Graylands Hospital Drug Bulletin

Antidepressant Combination and Augmentation Strategies

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Introduction

Depression is a common and serious mental illness affecting as high as 5.8% of the adult population of Australia in a twelve month period.[1] First line pharmacotherapy recommended by the WAPDC and RANZCP is an SSRI, mirtazapine or venlafaxine, however pooled results of double-blind randomised controlled trials estimate that remission rates are only 30-45%.[2] Currently there is little evidence to guide practitioners who wish to venture into augmentation and combination strategies to improve remission rates in treatment resistant depression. In light of this, large-scale clinical trials such as the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study are underway to improve the safety and efficacy profiles of combination and augmentation strategies for treatment resistant depression.

Incidence of Antidepressant Combinations

While being an "off-label" strategy, antidepressant combinations are becoming an increasingly utilised method of treating resistant depression. Data obtained from a drug utilisation review "snapshot" at Graylands Hospital in May 2008 showed 31% of all inpatients were taking at least one antidepressant (63 patients). Of these patients, 7.9% (5 patients) were taking a combination of antidepressants. This is an increased trend from the 2005 drug utilisation review in which only one patient was receiving a combination of antidepressants.

A recent Australian survey[3] was sent to 3053 consultant psychiatrists, trainee registrars and registered medical officers working in psychiatry, achieving 1107 replies. Of these, 76% of practitioners reported prescribing antidepressants in combination and 798 of these practitioners said they were more likely to combine antidepressants rather than use a single agent above the manufacturer's recommended maximum dose. The most frequently reported combinations were SSRIs + TCAs (41%), mirtazapine + venlafaxine (41%), mirtazapine + SSRIs (37%) and mirtazapine + other antidepressant (21%). Reboxetine was reported by 34% of practitioners as being used in combination with other antidepressants.

Argument For Antidepressant Combination and Augmentation[4]:

- Improve noradrenergic and sertonergic activity
- Build on partial response; patient doesn't have to "start over"
- More rapid onset of effect
- Fewer discontinuation syndromes
- May reduce side effects of first anti-depressant
- Improve remission rates
- Improve quality of life

Argument Against Antidepressant Combination and Augmentation[4]:

- Little evidence from controlled trials to guide clinical decisions
- Polypharmacy increases the risk of potentially dangerous drug interactions
- Reduced compliance
- Increased adverse effects
- Increased tablet load
- Increased cost

Abbreviations:

RANZCP: Royal Australian and New Zealand College of Psychiatrists
WAPDC: Western Australian Psychotropic Drug Committee
SSRI: Selective Serotonin Reuptake Inhibitors
TCA: Tricyclic antidepressant
MAOI: Monoamine Oxidase Inhibitor
HAM-D: Hamilton Rating Scale for Depression
T3: Liothyronine
CBT: Cognitive Behavioral Therapy
NIMH: National Institute for Mental Health (US)
RR: Remission Rate

Government of Western Australia
Department of Health
Mental Health

Contraindicated Antidepressant Combinations

MAOIs are contraindicated for use in combination with other antidepressants including SSRIs, TCAs, mirtazapine, reboxetine, venlafaxine and bupropion, due to high risk of serotonin toxicity and hypertensive crisis[5]. Very little evidence exists for these combinations due to safety concerns.

MAOIs have been used in combination with TCAs in the past and this is documented in several trials and case series.[6-10] This combination however is still a high risk strategy requiring close supervision and should only be initiated by an experienced consultant psychiatrist.

Risks of Antidepressant Combinations

The main risk associated with antidepressant combinations is an increased risk of serotonin serotonin syndrome. This phenomenon can occur with a high dose of a single drug, when more than one serotonergic drug is used together or when there is inadequate washout period between changing some antidepressants. Medications including stimulants, pseudoephedrine and illicit drugs such as ecstasy and LSD can also cause serotonin syndrome if taken in combination with antidepressants.[5]

When an excess of serotonin builds up in the neural synapse it may cause many side effects, listed below in Table 1. There is also an increased chance of pharmacokinetic and pharmacodynamic interactions that may increase this risk or may adversely affect levels of other medications or increase chances of side effects, e.g. lowering seizure threshold in TCAs.

Table 1. Signs and symptoms of serotonin syndrome[5]

Body System	Adverse Effects
Musculature	Hyperreflexia, Clonus, Tremor, Incoordination
Mental State Changes	Confusion, Hypomania, Aggression
CNS	Shivering, Sweating, Fever
Gastrointestinal	Diarrhoea

Due to these risks, well-designed and large-scale clinical trials are required, which will enable clinicians to make evidence based decisions. Up until more recently, few large clinical trials that investigated the safety and efficacy profiles of commonly used, off-label antidepressant combinations existed.

