression rating scale score to define a patient as a ‘responder’. This criterion can, of course, result in patients experiencing significant residual depressive symptomatology, despite being definitely improved. Overall, the current data suggest that clinicians need to use available treatment options (both pharmacological and psychological) to achieve symptomatic remission where this is at all possible (Fava et al, 2002).

### Optimising current treatment

The optimisation of treatment centres in concordance with current medication and dose–response issues. It is well recognised that tricyclic antidepressants (TCAs) can be more effective in higher dose, and doses greater than 150 mg daily of amitriptyline, imipramine and clomipramine can be used, provided that tolerance is satisfactory. Plasma monitoring of TCA levels is helpful at higher doses, to guard against toxicity, particularly if there is a possibility of pharmacokinetic interactions. It is prudent to avoid the use of high-dose TCA treatment in patients with a history of cardiac disorder or those who are taking other medications that might impair cardiac conduction.

Venlafaxine also appears to have greater efficacy at higher doses in treatment-resistant patients (de Montigny et al, 1999), but selective serotonin reuptake inhibitors (SSRIs) are said to have relatively flat dose–response curves. Despite this, if tolerance permits, increasing the dose of an SSRI can produce symptomatic improvement, particularly in patients who have shown a partial response (Fava et al, 1994).

### Switching antidepressants

If a patient does not respond to one antidepressant, the first step is usually to stop this medication and try another. Most published studies of this approach have studied patients in an open sequential way; clearly, this cannot control for the placebo effect or the possibility of spontaneous remission. Overall, however, there is reasonable evidence that switching to a second antidepressant produces benefit in about 50% of patients unresponsive to an initial medication trial (see Nelson, 2003).

If a patient has not responded to one kind of antidepressant, it would seem sensible to switch to an antidepressant with a different pharmacological profile. However, it must be acknowledged that open studies have shown equally good response rates when patients who failed to respond to one SSRI were switched to another (see Nelson, 2003). Switching from a drug with serotonergic properties to another serotonergic compound (for example, from citalopram to venlafaxine) should be carried out cautiously because of the risk of serotonin toxicity. This can be particularly problematic when switching from fluoxetine, because of the long half-life of its active metabolite norfluoxetine. However, cross-tapering can be employed when switching between agents with different pharmacological properties (for example, from citalopram to mirtazapine or reboxetine). Useful instructions are provided by the Maudsley Prescribing Guidelines (Taylor et al, 2003).

<table>
<thead>
<tr>
<th>Table 1 Switching antidepressants v. augmentation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Switching</strong></td>
</tr>
<tr>
<td>Better tolerated</td>
</tr>
<tr>
<td>Easier concordance</td>
</tr>
<tr>
<td>Less risk of drug interactions</td>
</tr>
<tr>
<td>Role of individual drug in response is clearer</td>
</tr>
<tr>
<td>Lower medication cost</td>
</tr>
</tbody>
</table>
For the broad range of patients with depression, currently marketed antidepressants have roughly equal efficacy. However, there is evidence from meta-analyses that amitriptyline (Barbui & Hotopf, 2001) and venlafaxine (Smith et al, 2002) may be a little more effective. It is therefore worth trying these drugs at some point in the management of patients unresponsive to initial medication.

**Monoamine oxidase inhibitors**

The use of non-selective, irreversible monoamine oxidase inhibitors (MAOIs) in patients resistant to TCAs and other antidepressants has some support from controlled trials. For example, Nolen et al (1988) studied 21 patients who had failed to respond to imipramine, fluvoxamine or oxprotiline (a selective noradrenaline reuptake inhibitor). Individuals were randomly allocated to double-blind treatment with nomifensine (a dopamine and noradrenaline reuptake inhibitor) or the MAOI tranylcypromine. Of 11 patients receiving tranylcypromine, 5 showed a clinical response. In a subsequent cross-over, 5 of 8 non-responders to nomifensine responded to tranylcypromine. Of the 10 patients who responded to tranylcypromine, 8 maintained their response for at least 6 months.

There is also evidence that patients with certain clinical features may have a preferential response to MAOIs. For example, patients with symptoms of atypical depression (Box 2) have significantly higher rates of response to phenelzine than imipramine, and the same may be the case for patients with ‘anergic’ bipolar depression (Quitkin et al, 1989; Himmelhoch et al, 1991).

Although MAOIs are undoubtedly useful drugs in treatment-resistant depression, their adverse effect profile and liability to produce dietary and drug interactions makes their use unlikely until most other options have been exhausted. The reversible type-A MAOI moclobemide is relatively free from tyramine interactions and is better tolerated than conventional MAOIs. Whether moclobemide is effective as a sole agent in treatment-resistant depression is doubtful. However, Kennedy & Paykel (2004) described useful effects of moclobemide combined with tricyclic antidepressants and lithium in severely treatment-refractory patients in a tertiary referral centre.

**Combination treatment with antidepressants**

Combination strategies aim to supplement the antidepressant effect of an ineffective or partially effective medication with another antidepressant agent. This approach can therefore be considered an augmentation strategy, although if the patient’s condition remits it may be unclear whether the response is due to the combined effect of the two antidepressants or the second agent acting alone.

The pharmacological rationale of combination treatment is the use of two agents to produce a broader spectrum of activity on monoamine pathways than either agent could produce alone. In practice, this means that SSRIs or venlafaxine are usually combined with noradrenergic promoting agents such as TCAs, reboxetine or mirtazapine (which increases noradrenaline function through blockade of auto-inhibitory α₂-adrenoceptors). In the USA, the combination of bupropion with SSRIs is also common. This has the aim of supplementing serotonin potentiation with dopamine and noradrenaline activation. The addition of the anxiolytic drug buspirone to SSRI treatment has also been found to be useful in open case series. However, results from two controlled trials have not been supportive (see Nelson, 2003).

The evidence for any of these strategies is limited, although they are endorsed in case series and expert reviews. The best evidence is probably for the addition of mirtazapine or its predecessor, mianserin, to ineffective SSRI treatment, although a large randomised trial in resistant depression failed to find a benefit of combined sertraline and mianserin over mianserin alone (Carpenter et al, 2002; Licht & Qvitzau, 2002).

