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If at First You Don't Succeed

A Review of the Evidence for Antidepressant Augmentation, Combination and Switching Strategies

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Abstract

Major depressive disorder is a common and disabling illness that leads to significant reductions in quality of life and considerable cost to society. Despite numerous advances in the pharmacological treatment of depression, many patients remain ill despite initial treatment. Beyond first-line treatment, current guidelines recommend either augmentation or switching of the initial antidepressant. In this narrative review, we summarize the data from randomized controlled trials and meta-analyses in order to concisely discuss how the impact of current research can be translated into clinical practice and, ultimately, into lasting improvements in patient outcomes. The augmentation strategies reviewed are lithium, thyroid hormone, pindolol, psychostimulants and second-generation antipsychotics. The data on switching from first-line antidepressants to other antidepressants are also reviewed, and include switching within the same class, switching to other first-line antidepressant classes and switching to less commonly prescribed antidepressants. Finally, the strategy of antidepressant combinations is examined. Overall, the strength of evidence supporting a trial of augmentation or a switch to a new agent is very similar, with remission rates between 25% and 50% in both cases.

Our review of the evidence suggests several conclusions. First, although it is true that adjunctive lithium and thyroid hormone have established efficacy, we can only be confident that this is true for use in combination with tricyclic antidepressants (TCAs), and the trials were done in less treatment-resistant patients than those who typically receive TCAs today. Of these two options, triiodothyronine augmentation seems to offer the best benefit/risk ratio for augmentation of modern antidepressants. After failure of a first-line selective serotonin reuptake inhibitor (SSRI), neither a switch within class nor a switch to a different class of antidepressant is unequivocally supported by the data, although switching from an SSRI to venlafaxine or mirtazapine may potentially offer greater benefits. Interestingly, switching from a newer antidepressant to a TCA after a poor response to the former is not supported by strong evidence. Of all strategies to augment response to new-generation antidepressants, quetiapine and aripiprazole are best supported by the evidence, although neither the cost effectiveness nor the longer-term benefit of these strategies has been established.

The data to guide later steps in the treatment of resistant depression are sparse. Given the wide variety of options for the treatment of major depressive disorder, and the demonstrated importance of truly adequate treatment to the long-term outcomes of patients facing this illness, it is clear that further well conducted studies are needed.

Major depressive disorder is a common and disabling illness that affects up to 15% of people over the course of their lives.[1] Those affected face significantly reduced quality of life, impaired ability to work and poorer overall health, while society incurs considerable economic costs.[1,2] The introduction of newer-generation antidepressants has improved our ability to treat depression, although only about 50–60% of patients will respond to first-line treatment and only 35–40% will experience a remission of symptoms during an initial 8-week trial.[3] Clearly, evidence-based second steps are needed if patients are to begin to recover from this serious illness.

The question of how to proceed with the next step in depression treatment after an initially unsuccessful trial is a vital one; a good choice can improve outcomes and resolve illness, while

persistent depression may lead to a more chronic and morbid course.[4,5] A number of options exist and are recommended in clinical guidelines, but guidance as to which option is best remains limited.

This review aims to synthesize results from randomized clinical trials, meta-analyses and evidence-based clinical guidelines to make recommendations for the next step in the pharmacological treatment of adults with major depressive disorder who have not had an adequate clinical response to their first antidepressant medication treatment.

1. Methods of Literature Review

For this review, a search for evidence-based guidelines for the treatment of adults with major depressive disorder was performed on 1 March 2010, using the National Guideline Clearinghouse database, the Agency for Healthcare Research and Quality Evidence Reports database and the Cochrane Database of Systematic Reviews. In addition, a 'clinical query' of the PubMed database and searches of drug manufacturers' websites (for unpublished trials) were performed to identify randomized controlled trials (RCTs) and meta-analyses evaluating strategies to treat resistant depression.

2. Clinical Guidelines

Although many guidelines exist to aid in the initial management of major depressive disorder, recommendations for treatment-resistant depression are more limited. The following depression guidelines were identified and reviewed:

- *American Psychiatric Association Practice Guideline for Treatment of Patients with Major Depressive Disorder* (2000; Guideline Watch Update 2005);[6]
- *Clinical Practice Recommendations for Depression* (2009);[7]
- *Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical Guidelines for the Management of Major Depressive Disorder in Adults* (2009);[8] and
- *Institute for Clinical Systems Improvement (ICSI) Healthcare Guideline for Major Depression in Adults in Primary Care*.[9]

