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Combination antidepressants

Use by GPs and psychiatrists

Background
Current treatment of depression fails to achieve remission in 50% of patients. Combinations of two antidepressants are used by some Australian psychiatrists.

Objective
This article investigates the pros and cons of combination antidepressant therapy and provides suggestions for when to consider their use, which combinations to choose, and how to introduce combination antidepressant therapies.

Discussion
Combining two antidepressants is a controversial strategy, with supporters and critics arguing its efficacy and safety from opposing perspectives. The use of combination antidepressant therapies may facilitate remission from depression. However, there is limited evidence supporting these treatments, and safety concerns are often cited. There is some support for combination therapies in selected cases from international bodies. After considering risks and benefits on a case-by-case basis, careful use of selected combination antidepressant therapy may be one of a range of effective treatments for some individuals suffering from depression.

Keywords: depression; combination antidepressants

For 50% of sufferers, depression is a lifelong illness. A 23 year follow up of first episode depression showed the illness to be unremitting in 15% of patients, and recurrent in 35%.[1] Analogous to cancer, failure to achieve total eradication of depressive illness (remission) by vigorous treatment worsens the prognosis regarding recovery and relapse.

Despite government initiatives in recent years, many doctors still report to the authors a lack of easy access to psychiatrists for advanced pharmacological management of depression, increasing the burden on general practitioners. This article aims to examine the evidence regarding combination antidepressants, and discusses practical aspects of their use in the minority of patients who may benefit from this approach.

Australian and international views

A number of guidelines have been published since 2008, summarising psychiatric practice in various countries. In the United Kingdom, the 2009 National Institute for Health and Clinical Excellence (NICE) *National Clinical Practice Guideline 90* stated that 'combining antidepressant drugs with different modes of action is increasingly used in clinical practice';[2] and the 2009 *Maudsley Prescribing Guidelines* describe a selective serotonin reuptake inhibitor (SSRI) or venlafaxine combined with mirtazepine or mianserin for refractory depression as options among the 'commonly used treatments generally well supported by published literature'.[3] In Canada, the 2009 Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines state (with respect to combination antidepressants) 'the best available evidence is for add on treatment with mirtazapine/mianserin, or bupropion', and state there is level 2 evidence for these combinations.[4] The 2010 depression treatment guidelines of the American Psychiatric Association state that, for refractory depression, 'the addition of a second non-MAOI [monoamine oxidase inhibitors] antidepressant may be helpful, particularly for patients who have had a partial response to antidepressant monotherapy'.[5]

The Australian *Therapeutic Guidelines: Psychotropic* (2008) take a different position, stating 'there is little evidence supporting the use of combined antidepressants in treatment resistant depression, and there are significant concerns regarding the potential for serious drug interactions'.[6]

A 2004 survey sent to all Australian consultants and nonconsultants in psychiatry (with a 33% response rate) showed that 76% of respondents (including 79% of consultant psychiatrists) had already used combination antidepressants.[7] Some Australian authors have argued that, due to a paucity of evidence, combination antidepressant therapies should only be used as a last resort in specialist settings.[8]

What is the evidence base?

The only published, well funded trial of combination antidepressants has been as a treatment arm involving 565 patients as part of the STAR*D study.[9] In this study, in part funded by the United States of America National Institute of Health, no additional safety precautions were considered necessary for the combinations used in this trial, being citalopram with the addition of sustained release bupropion (not available on the Pharmaceutical Benefits Scheme [PBS] in Australia for the treatment of depression), and at another level in the trial being venlafaxine combined with mirtazepine.

Small and medium sized trials, and multiple case reports, suggest there are benefits from combination antidepressants.[10] In a meta-analysis of 27 trials involving 667 patients failing to respond adequately to monotherapy, Lam et al[11] reported a 62% response rate from combination antidepressants. This result must be tempered by the very small number of randomised controlled trials and the large number of small case series included in this meta-analysis.

Carpenter et al[12] reported a double blind placebo controlled trial of adjunctive mirtazapine or placebo after failure to respond to antidepressant monotherapy in depressed patients (N=26), showing that 64% of combination antidepressant treated patients responded, including 45.4% achieving remission, whereas only 20% of monotherapy treated patients responded and 13.3% achieved remission.