In 2006 the largest most comprehensive clinical trial began – STAR*D. To date this study has generated more than 80 publications. The main results of the treatment levels are presented here.

Sequenced Treatment Alternatives to Relieve Depression STAR*D

STAR*D is a multi-site, prospective, randomised, multi-step clinical trial enrolling outpatients with a non-psychotic major depressive disorder. This study is supported by the NIMH and is the largest, most comprehensive study looking into combination and augmentation strategies for patients who do not attain a satisfactory response with an SSRI, citalopram. After failing an adequate treatment course with citalopram patients move to level two of the study and are given the choice to either switch to a different antidepressant, or to add an antidepressant or an augmenting medication to their regime. If still no remission is achieved patients then move through level three and four. Pharmacological treatments in combination with cognitive behavioural therapy was also studied however the results are not discussed here. See the adjacent page for a flow diagram of the study with the medications used and the remission rates at each step. Response and remission was measured using both HAM-D and the Quick Inventory for Depressive Symptomatology tests.

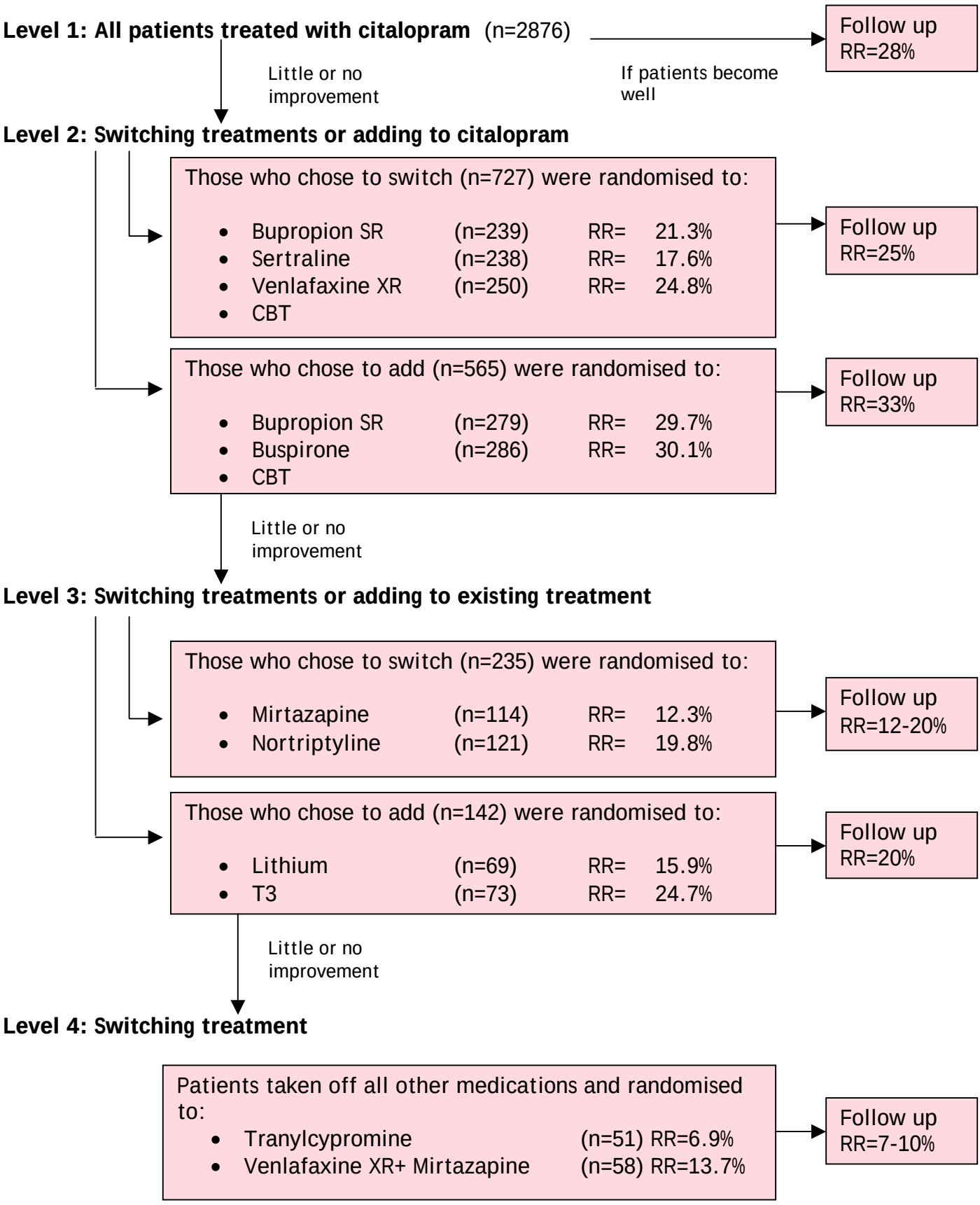
Level 1 Results[11]