These guidelines provide the following evidence-supported first-line recommendations after the failure of an initial antidepressant trial that has been optimized in dose and duration:

- the addition of psychotherapy;[6,9]
- lithium augmentation;[6-9]
- augmentation with second-generation antipsychotics (SGAs);[8,9]
- augmentation with triiodothyronine (T_3);[6-9] and
- switching to another antidepressant.[6-9]

We summarize the evidence for each of the medication options noted in order to help clinicians decide which option is the best next step. These guidelines note that the strategies of combination therapy with two antidepressants and augmentation with stimulants or buspirone are commonly practiced but relatively unsupported by evidence; combination therapy is understudied, while there is evidence against the efficacy of buspirone for this purpose. The use of neurostimulation therapies (electroconvulsive therapy and transcranial magnetic stimulation) is recommended later in the treatment course.[8] We note that the addition of psychotherapy is a helpful option, and one that is not incompatible with further medication changes, but that a discussion of psychotherapy is beyond the scope of this review.

3. Augmentation

Augmentation is the addition of an agent – not thought to be an antidepressant itself – to an antidepressant regimen in order to improve efficacy. Also referred to as adjunctive therapy, currently recommended agents include lithium, SGAs and T_3. These agents are recommended as adjuncts to first-line antidepressants, which, as per the guidelines in section 2, include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), bupropion and mirtazapine.[7,8] Stimulants and buspirone are also used for adjunctive therapy, although they are not considered first line in current guidelines due to a lack of strong supporting evidence.

3.1 Lithium

Lithium salts are among the oldest drugs used in psychiatry and have been used since the 1960s

in attempts to augment antidepressants.[10] Since then, of all of the strategies used to augment antidepressants, lithium remains one of the most extensively studied in RCTs.[11] It was initially proposed to act by increasing serotonergic neurotransmission; 30 years of subsequent research has not produced a more definitive answer, and this remains a viable hypothesis.[12,13]

A recent meta-analysis by Crossley and Bauer[14] (2007) found five studies of lithium as an 'accelerator' of antidepressant response and ten studies of lithium augmentation of antidepressant medications that warranted inclusion in their meta-analysis. No significant effect of lithium on the speed of antidepressant response was noted.

By contrast, the efficacy of lithium augmentation was confirmed, with an overall odds ratio for response of 3.1 (1.8–5.4) favouring lithium.[14] Eight of the ten RCTs included in the meta-analysis showed a significant benefit of lithium added to an antidepressant; pooling the results of the ten trials, the number needed to treat (NNT) to achieve one clinical response can be calculated as 4.

Of the two studies that failed to observe a statistically significant effect favouring lithium augmentation, it is plausible that one failed to do so because of the low doses of lithium used (the mean plasma concentration was only 0.25 mEq/L).[15] However, this was unlikely in the second study.[16]

In that study, depressed patients with a history of significant treatment resistance (defined as at least one, but no more than five, unsuccessful antidepressant treatment trials in the current episode) were first treated for 6 weeks with nortriptyline alone (mean dose 116.7 mg/day, plasma concentration 95.7 ng/mL), with those who did not respond (n = 92) randomized to 6 weeks of additional double-blind augmentation therapy with either lithium or placebo. There was no evidence of efficacy whatsoever; intent-to-treat response rates were 11.1% and 17.6%, respectively. A possible explanation is that most of the patients in this study had already received one or more adequate trials of therapy with SSRIs before the sequenced combination of nortriptyline and lithium, and, therefore, had little potential to benefit from lithium, with its comparatively weaker effects on serotonergic neurotransmission; that is, if enhancing serotonergic neurotransmission were to be effective for these patients, then responses would likely have already been seen with SSRIs. If this is true, one might hypothesize a lower efficacy for lithium as an augmenter of SSRIs, the most commonly recommended first-line antidepressants.[7,8]

Lithium effectively augments response to tricyclic antidepressants (TCAs). However, since that first generation of research, the TCAs have been replaced as the first line of antidepressant therapy by the SSRIs and several other antidepressants, and surprisingly few data exist on these combinations. Thus, it is unclear that lithium provides similar benefits when added to other antidepressant medications. Nevertheless, the majority of open-label or uncontrolled trials suggest a beneficial effect of this combination and the small randomized, placebo-controlled trial by Baumann and colleagues[17] found a large benefit of this combination in 24 patients for whom citalopram monotherapy had proved ineffective; 60% versus 14% response with lithium and placebo augmentation, respectively.[17-20]

