

RGH Pharmacy E-Bulletin

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A joint initiative of the Patient Services Section and the Drug and Therapeutics Information Service of the Pharmacy Department, Repatriation General Hospital, Daw Park, South Australia. The RGH Pharmacy E-Bulletin is distributed in electronic format on a weekly basis, and aims to present concise, factual information on issues of current interest in therapeutics, drug safety and cost-effective use of medications.

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Combination antidepressant therapy: safety versus efficacy

In trials involving patients with moderate to severe major depression, antidepressants have improved response in the short term by approximately 50–65%. However, only 25–35% of treated patients achieve remission, and therefore up to 75% of patients have only partial or no response to antidepressant treatment. The use of antidepressant combinations as an early option for treatment-resistant depression has become increasingly common. A large amount of information has been published in medical literature about combination antidepressant therapy, but this is predominantly in the form of reviews, case series, case reports, surveys, treatment algorithms and opinions. There is currently little evidence to support the efficacy of antidepressant combinations (see table below); however, post marketing data indicate increased risk of serious adverse effects, even when modest doses of each agent are used.

Where antidepressant monotherapy has been unsuccessful, prior to considering unproven strategies such as antidepressant combinations, it is essential to ensure the diagnosis is correct, psychosocial issues have been addressed, and that antidepressant monotherapy has been optimised (including a consideration of adherence and whether the antidepressant dose and duration have been adequate).

There are three main safety concerns with antidepressant combinations:

- Serotonin syndrome, a theoretical risk with any antidepressant combination. Published case reports describe serotonin syndrome possibly in association with SSRIs plus mirtazapine; venlafaxine plus mirtazapine; SSRIs plus venlafaxine; and moclobemide plus SSRIs - see E-bulletin volume 18(4).
- Pharmacokinetic interactions: potential for increased antidepressant blood levels and hence adverse effects and/or toxicity with some combinations. For example, significantly increased TCA blood levels have been observed with TCA/SSRI combinations in some patients (resulting in serious adverse effects), and mirtazapine blood levels have been markedly increased when combined with fluvoxamine.
- Seizures: risk may be increased.

Evidence with combinations of antidepressants (not every possible antidepressant combination has been included):

Combination	Published anecdotes or case reports	Observational trials (e.g. open trials)	Randomised controlled trials
TCA plus SSRI	Yes	Yes	One small RCT found lack of benefit
SSRI plus mirtazapine	Yes	Yes	Two small RCTs (26 and 60 patients) suggested benefit.
mirtazapine plus venlafaxine	Yes	No	One small RCT (109 patients) suggested small benefit.
reboxetine plus an SSRI, venlafaxine or mirtazapine	Yes	Yes	No
SSRI plus venlafaxine	Yes	No	No
TCA plus venlafaxine	Yes	No	No
moclobemide plus SSRI	Yes	Yes	No

Based on the limited evidence of efficacy, and concerns about toxicity, antidepressant combinations cannot be generally advocated for use in the general practice setting. This approach might be considered by psychiatrists after a careful evaluation of risks and potential benefit for the individual patient. Close monitoring of the patient is paramount. Combination therapies that include the use of an irreversible MAOI (e.g. tranylcypromine or phenelzine) are either absolutely contraindicated or not recommended, as these combinations have previously been associated with fatalities.

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FOR FURTHER INFORMATION – CONTACT THE PHARMACY DEPARTMENT ON 82751763 or email: chris.alderman@rgh.sa.gov.au
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