Augmentation and Combination Strategies in Antidepressants treatment of Depression

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Background

- The response rates reported for most newer antidepressant medications were in the range of 60–70% in placebo-controlled clinical trials. (12%-15% exhibit partial response, 19%-34% nonresponders)

- 30% of those treated for MDD do not benefit from a series of treatment trials (Thase, 2004).

- Selective serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake inhibitors (SNRIs) tend to show remission rates of just 25% to 45% in acute trials (Thase et al., 2001).

- STAR*D study: initial remission rate with citalopram: 28%
### Terms used to describe treatment response

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tr>
<td>Nonresponse</td>
<td>A lack of response or response poor enough to require a change in treatment plan [e.g., failure to achieve ≤ 25% reduction in HAM-D score]</td>
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<td>Partial response</td>
<td>Improvement in HAM-D ≥25% but &lt;50% from baseline</td>
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<td>Response</td>
<td>Therapeutic response good enough to indicate continuing present treatment plan [e.g., ≥ 50% reduction in HAM-D score]</td>
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<td>Remission</td>
<td>Attainment of virtually asymptomatic status [e.g., 17-item HAM-D ≤ 7] for at least 2 consecutive weeks</td>
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<td>Recovery</td>
<td>Remission for ≥ 6 consecutive months</td>
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<td>treatment resistant depression (TRD)</td>
<td>Nonresponse despite ≥ 2 treatment trials with drug from different pharmacologic classes, each used in an adequate dose for an adequate period</td>
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Thase ME, Rush AJ, 1995

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### Lack of Response

- **Correct diagnosis?**
- **Comorbid conditions?**
- **Optimize dosage**
Strategies for managing treatment resistant depression

- Optimize administration of the current medication
- Switch to a different antidepressant in the same class
- Switch to a antidepressant in a different class
- Combine with a second antidepressant
- Augment with a nonantidepressant agent
- Augment with a nonpharmacologic modality

Augmentation and combination strategies

- Augmentation and combination strategies are particularly helpful in managing treatment-resistant patients who have had a partial response to treatment.
- These strategies allow the patient to maintain the improvement already achieved, and positive effects may appear rapidly and avoid withdrawal symptoms.
- Improvement tends to occur within 3 to 4 weeks
- A typical approach is to maintain the augmenting agent for 6 to 9 months after obtaining remission
- Disadvantages: cost, side effect, drug interaction
Favored SSRI augmentation strategies

- Bupropion
- Atypical antipsychotics
- Psychostimulants/dopamine agonists
- Lithium
- Modafinil
- Thyroid hormone
- Tricyclics

Thase, 2004, Pies 2005

Lithium

- At least ten double-blind, placebo-controlled studies; four randomized comparator studies; 13 open-label studies.
- Overall, approximately 50% of patients respond to lithium augmentation, usually within 2–6 weeks.
- 600mg/day or more lithium, typically in divided doses and with adequate blood level leads to increase in the chance of response.
- Thase (2004) acknowledges the possibility that lithium may be less useful in combination with SSRIs than tricyclics.
- There is risk of toxicity, the need for blood monitoring.
Thyroid hormone

- Meta-analysis of eight controlled trials (four randomized, double-blind) showed that patients treated with T3 augmentation of TCAs were twice as likely to respond as controls.
- Liothyronine (T3) has been used in preference to thyroxine (T4) because of its rapid onset and offset of action.
- T3 augmentation (25µg to 50µg/day) has been used successfully among TCAs nonresponders.
- Most published studies concern TCAs and not SSRIs.
- S/E: nervousness, insomnia


- Remission rates with lithium (15.9%) and T3 (24.7%) augmentation for participants who experienced unsatisfactory results with two prior medication treatments were modest and did not differ significantly.
- The lower side effect burden and ease of use of T3 augmentation suggest that it has slight advantages over lithium augmentation for depressed patients who have experienced several failed medication trials.
Psychostimulants

- No controlled, double-blind studies of amphetamine augmentation.
- One small positive open study showing methylphenidate effectively augmented citalopram in elderly depressed patients (Lavretsky et al., 2003).
- Methylphenidate (10-40mg), dextroamphetamine (5-20mg), in divided dose, Modafinil (200mg/day)
- Disadvantage: potential for abuse and short half-life, long term use - tolerance
- S/E: worsen anxiety and irritability

Modafinil

- Several positive open studies of modafinil in SSRI non-responders.
- Two double-blind, placebo-controlled studies failed to show robust effects on primary outcome measures of depression, but showed modest augmentation on secondary outcomes, including sleepiness/fatigue (DeBattista et al., 2003, Fava et al., 2005).
- Side effects include headache, nausea, nervousness, anxiety, insomnia, possible exacerbation of mania, psychosis.
Dopaminergic Drugs

- Several open studies have shown pergolide (0.2-2mg/day) or amantadine (100-200mg twice a day), and pramipexole (0.125-0.25mg 3 times a day) showed usefulness of augmentation.
- The effectiveness is remains to be established.