This dramatic effect was not replicated in the more recent STAR*D (Sequenced Treatment Alternatives to Relieve Depression) trial, which compared lithium and T_3 augmentation in 142 patients who failed to respond to two sequential trials with newer antidepressants (i.e. citalopram, followed by sertraline, bupropion or venlafaxine extended release [XR]).[21] This study used a randomized but open-label design, with the primary outcome assessment completed by an independent evaluator without knowledge of treatment assignment. In this trial, only 15.9% of the patients treated with lithium augmentation remitted, compared with 24.7% of the patients treated with T_3 augmentation; this difference was not statistically significant. Four caveats are noteworthy. First, the primary outcome of remission (specified as ≤7 on the 17-item Hamilton Depression Rating Scale [HDRS]) is far more stringent than that of response (50% improvement), which had been the typical outcome measure in prior studies. Second, lithium doses were relatively low and indices of tolerability, including

weeks 'on therapy', favoured the group treated with T_3 augmentation. Third, the randomization strategy used in STAR*D, an equipoise stratified randomization that took patient preference into account, skewed the population of the augmentation study to include a disproportionate number of patients who were partial responders to antidepressant therapy. If response to lithium augmentation is better among patients with more severe symptoms, the randomization procedure may have biased the trial in favour of T_3 augmentation. Finally, as in the study of Nierenberg et al.,[21] which failed to detect a significant drug versus placebo difference in favour of lithium augmentation, all patients in the STAR*D trial had not obtained adequate benefit from at least two courses of antidepressant therapy.

Lithium is one of the oldest and most studied agents used to improve outcomes in patients who experience inadequate results from an antidepressant trial. The evidence is strongest for patients whose depression is inadequately treated by an initial trial of a TCA. However, the data for augmentation of newer antidepressants are weak, and significant benefit has not been observed in the two most recent trials of this strategy (table I).

As the TCAs are now typically reserved for patients with more advanced levels of treatment resistance, the relevance of lithium augmentation in contemporary practice is less clear than might be assumed from the strong recommendations found in current guidelines; given the adverse effects, relatively low therapeutic index and longer-term risks of thyroid and renal compromise associated with this agent, it should be used to augment SSRIs with caution.

Table I. Lithium and triiodothyronine (T_3) augmentation in randomized, placebo-controlled trials (RCTs)

Agents	N in RCT	NNT
Lithium for TCA nonresponse[14]	269	4
Lithium for SSRI nonresponse[17]	24	2.2
T_3 for TCA nonresponse[22]	292	4.3
T_3 for SSRI nonresponse[23]	36	No advantage found

N = number of subjects; **NNT** = number needed to treat for one clinical response; **SSRI** = selective serotonin reuptake inhibitor; **TCA** = tricyclic antidepressant.

3.2 Triiodothyronine

Thyroid hormones have been less extensively studied than lithium as augmenters of antidepressant efficacy. In contrast to practice guidelines for the treatment of hypothyroidism, which recommend levothyroxine (T_4), the preferred form of thyroid hormone for adjunctive use in combination with antidepressants is T_3 because of theories of its activity within the CNS and perceived rapid onset of action.[24] Like lithium, T_3 was initially proposed as a strategy to accelerate TCA response. The first placebo-controlled study was conducted by Prange and colleagues[25] in 1969, and reported that T_3 was effective at improving and accelerating antidepressant response to imipramine. Since this classic study, numerous others have investigated the potential role of T_3 in improving antidepressant response.

A meta-analysis by Aronson et al.[22] (1996) focused on the efficacy of T_3 augmentation in studies of patients who had not responded to TCAs. Compared with placebo-treated patients, those who received augmentation with T_3 were twice as likely to respond; the absolute increase in response rate was 23.2%, for an NNT of 4.3.[22]

As with lithium augmentation, an important question remains as to whether these findings can be generalized to treatment with newer antidepressants. Though the STAR*D results discussed in section 3.1 suggest that T_3 may have an advantage compared with lithium in this regard, this study did not include a placebo control and the difference between the two augmentation groups was not statistically significant on the primary dependent measure.[21]

Five RCTs have been reviewed by Cooper-Kazaz and Lerer[26] to evaluate the ability of T_3 to 'enhance' (improve response by initial coadministration of SSRI and T_3) or augment response to SSRIs. Of note, the single trial that demonstrated a statistically significant benefit over placebo actually did not test T_3 augmentation, but rather evaluated coadministration of T_3 from the outset of therapy with a relatively modest dose of sertraline (maximum dose 100 mg/day).[27] Remitters showed lower baseline T_3 and a greater suppression of thyroid-stimulating hormone than did

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