Safety is obviously a key consideration in combination therapy. Of the SSRIs, fluoxetine, fluvoxamine and paroxetine can elevate levels of other psychotropic drugs through inhibition of the hepatic cytochrome P450 system. Therefore their use in combination with cardiotoxic TCAs requires special caution. Venlafaxine and citalopram are not significant P450 inhibitors and sertraline has relatively modest effects. Quite apart from the risk of drug interactions, the side-effect burden is likely to increase when two antidepressants are given together. For this reason it is wise to add a second agent cautiously at low dose and to increase the amount gradually according to tolerance.
Tricyclics and MAOI combination

The combination of TCAs and MAOIs has been in use since the 1960s, when the efficacy of this approach was strongly advocated by William Sargent. Although this combination is reported to be hazardous, the risks of significant interactions can be minimised if reasonable precautions are taken. The combination of amitriptyline and trimipramine with MAOIs appears to be safe, but imipramine and clomipramine should definitely be avoided because of the risk of fatal serotonin toxicity. It is usually thought best to start the MAOI and TCA treatment simultaneously at low dose or cautiously to add MAOI treatment to established TCA medication.

In patients not selected for treatment resistance, the combination of TCA and MAOI does not appear to confer additional therapeutic benefit over either drug used alone. In treatment-resistant patients, however, there is some evidence that combined treatment may be of value (Tyrer & Murphy, 1990). As noted above Kennedy & Paykel (2004) found that the combination of moclobemide and TCA (combined in some cases with lithium) produced benefit in a significant number of severely treatment-resistant patients.

Generally, the adverse effects of TCA–MAOI combinations are little worse than those of either drug given alone, although weight gain and postural hypotension may be more troublesome. Conversely, combination of an MAOI with trimipramine or amitriptyline may prevent MAOI-induced insomnia. Trazodone in low doses (50–150 mg) is also sometimes used to treat MAOI-induced insomnia and is generally well tolerated for this purpose. However, there are reports suggestive of serotonin toxicity where trazodone has been combined with SSRIs or MAOIs.

Lithium addition

Lithium given alone has modest antidepressant properties in patients with bipolar disorder, but other patients with depression generally show little response when lithium is used as a sole agent. There is now good evidence from randomised trials that lithium added to ineffective antidepressant treatment can produce useful clinical improvement in patients who fail to respond or only partially respond to antidepressant medication. In a meta-analysis, Bauer & Döpfner (1999) reported that the addition of lithium to antidepressant treatment increased the chance of responding threefold relative to placebo (odds ratio = 3.3; 95% confidence interval 1.5–7.5), yielding a number needed to treat (NNT) of 3.7.

Lithium appears to be effective in improving antidepressant response when added to different kinds of antidepressant treatment including TCAs and SSRIs. It has also been suggested that the combination of lithium with MAOIs may be particularly helpful in patients with severe refractory depression (Price et al, 1985; Kennedy & Paykel, 2004). Lithium has the ability to increase the release of serotonin from pre-synaptic terminals; therefore, caution is needed when using lithium together with SSRIs and venlafaxine, because of the risk of serotonin toxicity. In view of this, it is usually best to initiate lithium addition at a low dose (for example, 200 mg daily) and increase it by 200 mg weekly. The plasma level of lithium required to produce an antidepressant effect in treatment-resistant patients has not been clearly identified, but 12-hour levels of 0.4–0.6 mmol/l are usually adequate; this typically requires doses of 400–800 mg daily. Used in this way, together with slow initiation, the tolerance of lithium in treatment-resistant depression is usually satisfactory.

Antipsychotic drugs

Depressive psychosis

Both clinical experience and controlled studies suggest that antidepressant agents are relatively unhelpful as a sole therapy for depressive psychosis and that effective treatment of this condition requires the concomitant use of antipsychotic drugs. In a much-cited study, Spiker et al (1985) used a double-blind randomised design to allocate 51 in-patients with depressive psychosis to treatment with amitriptyline, perphenazine or both drugs used in combination. Remission rates were significantly higher in the combination treatment group (78%) than in patients taking amitriptyline (41%) or perphenazine (19%) alone. A meta-analysis of 597 patients who received combination treatment with TCAs and conventional antipsychotic drugs also suggested a high overall response rate (77%), and it seems likely that the combination of SSRIs and conventional antipsychotics is similarly effective (see Schatzberg, 2003).

Atypical antipsychotic drugs are increasingly used in depressive psychosis and there have been suggestions that they may be effective as a monotherapy. However, in a randomised trial of patients with psychotic depression, Muller-Siecheneder et al (1998) found that treatment with risperidone was less effective than a combination of amitriptyline and perphenazine. A more recent study demonstrated the value of combination treatment with fluoxetine and olanzapine, which produced a response rate of 56% in depressive psychosis, significantly greater than the response to either placebo (30%) or olanzapine alone (36%) (see Schatzberg, 2003).
Atypical antipsychotics in non-psychotic depression

Although typical antipsychotic drugs have little value in non-psychotic depression except to ameliorate agitation, there is preliminary evidence that some atypical antipsychotic drugs may have antidepressant effects when used in combination with SSRIs. In a randomised controlled trial, Shelton et al. (2001) found that, in patients resistant to fluoxetine treatment, the addition of olanzapine (5–20 mg) produced a significantly greater response rate than placebo addition or olanzapine monotherapy. Open studies also support the usefulness of low-dose risperidone augmentation for SSRI-resistant patients (Ostrow & Nelson, 1999). Large-scale randomised trials of these approaches are in progress.

The pharmacological mechanisms involved in the augmenting effects of atypical antipsychotic drugs in SSRI-resistant patients requires further study. It has been hypothesised that 5-HT2A/2C receptor blockade may play a role because this action might be expected to increase dopamine and noradrenaline release in cortical regions (Marek et al, 2003). Mirtazapine and mianserin are also potent 5-HT2A/2C receptor antagonists and so this action might contribute to their utility in combination with ineffective SSRI treatment.

