Beyond the evidence: is there a place for antidepressant combinations in the pharmacotherapy of depression?

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ABSTRACT

- Up to 45% of patients with debilitating and potentially lethal depressive illness do not achieve remission with initial drug treatment.
- Using combinations of antidepressants as an early option for treatment-resistant depression has become increasingly common.
- Before trying combination therapy, it is essential first to ensure diagnosis is correct, and then to optimise antidepressant monotherapy, using an effective dose for an adequate period.
- Subsequently, augmentation of antidepressants with lithium and triiodothyronine should be considered, as these strategies are strongly supported by numerous clinical trials. Electroconvulsive therapy is the most effective treatment for severe depression.
- There is little evidence to support use of antidepressant combinations. Risk of toxicity and drug interactions mandate that combinations be used as a last resort, and only in specialist settings.

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Depression is regarded as an illness with good prognosis, though liable to recurrence. Yet up to 45% of patients treated with an antidepressant medication do not achieve remission (Box 1).[1] About a third of patients experience chronic symptoms,[2] and about half of those diagnosed with major depression need ongoing treatment.[3] As depression is potentially lethal, causes enormous suffering, and is a leading cause of disability, the pressure on clinicians to achieve better outcomes can be substantial.

Psychiatrists have traditionally used a number of strategies when a patient has not responded to initial treatment: reviewing the diagnosis, increasing the dose of antidepressant, switching to another antidepressant, and augmenting an antidepressant with medications from other drug groups.[4] Use of combination antidepressants when the only options were tricyclics and monoamine oxidase inhibitors was recognised as extremely hazardous. With the introduction of better tolerated antidepressants, use of antidepressant combinations has become more common.[5] This may be related to pressure on doctors for early discharge because of shortage of psychiatric beds, although there is no evidence that combining antidepressants leads to a faster response.

Some recent review articles recommend the use of combination antidepressants,[6,7] elevate the use of antidepressant combinations ahead of augmentation with other drug classes such as lithium, and make scant reference to monotherapy optimisation. Our anecdotal observations of clinical practice (including general practice) indicate that some clinicians regard antidepressant combinations as proven therapy and a preferred therapeutic option in the initial stages of depression treatment. In this article, we review the evidence concerning pharmacotherapy of depression to evaluate the merits of the various options and make recommendations concerning the place of antidepressant combinations in clinical practice.

How should treatment-resistant depression be managed?

Is the diagnosis correct?

Treatment resistance may be due to diagnostic error. An easily misdiagnosed group are patients with personality disorder who typically present with "depression". Although some of these patients may be suffering a form of depression, many have symptoms that do not respond to pharmacotherapy.[8] Poor treatment adherence, alcohol and other substance dependence will contribute to apparent treatment resistance.

Mood stabilisers may be more appropriate than antidepressants in bipolar depression, and antipsychotics or electroconvulsive therapy (which has been consistently found to be superior to pharmacotherapy) may be needed in melancholic and psychotic depression. Schizoaffective depression has been shown to respond to atypical antipsychotics and mood stabilisers; antidepressants may also be indicated. Depression due to physical causes requires specific treatment.[4]

Has the optimal dose of antidepressant been used for an adequate period?

Patients regarded as treatment-resistant are often under-treated.[9] There are significant individual variations in absorption and metabolism of antidepressants. A population survey of CYP2D6 activity suggests that up to 10% of white people may be either poor metabolisers, or extensive metabolisers.[10] As a consequence, there is considerable individual variation in drug pharmacokinetics and dose requirements. Any benefit derived from combination treatment may be obtained more safely from antidepressant monotherapy at optimal dose.

There is evidence that response may occur given sufficient treatment duration. A large trial using fluoxetine found that 41% of non-responders at 6 weeks of treatment remitted by 12 weeks.[11] In another double-blind study, patients who had not responded to sertraline 50 mg per day for 4 weeks and then 100 mg per day for another 2 weeks were assigned to sertraline 100 mg plus mianserin 30 mg, sertraline 100 mg plus placebo, or sertraline 200 mg. Patients continuing on sertraline 100 mg achieved the same response over 5 weeks as patients on combined antidepressants; those on 200 mg did not show any advantage.[12]

Should the antidepressant be switched?

In a recent large study, patients who received no benefit from citalopram were switched to one of several different antidepressants, and a quarter subsequently remitted, irrespective of the drug to which they had been switched.[13] Change from sertraline to

1 Causes of resistance to drug treatment in depression*

- Incorrect diagnosis:
  - depression due to general medical condition;
  - personality disorder;
  - bipolar mood disorder;
  - schizoaffective disorder; or
  - adjustment disorder.
- Inappropriate antidepressant type and dose.
- Inadequate duration of drug treatment.
- Intrinsic illness characteristic (eg, depression that requires electroconvulsive therapy for response).

* Treatment resistance is defined as failure to achieve remission to a point indistinguishable from health. ◆

imipramine and vice versa had benefit for more than half of treatment-resistant patients in a double-blind study.[14]

Once monotherapy at optimal individualised dose has failed, a trial of another antidepressant is appropriate. In patients with inadequate response, a move to a different antidepressant class makes sense, but there is little evidence to guide clinicians' choice of the second drug. There is a view that depressive illness from the melancholic/biological domain needs to be treated with antidepressants that have multiple neurochemical effects (eg, venlafaxine, mirtazapine, tricyclics, monoamine oxidase inhibitors), in contrast to selective drugs (eg, selective serotonin reuptake inhibitors [SSRIs]).[8]

Which polypharmacy strategies are useful in treatment-resistant depression?