Buspirone

- Antianxiety drug with serotonin 1A partial agonist properties.
- 5 to 15mg twice a day
- Despite some positive open-label reports assessing buspirone as augmentation with an SRI (Bouwer and Stein, 1997) and sertraline (Sprenger, 1997), controlled studies have been less supportive.
- One possible advantage is in alleviating SSRI-induced sexual dysfunction (Landen et al. 1999)
- The main issues concerning is its efficacy.
Atypical antipsychotics


Atypical antipsychotics

- Olanzapine, quetiapine and aripiprazole have strongly supportive data from prospective, controlled clinical trials as augmenters of SSRIs for TRD.
- Although there is one positive controlled trial with risperidone, the data are not robust, and another longer-term outcome study was negative.
- Although AAPs may be effective augmenters, their place remains obscure. 

Shelton and Papakostas, 2008
Thase et al, 2008
Anticonvulsants

- There are uncontrolled and anecdotal reports of the usefulness of anticonvulsant augmentation of antidepressants in major depression, with drugs such as gabapentin, topiramate, carbamazepine, valproic acid and lamotrigine.
- There are no adequately powered, prospective controlled studies of anticonvulsant augmentation in the management of nonremission of MDD, nor as initial treatment with nonresistant depressed patients.

Fava and Rush, 2006

Other Augmentation strategies:

- Pindol
- Inositol
- Opiates
- Estrogen
- Dehydroepiandrosterone (DHEA)
- Folate and S-Adenosyl-Methionine (SAMe)
- Omega-3 Fatty acid
Bupropion + SSRIs

- Adding bupropion to an SSRI is a very popular strategy, even though all the supportive data come from uncontrolled studies.

- The rationale for this combination is that the catecholamine effects of bupropion would complement the serotonin effects of the SSRI.

- The main disadvantages of this approach are possibility of inducing tremor or panic attack.

- Positive effects of bupropion on SSRI induced sexual dysfunction reported in some cases.

Medication Augmentation after the Failure of SSRIs for Depression: A STAR*D report (2006)

- Bupropion (29.7%) and buspirone (30.1%) had similar rates of HRSD-17 remission

- Bupropion was associated with a greater reduction (from baseline to the end of this study) in QIDS-SR-16 scores than was buspirone (25.3 percent vs. 17.1 percent, P<0.04), a lower QIDS-SR-16 score at the end of this study (8.0 vs. 9.1, P<0.02), and a lower dropout rate due to intolerance (12.5 percent vs. 20.6 percent, P<0.009).
Mirtazapine + SSRIs

• Mirtazapine combined with SSRIs have been reported to be helpful in an open and double blind study of nonresponders to SSRIs (Carpenter et al. 1999, 2002).

• Mirtazapine combined with SSRIs may also help manage SSRI-induced sexual dysfunction.

• S/E: weight gain, sedation

SSRIs + TCAs

• Comparing the combination of desipramine and fluoxetine with either drug alone found the combination significantly more likely to result in remission.

• A more recent, prospective randomized trial (Nelson et al, 2004) found remission rates were significantly higher with desipramine plus fluoxetine than with either drug alone.

• SSRIs inhibit the cytochrome P450 2D6 pathway and thus can raise desipramine concentration 3-to-4-fold.

• Low doses of TCAs (25–75 mg/day) are used
SSRIs + Venlafaxine

- One case report of venlafaxine combination in SSRI nonresponders (Gonul et al, 2003).
- The main disadvantage is that venlafaxine is a substrate of CYP2D6, and there have been reports of accumulation of venlafaxine, leading to serotonin syndrome.

SSRI + SSRI

- Some secondary effect of the SSRIs differ
  - Paroxetine: weak norepinephrine effect
  - Sertraline: weak dopamine effect
- But these secondary effect appear weak at best and have not been shown to be clinically meaningful.
- The main disadvantage of this approach are an increase in the intensity of serotonergic side effects and serotonin syndrome.
Thank you very much for your attention!!