The use of atypical antipsychotics to augment SSRIs employs lower doses than would be used to treat schizophrenia, perhaps because effective 5-HT2A/2C receptor blockade occurs at lower doses than dopamine D2 receptor blockade. Despite this, olanzapine, even at low doses, can cause troublesome sedation and weight gain; concomitant use of risperidone produces a degree of weight gain together with hyperprolactinaemia.

L-tryptophan

There is evidence from controlled trials that the addition of the serotonin precursor, L-tryptophan, can improve the therapeutic effect of MAOI treatment in patients not selected for treatment resistance. However, there are no controlled trials to indicate that L-tryptophan produces therapeutic benefit in patients who have failed to respond to MAOIs or TCAs. Nevertheless, its use has been recommended to supplement the serotonin-potentiating effects of lithium–MAOI and lithium–clomipramine combinations (Barker et al, 1987; Hale et al, 1987).

L-tryptophan use has been associated with the development of the eosinophilia myalgic syndrome, a severe connective tissue disease that can have a fatal outcome. However, subsequent studies have shown that the syndrome was almost certainly caused by a contaminant that occurred in the production of L-tryptophan from a single manufacturing source (Slutsker et al, 1990). In the UK, it remains possible to prescribe L-tryptophan in combination with other antidepressant drugs for patients with chronic treatment-resistant depression. It should be noted, however, that the combination of L-tryptophan with MAOIs can lead to serotonin toxicity, so caution is needed. For the same reason the combination of L-tryptophan and SSRIs is not recommended.

Thyroid hormone

Some open and controlled studies have suggested that the addition of tri-iodothyronine (T3) in doses of 20–40 µg daily to ineffective TCA treatment can bring about a useful clinical response. In one of the best studies of this approach, Joffe et al. (1993) studied 50 out-patients with non-psychotic unipolar major depression who had failed to respond to 5 weeks’ treatment with a TCA (daily dose 2.5 mg/kg). They were randomly allocated to double-blind addition of T3 (37.5 µg daily), lithium carbonate or placebo for a further 2 weeks. At the end of treatment, 10 of 17 patients had responded to T3 addition and 9 of 17 to lithium; significantly fewer subjects (3 of 16) responded to placebo.

However, a meta-analysis of four published randomised trials that assessed the efficacy of T3 addition to ineffective TCA treatment was less encouraging (Aronson et al, 1996) and, overall, T3 failed to show a significant treatment effect.

A dose of T3 of 20 µg is equivalent to a dose of thyroxine (T4) of about 100 µg. The use of T3 augmentation treatment at the usual doses (20–40 µg daily) rarely produces clinical evidence of hyperthyroidism, but occasionally mild tachycardia and sweating may occur. Thyroid function tests typically show plasma levels of T3 in the high normal range with subnormal T4 levels. Thyroid-stimulating hormone (TSH) levels are low, but usually not completely suppressed.

Another approach employed by some groups is to add high-dose T4 to ineffective antidepressant treatment, with the aim of suppressing TSH and increasing plasma T4 into the mild hyperthyroid range. Bauer et al. (1998) described 17 patients with severe refractory depression (12 with bipolar depression) who were treated with thyroxine (mean dose 482 µg daily). Following 12 weeks of treatment, 10 individuals had remitted and 9 of these maintained a clinically important improvement over the next 2 years. Ten patients noted typical symptoms of hyperthyroidism, but these were reported as mild
and tolerable. At 1-year follow-up there was no evidence of significant cardiovascular changes or bone demineralisation. Useful effects of high-dose thyroxine treatment have also been reported in patients with rapid-cycling bipolar disorder (Bauer & Whybrow, 1990).

The use of high-dose T4 in patients with pre-existing cardiovascular disease clearly raises concerns and requires regular clinical and biochemical monitoring. It is somewhat easier to use T3, but again it should be avoided in patients with cardiac disease. A major drawback of T3 augmentation is that there is little information about its efficacy in combination with newer antidepressants such as the SSRIs.

Other augmentation approaches

The literature contains many other augmentation approaches for the management of resistant depression. Many of these are of theoretical and practical interest; none currently has a strong evidence base.

Pindolol

The β-adrenoceptor antagonist pindolol has 5-HT1A receptor antagonist properties and there has been much interest in whether pindolol might augment the action of SSRIs by blocking the inhibitory action of 5-HT1A autoreceptors in the raphe nucleus. It does appear that pindolol addition can speed onset of therapeutic effect of SSRIs (Artigas et al, 2001), although whether this occurs to a clinically useful degree is debatable. However, it seems doubtful that pindolol is able to augment the action of SSRIs in treatment-resistant patients (Perez et al, 1999). The caveat to this conclusion is that the dose of pindolol generally used in augmentation studies (7.5 mg daily) is probably too low to provide effective blockade of 5-HT1A receptors (Rabiner et al, 2001). Whether higher doses might be more effective is uncertain.

Omega-3 fatty acids

There has been much interest in the possible antidepressant effects of omega-3 fatty acids, particularly eicosapentaenoic acid (EPA) given in doses of 1–2 g daily. In a small double-blind randomised trial (n = 20), Nemets et al (2002) found that 2 g daily of an EPA derivative produced a significantly greater response in antidepressant-resistant patients (60%) than did placebo (10%). At these doses EPA is usually well-tolerated.

Electroconvulsive therapy

Among the indications for ECT is failure to respond to adequate antidepressant drug treatment. However, a history of medication resistance may lower the response to ECT.

Prudic et al (1990) studied the effect of previous antidepressant drug treatment on the response of 53 patients who received bilateral ECT. They found that, among those who had received previous adequate pharmacotherapy (defined as a TCA at a dose of at least 200 mg daily for at least 4 weeks), the response rate to ECT was 50%. In contrast, the response rate in patients who had not received adequate drug treatment was significantly greater (86%).

Another point that needs to be considered is outcome after ECT. Sackheim et al (1990) followed 58 patients who responded to ECT and found that 1 year after treatment, 50% had relapsed. The relapse rate in patients who had received adequate antidepressant treatment prior to ECT (64%) was significantly higher than in those who had not (32%). The relapse rate after ECT was only weakly influenced by whether or not patients had received adequate antidepressant treatment after the ECT. Development of appropriate pharmacological continuation therapy after ECT is clearly a priority. It seems that the common clinical practice of continuing with the same medication that the patient was taking before the ECT is not a generally effective strategy.