Polypharmacy has traditionally been discouraged in psychiatry, because of the increased risk of drug interactions and toxicity. Although mood stabilisers and antipsychotics are frequently combined in the treatment of mania, in most other circumstances polypharmacy is only used in exceptional situations.[15] Because of the risk of interactions for antidepressant combinations, research into treatment of resistant depression has extensively investigated non-antidepressant drugs as adjuncts to antidepressants. The use of antidepressant combinations is a recent and as yet largely unexplored phenomenon.

Is it appropriate to augment antidepressants with drugs from other groups?

More than 50 mostly positive double-blind studies support the use of lithium to augment antidepressants in resistant depression.[16] However, about 50% of patients do not respond, potential adverse effects are substantial, there has to be haematological monitoring of renal and thyroid function and serum lithium, and many patients are reluctant to pursue this course.

Also supported by evidence is thyroid hormone augmentation in euthyroid patients.[17] Triiodothyronine has been extensively studied and found in double-blind studies to be similar to lithium in effectiveness, although only in augmenting tricyclic antidepressants. Risks include osteoporosis and hypothyroidism, and the strategy is rarely used in practice.[18]

Addition of an atypical antipsychotic to antidepressant therapy is increasingly used in clinical practice, particularly in agitated and psychotic patients.[19] Olanzapine and fluoxetine have been found to be more effective than either drug alone in non-psychotic treatment-resistant patients,[20] and similarly limited evidence supports combined use of risperidone and quetiapine in depression.

Many other augmenters have been proposed, but evidence is lacking: pindolol, lamotrigine, gabapentin, carbamazepine, valproate, stimulants, opiates, benzodiazepines, hydrocortisone, testosterone, dehydroepiandrosterone and dopamine agonists. A recent large study of treatment-resistant major depression found adjunctive buspirone improved patients previously unresponsive to citalopram alone.[21]

What is the evidence supporting combinations of antidepressants?

Combinations involving monoamine oxidase inhibitors with stimulants, tricyclics and SSRIs are well known to have potentially lethal consequences.[17] Toxicity may be serious, and includes serotonin syndrome (nervousness, confusion, tremor, restlessness, sweating, hyperreflexia, shivering and myoclonus).

The combination of tricyclic antidepressants with SSRIs is less effective than raising SSRI dose alone.[22] A double-blind study did not show any difference between monotherapy and fluoxetine–desipramine combination.[23] Furthermore, drug interactions are likely, as some SSRIs inhibit tricyclic metabolism through the cytochrome P450 system, increasing the risk of cardiotoxicity, seizures and delirium.

Two double-blind placebo-controlled trials have shown that adjunctive mianserin augments response to SSRIs in resistant major depression.[24,25] Another large study found no advantage of sertraline plus mianserin over sertraline alone, and combination was associated with increased sedation and weight gain.[12]

A double-blind study enrolled 26 patients who had not responded to SSRIs, venlafaxine and bupropion at various doses for variable but prolonged periods. Patients then received mirtazapine or placebo augmentation for 4 weeks. Mirtazapine augmentation resulted in a 64% rate of response, compared with 20% for placebo; side effects were not marked.[26]

In 2001, a large double-blind study of patients resistant to citalopram compared adjunctive bupropion with buspirone. Both adjuncts were associated with improvement, but bupropion (not available as an antidepressant in Australia) was superior and better tolerated (there was no comparison group of patients continuing on citalopram only).[20] These studies do not constitute persuasive evidence in favour of antidepressant combinations.

Caution: make sure that strategies supported by evidence have been considered first

Before embarking on polypharmacy strategies in the management of treatment-resistant depression, it is essential to address diagnostic re-evaluation and dose optimisation (Box 2). A deficiency of randomised controlled trials is their failure to provide information on the dose ranges that will actually be required for effective treatment of patients in routine clinical practice.[27] Dose optimisation should be based on assessment of efficacy and tolerability. Adequate duration of therapy is needed — many patients respond if given time.

Of the augmentation and combination strategies, evidence supports use of adjunctive lithium and triiodothyronine. There is no persuasive evidence supporting the efficacy of combination antidepressants, and there is no guide to ongoing treatment. Antidepres-

2 Guidelines for drug management of treatment-resistant depression

- Review diagnosis and institute other treatment as appropriate
- Optimise antidepressant dose
- Ensure adequate duration of treatment (if practicable)
- Optimise psychotherapy and social assistance as appropriate
- Switch to another antidepressant class
- Consider augmentation with lithium
- Consider other augmentation options: thyroid hormone, atypical antipsychotics, mood stabilisers
- Consider use of electroconvulsive therapy
- Consider use of antidepressant combinations that are least prone to toxicity and interactions
- Consider specialist referral ◆

sants differ significantly from each other, even within a class, and some antidepressant combinations are more dangerous than others. The effectiveness of combinations has not been tested against augmentation strategies, and long-term safety has not been established.[28]

Circumstances do arise where clinicians have to work "beyond the evidence". Specialist opinion and monitoring with investigations such as electrocardiography and plasma drug concentrations should be used. The use of antidepressant combinations may be justified, but only where treatments supported by evidence have proven ineffective or are inappropriate.

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