Approximately 28% of the 2876 patients went into remission based on HAM-D scores when treated with citalopram alone. The response rate to treatment including those who went into remission was 47% of patients. These results were comparable to other smaller efficacy studies.[12] The mean time to remission in these patients was 6.7 weeks, and mean time to response was 5.7 weeks. The mean dose of citalopram when patients exited this level was 41.8 mg daily. It was noted in this study that patients who were white, female, married, more educated, had higher income, had private health insurance and were employed had a significantly higher remission rate with citalopram. Those who had increased co-morbidities, poorer function and quality of life had significantly lower remission rates.

Level 2 Results[13-14]

From the patients in level 1, 1439 either were intolerant to citalopram or did not achieve remission and moved to level 2. Most participants in this study elected to allow either switch or augmentation randomisation, not both. This meant the results of this study did not provide statistical power to compare an outcome for switch versus augment. For patients that chose to switch treatments, about one quarter went into remission. There was no significant difference between bupropion-SR, sertraline and

Treatment Algorithm and Remission Rates in STAR*D



Note: Bupropion and buspirone are not indicated for depression in Australia. Figure adapted from STAR*D

venlafaxine-XR. For those who went into remission, the mean time was 5.4 to 6.2 weeks. For patients who chose to augment treatment, about one third went into remission with both buspirone or bupropion-SR augmentation, with no significant difference between each strategy. Participants that were treated with bupropion-SR exhibited greater improvement in symptom severity and a lower dropout rate due to intolerance.

Level 3 Results[15-16]

From the patients in level 2, 377 did not achieve adequate response or had intolerance and moved to level 3. For patients that chose to switch treatments, there was no significant difference in remission rates, response rates or time to remission or response when comparing mirtazapine and nortriptyline after two failed attempts at treatment. The remission rates as measured by HAM-D were 12.3% and 19.8% respectively. For patients that chose to augment treatment, there was no significant difference in remission rates, response rates or time to response between lithium and T3 augmentation. The remission rates as measured by HAM-D were 15.9% and 24.7% respectively. The remission rates were not significantly different to the strategies used in level 2. It was noted that T3 augmentation might be the preferential augmentation strategy as fewer patients reported intolerance, however long term safety data has not been established.

Level 4 Results[17]

There were 109 patients who were yet to reach remission and were moved to level 4. Of these 58 were treated with tranylcypromine and 51 were treated with a combination of venlafaxine-XR plus mirtazapine. Remission rates were low, 6.9% and 13.7% respectively. It was noted however that the patients in the tranylcypromine group did not reach the protocol recommended maximum dose of 60mg daily. There was no difference between the groups for response, remission or time to response/remission. Patients taking tranylcypromine were more likely to leave the study due to side effects and dietary restrictions, thus the combination of mirtazapine and venlafaxine-XR may be the better option.

Conclusions of STAR*D

The total remission from treatment resistant major depression was approximately 50% after two levels of treatment, which is a good result in comparison to other chronic illnesses.

The authors also note that the small remission rates in level three and four suggest that it may be of benefit for combination and augmentation therapy to commence earlier in treatment, to achieve a more rapid remission of depressive symptoms. A limitation of this study therefore is that it did not assess using combination therapy versus monotherapy at the initiation of treatment. The authours conclude that the differing pharmacological approaches did not translate into large clinical difference and treatment options should be chosen using clinical characteristics for each patient. If a practitioner decides to commence a patient on the strategies presented in this study, it should be made clear that risk for drug interactions, adverse and long term effects, and increased cost should all be individualised and taken into account when commencing a patient on combination and augmentation therapy.

Evidence for other antidepressant combinations – Reboxetine

Rubio et al studied the combination of reboxetine with SSRIs, mirtazapine or venlafaxine in an open label trial.[18] In this 6-week trial, reboxetine was added to the regimen of 61 patients who had not or only partially responded to an adequate monotherapy with the aforementioned antidepressant agents. The mean decrease in depressive symptoms as measured by HAM-D was 48.9%. From 62.3% of patients who were measured as improved, 54.1% responded to treatment and 45.9% went into remission. No significant side effects were observed, except an increase in sweating (8.2%), and dry mouth (6.6%) in the combination group. In light of this, reboxetine offers a promising, tolerable strategy to augment current antidepressant therapy in patients with treatment resistant depression.

For an extensive list of previous trials with antidepressant combinations see Graylands Drug Bulletin February 2003, available on the NMHS Graylands intranet.

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This Drug Bulletin was reviewed by the Graylands Pharmacy Department and Dr Dell

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Comments are welcome at the email address: DrugInformation.Graylands@health.wa.gov.au

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