Focus

When antidepressants don't work well: pharmacological options to improve the response

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Introduction

In the past decade we have witnessed the development of new, highly effective and safe antidepressants. Despite the increased use of these agents, a substantial number of depressed patients, up to 45 per cent, still show partial or non-response to treatment.1 Even among those who improve on antidepressants, a subset still have residual symptoms.

Examples of residual symptoms can be poor concentration, improved mood but still not baseline, decreased libido and insomnia.

Aside from causing disability, residual symptoms are also associated with poorer prognosis and higher chance for relapse.2

KEY POINTS

- The goal for antidepressant therapy is full remission
- Partial response to antidepressant therapy is a common phenomenon and patients suffer with residual symptoms
- Pharmacological options include dose optimisation, switching to another agent and augmentation
- If properly administered, augmentation with lithium, thyroid hormone or low dose tricylics can result in further antidepressant response

Because of funding limitations in New Zealand, access to the newer antidepressants (eg, bupropion, venlafaxine and mirtazapine) with novel mechanisms is extremely difficult, if at all possible. We are limited to serotonergic antidepressants like fluoxetine (Prozac), paroxetine (Aropax), citalopram (Cipramil) and nefazodone (Serzone), tricyclics and MAOIs. With a limited choice, switching to newer, safer and more tolerable agents is significantly reduced.

What are our options when our patients show only partial improvement or partial response to antidepressants?

(1) optimise – maximising the dose and duration of antidepressant trial

(2) switch – changing antidepressants to similar or different class

(3) augment – adding another medication to enhance antidepressant response (see box).

Optimising antidepressant therapy means using an appropriate dose with an

adequate duration. It is not uncommon for antidepressants to be underdosed. For SSRIs like fluoxetine, paroxetine and citalopram, doses of 60-80mg have been used successfully in patients who only responded partially at "regular" doses of 20-40mg. For tricyclics, the clinician has to be guided both by patient reports of side effects as well as serum levels. One has to make sure the person is tolerating the current dose before it is increased. Duration of treatment is also a key in optimising treatment. A trial of four to six weeks at therapeutic doses is recommended (see table).

Another approach is to **switch** to another agent after an appropriate washout period. This varies depending on the current medication's serum half-life. The disadvantages of a switch are:

• the washout period may put the vulnerable patient at risk for worsening of the depression

• there is a risk of non-response to the new agent meaning the patient has to undergo another washout and a further trial with a third agent.

A popular intervention in the US for partial responders to antidepressants is **augmentation**. Augmentation is the addition of another pharmacologic agent to enhance the effects of the current antidepressant.1 The American Psychiatric Association practice guidelines (revised) for the treatment of major depressive disorder mention augmentation as an option for partial responders to antidepressant monotherapy.3 A survey of 432 psychopharmacologists by Mischoulon4 reveals augmentation as a second favoured option for partial responders to SSRI. In this study, the first option was to raise the dose of the current antidepressant and the third option was to switch to another antidepressant.

Several medications from different classes are currently being used for augmentation. These include lithium, thyroid hormones, tricyclic antidepressants, novel antidepressants, stimulants, anticonvulsants, dopamin-ergic agents, atypical antipsychotics and beta blockers.

TABLE: ANTIDEPRESSANT DOSES

Antidepressant	Dose range	Plasma level
Imipramine	150-250mg	= 180 ng/ml
Desipramine	150-250mg	= 150 ng/ml
Nortriptyline	50-100mg	50-150 ng/ml
Fluoxetine	20-60mg	N/A
Paroxetine	20-60mg	N/A
Citalopram	20-40mg	N/A

The three most commonly used and studied will be discussed in this article. These are lithium, thyroid hormones and tricyclic antidepressants.

Lithium added to antidepressants

Lithium has been one of the longest used augmenting agents. It was first used to further the antidepressant response to tricylics in 1981.5 Later studies and clinical use extended to SSRIs including fluoxetine and citalopram.6-8

Two meta-analyses in 1991 and more recently in 1999 support the case for lithium augmentation in depression.9,10

The mechanism for lithium's antidepressant effect is most likely via the serotonin neurotransmitter system.11 In combination with SSRIs, it is possible there is a synergistic effect on the serotonergic system.

As an augmenting agent to an antidepressant, the dosage for lithium is much lower than its dose for bipolar disorder. The initial dose is from 400-600mg once at night. The target lithium level, which should be checked about five days after a dose change, should be between 0.4 and 0.8 mmol/L. Elderly patients and patients with compromised renal function need to have lower doses to achieve the recommended serum level.