Bipolar depression

The management of bipolar depression is outside the scope of this article [for a review of the topic, readers are referred to Frangou, 2005, this issue. Ed.] but patients with bipolar disorder who present with resistant depression can pose additional problems in terms of pharmacological management. These problems can extend to patients with bipolar II disorder. Among the relevant issues is the possibility that antidepressant drugs will induce mania or rapid cycling. Where patients are having what appears to be a rapidly relapsing depressive illness it is important to establish whether or not the clinical picture is, in fact, rapid cycling, with periods of mild hypomania interspersed with depression (Hurowitz & Liebowitz, 1993). Daily mood charting can be helpful in diagnosis. If rapid cycling is confirmed, withdrawal of antidepressant treatment and institution of mood stabilising treatment can be a useful strategy (for guidelines describing the treatment of bipolar depression, see Goodwin, 2003).

The treatment of bipolar depression (Box 3) should generally include a mood stabiliser because this
lessens the risk of manic upswing. Although lamotrigine may not be as effective as lithium in preventing mania, it probably has superior antidepressant efficacy in patients with bipolar disorder (see Goodwin et al, 2004). However, it is not yet licensed for use in mood disorders in the UK. Atypical antipsychotic drugs are also gaining a growing role in the treatment of bipolar depression. Tohen et al (2003) reported a randomised study of olanzapine and combined olanzapine and fluoxetine treatment in 833 patients with bipolar depression. Remission rates were best in the olanzapine–fluoxetine treatment group (48.8%), followed by olanzapine alone (32.8%) and then placebo (24.5%). Rates of mania onset did not differ between any of the treatment groups.

Conclusions

General and old age psychiatrists need to have confidence in their ability to manage the pharmacological aspects of treatment-resistant depression. It is important to retain the belief that recovery is possible, because even several years of treatment-resistant depression can be followed by eventual clinical remission (Mueller et al, 1996). At the same time, it is necessary to recognise and acknowledge to the patient the limitations and discomforts of contemporary drug treatments.

Thase & Rush (1997) warn that it is important for the clinician not to become demoralised or frustrated when treatments prove ineffective and point out that even where promising pharmacological options appear to be limited, supportive psychological treatment has an important life-sustaining function.

References


**MCQs**

1. **In the treatment of resistant depression, monoamine oxidase inhibitors:**
   a. are not effective in patients who have failed to respond to TCAs or venlafaxine
   b. may be effective in patients with hypersomnia and hyperphagia
   c. can cause postural hypotension at higher doses
   d. should not be combined with lithium

2. **Controlled trials have shown that the following treatments can augment SSRIs in unresponsive patients:**
   a. lithium
   b. mirtazapine
   c. pindolol
   d. tri-iodothyronine

3. **Lithium augmentation of ineffective antidepressant treatment:**
   a. does not work in unipolar depression
   b. is contraindicated with SSRIs
   c. requires a plasma concentration above 0.8 mmol/l
   d. has an NNT between 3 and 4

4. **The following combinations can cause severe drug interactions:**
   a. SSRIs and tricyclic antidepressants
   b. SSRIs and tryptophan
   c. amitriptyline and tri-iodothyronine
   d. mianserin and venlafaxine

5. **In the treatment of bipolar depression:**
   a. mood stabilisers are not usually necessary
   b. antidepressant treatment can provoke rapid cycling
   c. lamotrigine has antidepressant properties
   d. anergic states respond well to TCAs.

**MCQ answers**

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>a</td>
<td>F</td>
<td>a</td>
<td>T</td>
<td>a</td>
</tr>
<tr>
<td>b</td>
<td>T</td>
<td>b</td>
<td>T</td>
<td>b</td>
</tr>
<tr>
<td>c</td>
<td>T</td>
<td>c</td>
<td>F</td>
<td>c</td>
</tr>
<tr>
<td>d</td>
<td>F</td>
<td>d</td>
<td>T</td>
<td>d</td>
</tr>
</tbody>
</table>

*New drugs, old problems*
Pharmacological management of treatment-resistant depression

P. J. Cowen

The management of patients with depression who have failed to respond to antidepressant medication is a common problem in general and old age psychiatry. It has been estimated that about 20–30% of patients with major depression fail to respond to treatment with a single antidepressant drug given in adequate dosage for an appropriate period of time. At the current time there are many possible ways to pursue pharmacological treatment, but few controlled trials to help us choose between the various options. In addition there are few clinical predictors to help match patients to an appropriate treatment.

Definition

The definition of treatment-resistant depression is somewhat arbitrary, but in pharmacological terms there is the presumption that the depressive syndrome has not responded to an adequate trial (in terms of dose and duration) of at least one effective medication. It may be useful to identify different stages of resistant depression depending on the nature of treatments that have been unsuccessfully deployed (Box 1; Thase & Rush, 1997). Some patients may present with chronic untreated depression that has failed to remit spontaneously. Such patients can respond well to pharmacotherapy, although there is disagreement about whether remission rates are lower than in depressed patients with more acute presentation (Kupfer & Frank, 1996).

Assessment

Patients with depression are often now referred to psychiatrists after some considerable period of illness and after a number of different drug treatments have been tried. It is important to confirm the diagnosis of major depression and exclude possible general medical disorders. Some medical treatments may themselves precipitate or perpetuate depression; for example, recent epidemiological studies have drawn attention to excess rates of depression and suicide in patients taking calcium channel antagonists (Lindberg et al., 1998). Psychiatric comorbidity, for example substance misuse, can also worsen the outcome of depressive disorder.