Comparing combining antidepressants with switching antidepressants, half of the 61 patients who failed to respond to two monotherapy trials were given a third monotherapy of citalopram or bupropion, while the other half took combined citalopram and bupropion. Remission was four times more common in the combination antidepressant group than in the switched antidepressant group, with no significant difference in side effect burden when compared to monotherapy.[13]

A double blind study of 61 patients showed significant benefit when paroxetine was combined with mirtazapine, compared with monotherapy with either medication alone. Nonresponders to either antidepressant did significantly better when the other antidepressant was added.[14] In a recent study, 105 patients were randomly assigned over 6 weeks to fluoxetine alone (25% achieved remission), or to three different combinations of antidepressants, achieving 52% remission for mirtazapine plus fluoxetine, 58% remission for mirtazapine plus venlafaxine, and 46% remission for mirtazapine plus bupropion. Furthermore, double blind withdrawal of one component of the combination over 6 months produced a relapse in 40% of subjects.[15] In the same journal, examination of the findings raised issues such as the low dose of fluoxetine used and the 6 week duration of the trial. The results were seen as mainly supporting the addition of mirtazapine to reuptake inhibitors.[16]

A search of clinical trial registries shows that many further trials are underway or recently completed, including a National Institute of Health funded trial of combinations of bupropion, escitalopram, mirtazapine, and venlafaxine (ClinicalTrials.gov Identifier: NCT00590863).

When to combine antidepressants

Before considering treatment for depression it is necessary to first consider and exclude any factors which may prevent remission, including accurate diagnosis, comorbitities, psychosocial factors and treatment adherence.[10] Psychological therapies should also be considered as a first line treatment or as an add-on to pharmacotherapy.

While the evidence base for antidepressant monotherapy as a first line treatment for depression is strong, the evidence base for second line treatments when remission is not achieved is not as strong. Before considering combination antidepressants, numerous alternative therapies can be chosen, including antidepressant dose escalation, or switching to another antidepressant monotherapy. It is generally agreed that the addition of lithium or of atypical antipsychotics are effective treatment strategies for depression that has partially responded to an antidepressant. However, many of these options also have limited evidence bases, limited efficacy or their own safety concerns. Where such strategies have failed, or are not feasible financially, combination antidepressants may represent an effective next step. Initiating a nonpharmacological (psychological) therapy may be useful and is supported by both sides of this controversy.

In Australia, combination antidepressants are used more commonly as a later treatment option, especially for partial responders to monotherapy. Blier et al[15] point out that half of all patients discontinue antidepressant treatment within 6 weeks from initiating treatment, highlighting the importance of initiating treatment with effective medications, or moving rapidly to consolidate and hopefully add to initial, but limited, treatment gains.

How to combine antidepressants

In the absence of robust large trials in this area, *Table 1* represents the experience and specialist discussions of one author (DH), who has used combination antidepressants in selected patients over a 20 year period. The second antidepressant should ideally have a complementary biochemical mechanism of action and acceptable side effects, such as adding reboxetine or mirtazapine to an SSRI.

Ongoing titration of antidepressants to the patient's symptoms is very useful in achieving compliance and remission. Patients can be advised to contact their doctor if there is symptom recurrence, such as when faced with extra stress, after a virus, or premenstrually, or if symptoms of overmedication appear, such as the 'YES' syndrome (Yawning, Expression/word finding difficulty, Silly mistakes).[17] The effects of dose change are usually evident within 2–3 days (based on the author's clinical experience with many patients). As the use of combined antidepressants remains controversial in Australia, and is outside manufacturers' guidelines, it is appropriate to notate that you have discussed this issue with the patient, and ideally with a psychiatrist, if this can be arranged.

Which medications to combine

The ideal aim is to supplement the initial antidepressant (usually an SSRI) with an

antidepressant utilising a different chemical mechanism of action. A survey of Australian psychiatrists showed that combinations of various antidepressants with mirtazapine or reboxetine (both involving noradrenergic mechanisms) were among the most commonly used (*Table 2*).[7] This survey preceded the recent reservations about the effectiveness of reboxetine as monotherapy. In all combinations, one must be aware of the potential extra side effects involving the use of two antidepressants, such as weight gain from mirtazapine, sexual problems from SSRIs, and anticholinergic side effects from reboxetine. The newly released antidepressant agomelatine (which is reported not to have these side effects) states in its product information that it does not interact with paroxetine.[18] Agomelatine has no effect on serotonin, so the serotonin syndrome would not be expected; it acts on melatonin, noradrenaline and dopamine pathways. Agomelatine may therefore become the antidepressant of choice for addition to SSRIs. In the USA, the antidepressant bupropion (indicated in Australia only for tobacco cessation) is frequently combined with SSRIs.