The antidepressant response from lithium augmentation is sometimes very rapid, as early as 48 hours, but can extend up to three to six weeks.7 Overall response rates can be up to 70 per cent. If there are no effects after four weeks at the recommended serum levels, the augmentation has to be terminated. If there is a positive response, lithium needs to be administered together with the antidepressant. Patients need to continue on this regimen for at least six months and often longer, depending on the severity and duration of the depressive disorder.7

Prior to commencing lithium augmentation, baseline laboratory tests involving blood count, renal, cardiac and thyroid functions should be obtained. With long term lithium treatment, kidney and thyroid functions can be affected. After reaching a steady serum level, lithium levels can be checked every four to six months. Kidney and thyroid functions should be checked at least every six months.

The most common side effects with lithium include tremors, nausea, diarrhoea and sweating. Though not frequently encountered, "serotonin syndrome" can result when lithium is combined with a serotonergic antidepressant. This syndrome presents with hyperthermia, seizures, delirium and autonomic instability. In terms of drug-drug interactions, lithium interacts with thiazide diuretics, NSAIDs and ACE inhibitors. This can result in toxic lithium levels.

Tricyclics added to SSRIs

SSRIs and tricyclic antidepressants have been combined since the late 1980s. Tricyclic antidepressants were first added to fluoxetine and because of the reported increased efficacy, clinical trials ensued.12,13 Nelson and colleagues at Yale University reported a significant improvement in their cohort of depressed patients with the combination of desipramine and fluoxetine.13 What was interesting was the reported rapid response of less than a week with the combination. A retrospective study on the onset of response after augmentation was done in Auckland by Fernando.14 In this small study, low dose desipramine (25-50mg) was added to serotonergic antidepressants in a group of partial responders. In three days, the responders reported improvements.

The accepted mechanism for this combination of a serotonergic antidepressant (SSRI) and a noradrenergic agent (TCA) is the activation of two neurotransmitter systems that are known to be dysfunctional in depressed states. In fact, an antidepressant, venlafaxine, has this dual activity of raising serotonin and noradrenaline in the synapse. It is considered to be effective in resistant depressions. The dual activity of venlafaxine allows for monotherapy and lower potential for drug-drug interactions. However, this medication is not funded in New Zealand.

The more common tricyclics used as augmenting agents include desipramine and

nortryptiline.

Desipramine is used for its mildly activating property and hence is dosed in the morning while the more sedating nortryp-tiline is dosed before sleep.

It is important to remember that SSRIs can raise tricyclic levels through their effects on the cytochrome P450 system.15 Fluoxetine and paroxetine are potent with their effects of raising tricyclic levels in the serum.

Citalopram has the least ability to raise tricyclic levels and therefore is the safest.16 Because of this P450 interaction, the addition of low dose tricyclic (eg, 25mg of desipramine or 20mg nortriptyline) is safer when being added to a serotonergic agent, particularly citalopram. Ideally, serum levels should be monitored. Though a popular practice to boost a partial response to serotonergic agents in the US, the addition of low dose tricyclic antidepressants to SSRIs is not officially endorsed by the Royal Australia and New Zealand College of Psychiatry.17

With the potential for increased serum levels of tricyclics, the main adverse events to monitor are the anticholinergic signs including dry mouth, blurring of vision, urinary incontinence and constipation. The worst event that can ensue with tricylic toxicity is a cardiac arrhythmia. However, in the Fernando study,14 most patients did not report any side effects at all.

Thyroid hormone added to antidepressants

The use of thyroid hormones as an augmenting agent dates back to the late 1960s. Thyroid hormones were successfully used among depressed patients who were refractory to tricyclics.18

Triiodothyronine (T3) appears to be more effective as an augmenting agent than tetraiodothyronine (T4).19 T3 can be used to augment TCAs, MAOIs, and SSRIs and has been shown to have as high as 65 per cent response rate compared to 19 per cent in placebo.20 In the same study, its efficacy was superior to placebo and equal to lithium augmentation.

Although the mechanism of action of thyroid hormones as augmenting agents is not clear, 21 a suggested hypothesis was that the addition of thyroid hormone will make the noradrenergic receptors more sensitive to the noradrenergic effect of the TCAs.22

Triiodothyronine is effective in the dosage range of 25-50µg per day.23 As in other augmenting strategies, a trial of two to four weeks is recommended. If a patient responds to this adjunctive treatment, a reasonable strategy is to test whether the augmentation is still necessary by a trial of discontinuation eight to 12 weeks after the response. If the patient experiences relapse, then thyroid augmentation can be restarted.23

Although it is a relatively safe augmenting agent, it is important to monitor thyroid function prior to administering T3 as well as after. As expected, the TSH levels will be suppressed while exogenous T3 is being administered.

Other adverse effects associated with excess T3 include irritability, sweating, insomnia and possible cardiac effects.19 It should be avoided in patients with a history of cardiac problems. ECG should be taken at baseline because of the potential for cardiac arrythmias.