The assessment should attempt to establish how long the depression has been present, its nature and course and the treatments that have been used. Often, patients will have improved to some extent and this may influence whether or not major changes in management are needed. It is helpful to try to

Box 1. Stages of treatment resistance in depression (adapted from Thase & Rush, 1997)

<table>
<thead>
<tr>
<th>Stage 1</th>
<th>Failure of at least one adequate trial of one major class of antidepressant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 2</td>
<td>Stage 1 plus failure to respond to adequate trial of antidepressant from a different class</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Stage 2 plus failure to respond to lithium augmentation</td>
</tr>
<tr>
<td>Stage 4</td>
<td>Stage 3 plus failure to respond to monoamine oxidase inhibitor</td>
</tr>
<tr>
<td>Stage 5</td>
<td>Stage 4 plus failure to respond to electroconvulsive therapy</td>
</tr>
</tbody>
</table>

Philip Cowen has studied basic neuropharmacology and its application to clinical psychopharmacology. Since 1983 he has been an MRC Clinical Scientist and Honorary Consultant Psychiatrist at the University Department of Psychiatry, Oxford (Warneford Hospital, Oxford OX3 7JX). His main interests are the biochemistry and treatment of mood disorders.
establish how far psychosocial and personality factors may have played a role in the onset and maintenance of the depression. For this purpose it is usually necessary to interview an informant. Although knowledge of these factors does not necessarily affect selection of drug treatment, it can influence prognosis.

### General measures

All patients need psychotherapy, in the general sense of supportive listening, reassurance and education. Often, patients with chronic depression are understandably demoralised, pessimistic and despairing. It is usually helpful to outline the treatment plan as a collaborative exercise in which the clinician uses their skill and experience to select potentially useful therapeutic options while the patient’s task is to stay in treatment and engage in normal day-to-day activities as far as possible. Cognitive techniques can be useful in helping patients to focus on achievements and identify and deal with negative thinking patterns.

### Medication

#### Dose–response issues

Many patients taking tricyclic antidepressants (TCAs) are treated with relatively low doses and may improve when the dose is increased to 150–200 mg daily. In individual subjects, where tolerance is good, additional benefit may be obtained by increasing the dose further, up to 300 mg of imipramine or its equivalent. Plasma monitoring of tricyclic levels may be helpful at higher doses to guard against toxicity, particularly if there is a possibility of pharmacokinetic interactions (Preskorn, 1993). In addition, when using high doses it may be prudent to monitor patients who have any previous history of cardiac disorder or who are taking other medication that might impair cardiac conduction.

Venlafaxine resembles TCAs, in that higher doses have greater efficacy, but selective serotonin reuptake inhibitors (SSRIs) are said to have relatively flat dose–response curves. Despite this, if tolerance permits, increasing the dose of an SSRI can produce symptomatic improvement, particularly in patients who have shown a partial response (Fava et al, 1994).

#### Switching antidepressants

If a patient does not respond to one antidepressant drug, it is comparatively simple to try a different preparation. Most of the published studies of this treat patients in an open, sequential way with a different class of antidepressant; clearly this cannot control for the placebo effect or the possibility of spontaneous remission. There is reasonable evidence that switching to another class of antidepressant can produce benefit in about 50% of patients unresponsive to an initial medication.

If a patient has not responded to one kind of antidepressant, it would seem sensible to switch to an antidepressant with different pharmacological properties – this is my practice. However, it must be acknowledged that open studies have shown equally good response rates when patients who failed to respond to one SSRI were switched to another (Thase & Rush, 1997).

In the broad range of patients with depression, currently marketed antidepressants have roughly equal efficacy. However, there is evidence from meta-analyses that drugs that produce potent potentiation of both serotonin and noradrenaline (amitriptyline, clomipramine and venlafaxine) may be more effective than SSRIs in patients with severe depressive symptoms (Anderson, 1997). This suggests that one of the former drugs should be tried at some point in patients unresponsive to initial medication.

#### Monoamine oxidase inhibitors

The use of non-selective irreversible monoamine oxidase inhibitors (MAOIs) in patients resistant to TCAs and other antidepressants has some support from controlled trials. For example, Nolen et al (1988) studied 21 patients who had failed to respond to treatment with imipramine, fluvoxamine or oxaprotiline. The subjects were randomly allocated to double-blind treatment with nomifensine, a dopamine and noradrenaline reuptake inhibitor (later withdrawn because of rare autoimmune reactions) or the MAOI tranylcypromine. Of 11 patients receiving tranylcypromine, five responded with a 50% decrease in their score on the Hamilton Rating Scale for Depression (HAM–D; Hamilton, 1967). In a subsequent cross-over, five of eight non-responders to nomifensine responded to tranylcypromine. Eight of the 10 patients who responded to tranylcypromine, maintained their response for at least six months.

There is also evidence that patients with certain clinical features may have a preferential response to MAOIs. For example, patients with symptoms of...
Atypical depression (see Box 2) have a significantly higher response rate to phenelzine (about 70%) than imipramine (about 45%; Quitkin et al., 1989).

Although MAOIs are undoubtedly useful drugs in treatment-resistant depression, their liability to produce dietary and drug interactions makes their use unlikely until most other options have been exhausted. The reversible type-A MAOI, moclobemide, is relatively free from tyramine interactions at standard doses and is better tolerated than conventional MAOIs. However, there is only limited evidence for its usefulness in resistant depression.

Stabl et al. (1995) compared moclobemide (450 mg daily) with a combination of moclobemide and thioridazine in the treatment of 78 depressed in-patients who had failed to respond to at least two previous trials of antidepressants. Overall, about 75% of the patients showed a useful clinical response (50% decrease in HAM–D score) with no difference between the two treatment regimes. Thus, moclobemide can be worth trying in treatment-resistant patients but if it proves ineffective, a switch to a conventional MAOI may still be warranted (Cowen, 1998).

A key issue for successful treatment with MAOIs is the use of adequate doses. For example, some patients may require up to 90 mg a day of phenelzine or 60 mg a day of tranylcypromine. With higher doses it is wise to monitor blood pressure for the development of postural hypotension.

**Augmentation strategies**

A problem in switching antidepressant preparations is that withdrawal of the first compound may not be straightforward. Patients may have gained some limited benefit from the treatment, for example, in terms of improved sleep or reduced tension, and this will be lost. In addition, if the first medication is stopped quickly, withdrawal symptoms may result. Alternatively, gradual tapering of the dose makes the change-over in medication rather protracted, which may not be easily tolerated by a despairing patient with depression. For this reason, in patients unresponsive to first-line medication, it may be more appropriate to add a second compound to the primary antidepressant, in the hope of producing an additive or even synergistic effect. The major disadvantage of this procedure is that the risk of adverse effects through drug interaction is increased.