Table 1. How to combine antidepressants with an SSRI or SNRI

- Increase the dose of the initial antidepressant at 1–2 week intervals while progressive improvement occurs, up to the maximum recommended dose or maximum tolerated dose
- Revert to previous dose when no improvement has occurred with the last dose increase. Consider adding lithium or an atypical antipsychotic, or second antidepressant
- Add a low dose of a second antidepressant, eg. add mirtazepine or reboxetine to an SSRI
- Avoid combinations with MAOIs or fluvoxamine
- If benefit appears within 2 weeks, further increases in this second antidepressant are indicated
- Titrate doses of antidepressants in response to symptom relapse, or overmedication symptoms such as yawning and word finding difficulties. If using tricyclics (not the ideal combination), measure trough serum levels
- Normal concentration and memory are the endpoint hallmarks of good biochemical control
- Expert opinion

Weighing relative risks

Critics often highlight unsafe combinations, which often include MAOIs resulting in severe reactions. However, MAOI combinations are now not recommended for general use by proponents of combination therapies. The most commonly reported life threatening situations due to the serotonin syndrome involve the use of MAOIs in combination with serotonin reuptake inhibitors, such as SSRIs and the phenylpiperidine series opioids.[19] An Australian review stated 'most cases of serotonin syndrome are self limiting'.[20] Rare severe or life threatening cases were associated mainly with the use of MAOIs as part of combined antidepressants. It is therefore strongly advised that MAOIs not be initiated within 14 days of stopping any other antidepressant (or within 5 weeks of stopping fluoxetine). Similarly, 14 days needs to elapse after ceasing an irreversible MAOI, before initiating another antidepressant.

As the rate of combination antidepressant use is unknown in Australia, the frequency risk of the serotonin syndrome cannot be measured. Serotonin syndrome usually occurs within 24–48 hours of increased serotonin availability, manifesting initially with sweating, tachycardia, tremor and hyper-reflexia. Abdominal cramps, diarrhoea, tachycardia and blood pressure changes may also occur. Agitation, confusion and coma are more serious events, and some fatalities have occurred in the past. Cyproheptadine 8–16 mg reverses the symptoms in less severe cases, together with withdrawal of the causative agent. Patients with severe symptoms should be referred immediately to an emergency department.[6,20] Failure to achieve full remission from depression is associated with more chronic and recurrent illness, increased medical and psychiatric comorbidities, poorer social and functional outcomes, and increased economic costs.[21] Depression which has not been effectively treated is highly correlated with Australia's weekly rate of 40 suicides and an estimated 1300 episodes of deliberate self harm.[22]

There is no established evidence of long term complications from the use of combination antidepressants, but monitoring of blood pressure, biochemistry, haematology and electrocardiogram should be considered. The adverse effect burden of antidepressant combination treatment may approximate the cumulative adverse effect burden of the individual antidepressants. However, in two trials of antidepressants combined with bupropion or placebo, the sexual side effects of monotherapy were reduced,[23] suggesting that in some cases, antidepressant combination therapy may have a side effect burden less than the cumulative adverse effect burden of the individual antidepressant.

Table 2. Australian psychiatrists' use of combination antidepressants[7]

Combination of any two antidepressants	76%
SSRI + tricylic	41%
Venlafaxine + mirtazepine	40%
SSRI + mirtazepine	37%
Other antidepressants + mirtazepine	21%
Reboxetine + other antidepressants	34%

Combination antidepressants in general practice

In the survey of Australian psychiatrists quoted earlier, 75% of respondents stated they believed GPs should be educated in the use of combination antidepressants.[7] Balancing efficacy and safety, and considering at what stage to commence combination therapies, as well as whether or not such therapy requires a specialist setting or can be initiated by a GP, need to be decided ideally by considering the evidence. However, the evidence is equivocal, and the same evidence has been used to justify very different conclusions. There are no clear results based on solid, evidence based medicine to guide doctors in dealing with treatment resistant depression. General practitioners will have to consider the evidence for themselves and decide which, if any, combination therapy to initiate, and when to do so.

Combination antidepressants are one of several next-step options after limited benefit from an initial antidepressant; other options (especially dose escalation, switching

antidepressants, lithium and antipsychotics) are summarised elsewhere.[24] This article describes the rationale and mechanism for adding a second antidepressant to build upon the benefits of the first antidepressant. Referral may therefore be essential for doctors, especially when faced with treatment resistant depression and its foreseeable consequences. The ideal scenario is to have such therapy from a psychiatrist, or to have regular telephone or email access to a psychiatrist (such as psychsupport.com.au or 1800 200 588). However, where such specialist advice is not available, or where the advice is not acceptable to patients (such as advocating voluntary psychiatric hospitalisation and electroconvulsive therapy), there are potential benefits from considering the use of combination antidepressants.

Conclusion

There are many steps to potentiate the benefits of antidepressants, including lithium, antipsychotics and antidepressant combinations. Some combinations are associated with greater efficacy and equivalent safety compared to antidepressant monotherapy. As the evidence base has grown, and clinical experience has increased, combination antidepressants have been used more commonly in specialist settings. This article suggests that when adequate trials of monotherapy have not resulted in remission, a possible approach is to add a second antidepressant with a different mechanism of action, ideally with specialist review or liaison. Combination antidepressant treatment is widely accepted in many countries, particularly in large populations such as Canada and the USA.

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