**Antipsychotic drugs**

Naturalistic studies have shown that patients with depressive psychosis have low response rates to treatment with TCAs alone but may respond well when antipsychotic drugs are combined with a TCA. In a double-blind, random allocation study of 51 in-patients with depressive psychosis, Spiker et al. (1985) found that the response rate (final HAM–D <7) to amitriptyline alone was 41%, while that to perphenazine alone was 19%. However, patients receiving combined treatment with these drugs had a significantly higher response rate (78%) than either of the other two groups.

Most of the reports of the drug-treatment of depressive psychosis have involved TCAs. However, in an open study Rothschild et al. (1993) found that the combination of fluoxetine (up to 40 mg daily) and perphenazine (up to 35 mg daily) produced a 73% response rate (reduction in HAM–D rating of at least 50%) in 30 patients with DSM–III–R (American Psychiatric Association, 1987) depressive psychosis.

It therefore appears that a combination of SSRIs and antipsychotic drugs may be effective in depressive psychosis. However, in the above study 14 patients developed tremor and two experienced akathisia. SSRIs can cause extrapyramidal movement disorders and may potentiate the extrapyramidal effects of antipsychotic drugs through both pharmacodynamic and pharmacokinetic interactions (Young & Cowen, 1994).

There is interest in the role of new antipsychotic agents such as risperidone and clozapine in depressive psychosis, and a number of positive case reports and series have appeared. However, a controlled trial found that risperidone monotherapy was significantly less effective than a combination of amitriptyline and haloperidol in patients with psychotic depression (Muller-Siecheneder et al., 1998).

**Lithium**

Lithium given alone has modest antidepressant properties in patients with bipolar disorder, but other depressed patients show little response. There is now, however, good evidence from uncontrolled and controlled trials that lithium added to ineffective antidepressant treatment can produce
useful clinical improvement in patients with major depression. Whether this effect of lithium is a true potentiation (augmentation) of the primary antidepressant compound or simply represents an additive antidepressant effect of its own is debatable.

Uncontrolled trials have reported that lithium addition is followed by a rapid onset of antidepressant effect (within 48 hours) in a high proportion of subjects (60–70%). Double-blind, placebo controlled trials confirm that lithium is effective, but shows a more gradual onset of action over 2–3 weeks in about 40–50% of patients with depression (Cowen, 1998).

Lithium appears to be effective in improving antidepressant response when added to different kinds of primary antidepressant treatment, including TCAs, SSRIs and MAOIs (Johnson, 1991). Caution is needed when using lithium together with SSRIs because both treatments combine to potentiate brain 5-HT function leading to a risk of 5-HT neurotoxicity. This combination, however, does not seem to have greater therapeutic efficacy than other lithium–antidepressant combinations, despite the marked increase in brain 5-HT function that it produces (Katona et al., 1995). On the basis of open studies it has been suggested that the combination of lithium with an MAOI may be particularly helpful in treatment-resistant depression (Price et al., 1985).

The plasma level of lithium required to produce an antidepressant effect in treatment-resistant patients has not been clearly established, but levels of 0.5–0.8 mmol/l are usually adequate. It is usually best to initiate lithium treatment at a low dose, for example 200–400 mg daily, particularly where patients are taking serotonergic antidepressants such as SSRIs and MAOIs.

**Triiodothyronine**

Several open studies have indicated that the addition of triiodothyronine to ineffective TCA treatment can bring about a good clinical response, and this has been supported in three out of four controlled studies. In the most recent controlled investigation, Joffe et al. (1993) studied 50 out-patients with unipolar, non-psychotic major depression. They had failed to respond to five weeks’ treatment with a TCA (daily dose 2.5 mg/kg) after which they were randomly allocated to double-blind addition of lithium carbonate, triiodothyronine (37.5 mg/day) or placebo for two weeks. At the end of treatment 10 of 17 patients treated with triiodothyronine had responded (50% reduction in HAM–D with final HAM–D score <10). A similar response rate (nine of 17 patients) was noted in patients receiving lithium, while only three of 16 subjects responded to placebo.

The data suggest that addition of triiodothyronine is a useful means of augmenting TCA treatment in patients with depression. In the UK, triiodothyronine is available as a 20 mg tablet (equivalent to about 100 mg thyroxine). When added to TCAs this dose is usually well tolerated; however, caution should be used in patients with cardiovascular disease. If this dose is unsuccessful but tolerance is good there is the option of increasing to 40 mg. At the higher dose symptoms of tachycardia, sweating, hot flushes and anxiety may be experienced. There are at present no comparative data to show that triiodothyronine can augment the action of other classes of antidepressant drugs, but in clinical practice such combinations are sometimes used.

**L-tryptophan**

There is evidence from controlled trials that the addition of L-tryptophan can improve the therapeutic effect of MAOI treatment. However, there are no controlled trials to indicate that L-tryptophan can reliably produce therapeutic benefit in patients who have failed to respond to MAOIs or TCAs. Nevertheless, the use of L-tryptophan has been recommended to supplement the 5-HT potentiating effects of lithium–MAOI and lithium–clomipramine combinations (Barker et al., 1987; Hale et al., 1987).

L-tryptophan has been associated with the development of the eosinophilia myalgic syndrome, a severe connective tissue disease that can have a fatal outcome. Subsequent studies have shown that eosinophilia myalgic syndrome was almost certainly caused by a contaminant that occurred in the production of L-tryptophan from a single manufacturing source (Slutsker et al., 1990). In the UK it remains possible to prescribe L-tryptophan, in combination with other antidepressant drugs, for patients with chronic treatment-resistant depression. It should be noted, however, that the combination of L-tryptophan with MAOIs can lead to 5-HT neurotoxicity, so caution is needed. In addition L-tryptophan given with SSRIs can also result in 5-HT toxicity, so this combination is not recommended (Sternbach, 1991).

**Combining TCAs and MAOIs**

The combination of TCAs and MAOIs has been in use since the 1960s when the efficacy of this regime was first strongly advocated. Although the combination of MAOIs and TCAs is reported to be hazardous, the risks of significant interaction can be minimised if reasonable precautions are taken. These include avoiding imipramine and
clomipramine, and starting the drugs together at low dose or adding the MAOI cautiously to established TCA treatment (see Chalmers & Cowen, 1990).

In patients not selected for treatment resistance the combination of MAOIs and TCAs does not appear to confer additional therapeutic benefit over either drug used alone. However, Sethna (1974) carried out an open study of MAOI–TCA treatment in 12 patients with depression who had failed to respond to either TCAs or MAOIs given separately (or electroconvulsive therapy (ECT) in 10 cases). At follow-up periods of 7–24 months, nine subjects were reported to be without significant depressive symptomatology. Most of these subjects had chronic non-melancholic depression with prominent anxiety symptoms.

In addition to these series, case reports continue to appear where it seems well documented that a patient has failed to respond to either a TCA or an MAOI given alone, but achieves a good clinical response when both drugs are used together (Tyrer & Murphy, 1990). Therefore, although controlled evidence is lacking, it seems likely that individual patients with refractory depression are helped by MAOI–TCA combinations. Generally, the adverse effects of the combination are no worse than with either drug alone, although weight gain and postural hypotension may be more troublesome. Conversely, if an MAOI is given with a TCA such as amitriptyline or trimipramine, MAOI-induced insomnia may be prevented.

There is less information about the combination of other antidepressants with MAOIs. However, trazodone in doses of 50–150 mg is fairly commonly used to treat MAOI-induced insomnia and is generally well-tolerated (Nierenberg & Keck, 1989).

Combining TCAs and SSRIs

Some open case series have suggested that combining TCA and SSRI treatment may be helpful in refractory depression. For example, in a retrospective chart review, Weilburg et al. (1989) reported a positive response (defined as improvement noted by both patient and clinician) in 22 of 25 out-patients with depression when fluoxetine was added to ongoing TCA treatment. This study does not clarify whether or not the improvement was due to the fluoxetine alone or the combination of fluoxetine with the TCA. However, in eight patients the therapeutic response was lost when the TCA was withdrawn, and restored was it was recommenced.

Subsequently, Weilburg et al (1991), in a similar study, found resolution of depression in 13 of 20 out-patients in whom nortriptyline or desipramine were added to ineffective fluoxetine treatment. One patient worsened with severe agitation. Finally, Seth et al (1992) reported remarkable improvement in eight elderly patients with chronic refractory depression who received an SSRI–TCA combination (usually sertraline and nortriptyline). Some patients received concomitant lithium treatment.

The only prospective study of TCA–SSRI treatment was carried out by Fava et al (1994) who treated 41 out-patients suffering with depression who had failed to achieve a 50% reduction in HAM–D scores in response to a standard dose of fluoxetine (20 mg daily). Subjects were randomly allocated to three different groups: (a) high-dose fluoxetine (40–60 mg daily); (b) the addition of desipramine (25–50 mg daily); or (c) lithium. Taking response as a final HAM–D score (at five weeks) of <7, the most effective treatment was high-dose fluoxetine (53% response rate) while lithium and desipramine augmentation appeared of similar efficacy (response rates of 29% and 25% respectively). However, the plasma levels of lithium obtained in this study were low and probably sub-therapeutic.

Taken together the controlled evidence for the efficacy of TCA–SSRI combinations is not compelling. In addition there are numerous case reports of adverse reactions with agitation and, rarely, seizures. These reactions are generally associated with marked elevations in plasma TCA levels because SSRIs are potent inhibitors of the cytochrome P450 system by which TCAs are metabolised. While some SSRIs, for example, citalopram and sertraline, may be less likely to produce this effect, the use of low doses of TCAs in conjunction with plasma monitoring is advisable if combination treatment is used (Taylor, 1995). Another option may be to use treatment with a single drug such as clomipramine or venlafaxine which produces potent 5-HT and noradrenaline reuptake inhibition.

Another drug commonly used in combination with SSRIs is trazodone. Although there are some uncontrolled data suggesting that trazodone can augment the antidepressant effects of SSRIs (Weilburg et al., 1991), the usual reason for employing this combination is that the hypnotic effect of trazodone can ameliorate SSRI-induced sleep disturbance. Low doses of trazodone (50–150 mg) are usually sufficient and the combination is generally well tolerated, although there are rare reports of symptoms suggestive of serotonin toxicity.

Pindolol

Repeated administration of a number of antidepressant drugs, particularly SSRIs and MAOIs, desensitises inhibitory 5-HT₁₅ autoreceptors on 5-HT cell bodies. It has been suggested that this effect contributes to the antidepressant effect of such drugs
by freeing 5-HT cell bodies from feedback control and thereby facilitating the release of 5-HT from nerve terminals (Blier & de Montigny, 1994).

Based on this idea, Artigas et al (1994) proposed that the addition of a 5-HT\textsubscript{1A} receptor antagonist to the medication of patients who had not responded to conventional antidepressants, particularly SSRIs, might produce a therapeutic effect. Because there are at present no selective 5-HT\textsubscript{1A} receptor antagonists available for clinical use, these authors employed pindolol, a β-adrenoceptor antagonist with 5-HT\textsubscript{1A} receptor antagonist properties.

Pindolol (2.5 mg three times daily) was added to the drug treatment of seven patients with major depression who had been resistant to multiple medication trials. Five subjects were currently taking an SSRI (four paroxetine, one fluvoxamine) while one received imipramine and one phenelzine. All subjects showed a decrease in HAM–D score of at least 50% after a week of pindolol addition and in five, HAM–D scores were less than eight, indicating full remission (Artigas et al, 1994).

Subsequently, Blier & Bergeron (1995) reported on the addition of pindolol to 18 patients with major depression who had failed to respond to treatment with an antidepressant together with the addition of another treatment, usually lithium. Pindolol (2.5 mg three times daily) was added to paroxetine (eight subjects), sertraline (five subjects), fluoxetine (three subjects) and moclobemide (two subjects). Overall, pindolol produced a significant improvement in depressive symptoms after one week. By two weeks all the patients, except those on sertraline, had a HAM–D score of 10 or less showing a good clinical improvement. Interestingly, none of the patients treated with sertraline responded. It is not clear whether or not this may represent a chance finding. Despite the intriguing results from open studies a recent small controlled study of pindolol addition to ineffective SSRI treatment showed no benefit over placebo (Moreno et al, 1997).

Pindolol addition is generally well tolerated, although careful clinical screening is needed to exclude patients with asthma or cardiac conduction disturbances. In open studies pindolol addition has been associated with irritability and one patient developed mania.

**Electroconvulsive therapy**

Among the indications for ECT is that of failure to respond to adequate antidepressant drug treatment. Trials of ECT typically report high response rates (about 80%), but patients who are unresponsive to drug treatment are not usually considered as a separate group.

Prudic et al (1990) studied the effect of previous antidepressant drug treatment on the response of 53 patients who received bilateral ECT. They found that among those who had received adequate pharmacotherapy (a TCA at a dose of at least 200 mg daily for at least four weeks) the response rate to ECT (defined as a 60% reduction in HAM–D score) was 50%. In contrast, the response rate of patients who had not received adequate drug treatment was significantly greater (86%). The presence of medication resistance, therefore, decreases the likelihood that a patient will respond to ECT. Nevertheless, at least half of such subjects are likely to experience significant improvement.

Another point that needs to be considered is the outcome after ECT. Sackeim et al (1990) followed 58 patients who responded to ECT and found that one-year post-treatment, 50% had relapsed. The relapse rate in patients who had received adequate drug treatment prior to ECT was significantly higher than in those who had not (64 v. 32%). The relapse rate after ECT was only weakly influenced by whether or not patients received adequate antidepressant drug treatment post-ECT.

The practical point from this is that if patients have been unresponsive to a particular medication prior to ECT, continuing with this medication after successful ECT treatment may not provide effective prophylaxis. Therefore consideration should be given to using another class of antidepressant or perhaps lithium prophylaxis if this has not been tried previously. Development of appropriate continuation therapy after ECT is a research priority.

ECT can be used at any point in the treatment of resistant depression. Clinical features that will encourage earlier use include severe depression with high acute suicidal risk, depressive psychosis and pronounced psychomotor features, especially where fluid intake is compromised.

**Bipolar depression**

The management of bipolar depression is outside the scope of this article, but it is worth noting that it poses additional problems to those encountered in the treatment of resistant unipolar depression. Among these problems are the possibility of induction of mania or rapid cycling by antidepressant drugs. Where patients are having what appears to be a rapidly relapsing depressive illness it is important to establish whether or not the clinical picture is, in fact, rapid cycling with periods of mild hypomania interspersed with depression (Hurowitz & Liebowitz, 1993). Recording of daily moods by the patient can be helpful in clarifying the diagnosis. If rapid cycling is confirmed, withdrawal...
of antidepressant treatment and the institution of mood stabilising medication can be a useful strategy.

In the treatment of bipolar illness the primary aim is that of mood stabilisation, and there is scope for the use of mood stabilising agents such as carbamazepine in depressive spells (Cowen, 1998). The clinical impression is that antidepressant drugs often seem somewhat less effective in bipolar depression, although bipolar depression with features of anergia and hypersomnia may respond better to MAOIs than to TCAs (Himmelhoch et al., 1991).

**Conclusion**

General and old age psychiatrists need to have confidence in their ability to manage the pharmacological aspects of treatment-resistant depression. It is important to retain the belief that ultimately the patient can recover, because it continues to be the case that even several years of severe depression can be followed by clinical remission (Mueller et al., 1996). At the same time it is necessary to recognise (and acknowledge to the patient) the limitations and discomforts of contemporary drug treatments.

Patients are usually aware that miracles are not on offer but do appreciate a practitioner who systematically follows a carefully explained stepwise approach. A stepwise approach organised along the lines suggested in this review is shown in Box 3. It is always helpful to have in mind what the next step will be if the current treatment regime fails. Thase & Rush (1997) warn that it is important for the clinician not to become demoralised or frustrated by a patient’s lack of response and point out that even where promising pharmacological options appear to be limited, supportive psychological treatment has an important, life-sustaining function (Holmes, 1995).

**References**


---

**Box 3. Approach for pharmacological treatment of resistant depression**

- (a) Adjust treatment to maximum therapeutic dose dependent on tolerance (add antipsychotic drug if depressive psychosis)
- (b) Switch antidepressant (e.g. TCA for SSRI and vice versa)
- (c) Augment with lithium
- (d) Augment with triiodothyronine
- (e) MAOI (can continue with lithium)
- (f) Other combinations (e.g. MAOI + TCA, lithium + MAOI + L-tryptophan, lithium + clomipramine + L-tryptophan)

ECT can be used at any stage, depending on clinical features and the need for quick response.


---

**Multiple choice questions**

1. In the treatment of resistant depression, monoamine oxidase inhibitors:
   a) are not effective in patients who have failed to respond to ECT
   b) may be effective in patients with hypersomnia and hyperphagia
   c) can cause postural hypotension at higher doses
   d) should not be combined with lithium.

2. Controlled trials have shown that the following treatments can augment tricyclic antidepressant treatment in unresponsive patients:
   a) lithium
   b) thyroxine
   c) pindolol
   d) triiodothyronine.

3. Lithium augmentation of ineffective antidepressant treatment:
   a) does not work in unipolar depression
   b) is contraindicated with SSRIs
   c) requires a plasma concentration of 0.5–0.8 mmol/l
   d) works within 48 hours in most patients.

4. The following combinations can cause severe drug interactions:
   a) SSRIs and tricyclic antidepressants
   b) SSRIs and tryptophan
   c) amitryptiline and triiodothyronine
   d) lithium and triiodothyronine.

**MCQ answers**

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>a</td>
<td>F</td>
<td>a</td>
<td>T</td>
</tr>
<tr>
<td>b</td>
<td>T</td>
<td>b</td>
<td>F</td>
</tr>
<tr>
<td>c</td>
<td>T</td>
<td>c</td>
<td>F</td>
</tr>
<tr>
<td>d</td>
<td>F</td>
<td>d</td>
<td>T</td>
</tr>
</tbody>
</table>

---
New drugs, old problems: Revisiting... Pharmacological management of treatment-resistant depression

Philip J. Cowen

Access the most recent version at DOI: 10.1192/apt.11.1.19