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Q/Can nonantidepressants help treat depression?

In terms of augmenting antidepressants, T_3 may have a slight advantage over lithium because it has fewer side effects.

EVIDENCE-BASED ANSWER

A/ **YES, LITHIUM, TRIIODOTHYRONINE (T_3), AND ATYPICAL ANTIPSYCHOTICS** are all effective adjuncts. Lithium (serum levels >0.5 mEq/L) can produce clinical improvement when added to ineffective antidepressant treatment (strength of recommendation [SOR]: **A,** meta-analysis of randomized controlled trials [RCTs]).

Thyroid supplementation using T_3 at doses no higher than 50 mcg per day also increases the effectiveness of antidepressant therapy (SOR: **B,** meta-analysis of RCT and cohort studies).

Atypical antipsychotic agents are less effective adjuncts for patients with treatment-resistant major depressive disorder (SOR: **B,** meta-analysis of RCT and cohort studies).

Evidence summary

As many as 30% of patients with major depression fail to respond to treatment with a single antidepressant drug given in adequate dosage for an appropriate period.[1] Pharmacologic approaches such as switching antidepressant classes are often attempted first, followed by augmentation with another agent if needed.

The most widely studied medications used for augmentation are lithium and T_3.[2] An important limitation to their use is that most of the supporting evidence comes from studies of patients who didn't respond initially to tricyclic antidepressants.

Lithium boosts response to antidepressants

A 2007 meta-analysis of 10 augmentation studies reported that adding lithium to various antidepressant agents increased the chances of clinical response 3-fold relative to placebo (odds ratio [OR]=3.11; 95% confidence interval [CI], 1.80-5.37), yielding a number needed to treat (NNT) of 5.[3] The mean response rate was 41.2% in the lithium group and 14.4% in the placebo group (P<.001). The meta-analysis included only RCTs that enrolled subjects with unipolar or bipolar disorder (depressive phase) who were treated with any antidepressant plus lithium in any dose compared with placebo.

A previous meta-analysis published in 1999 concluded that a lithium dose sufficient to produce serum levels of at least 0.5 mEq/L and a minimum treatment duration of 2 weeks resulted in a pooled OR of response to lithium augmentation compared with placebo of 3.31 (95% CI, 1.46-7.53).[4] Lithium augmentation is a reasonable alternative for depressed patients who don't respond to conventional antidepressants.

T_3 works well with tricyclics, but what about newer antidepressants?

A 1996 meta-analysis of 8 studies with a total of 292 patients found that patients who received T_3 augmentation of tricyclic antidepressant therapy were twice as likely to respond as controls (relative response=2.09; 95% CI, 1.31-3.32).[5] The corresponding pooled absolute difference in response rate was 23.2% with a corresponding NNT of 4.3.

T_3 dosage in the studies ranged from 25 to 50 mcg/day and duration varied from 7 to 35 days. Analysis of data from RCTs alone produced a lower pooled relative response of 1.53

(95% CI, 0.70-3.35) and an NNT of 12.5. A major drawback of T_3 augmentation is that little information is available about its efficacy in combination with newer antidepressant agents.

T_3 may have a slight edge over lithium in side effects

As a part of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, lithium and T_3 augmentation were compared directly in patients who had failed 2 medication treatments for depression. A total of 142 adult outpatients with nonpsychotic major depressive disorder who had not achieved remission with (or who were intolerant to) citalopram, and who similarly had no luck with either a therapeutic switch or an augmentation trial, were randomly assigned to lithium or T_3 augmentation for as long as 14 weeks.

After a mean of 9.6 weeks of treatment, remission rates were 15.9% with lithium and 24.7% with T_3, although the difference between the 2 drugs wasn't statistically significant. Because T_3 has fewer side effects and is easier to use, the researchers suggested that it may have a slight advantage over lithium.

Atypical antipsychotic agents are another alternative

A 2007 meta-analysis of 10 clinical trials involving 1500 outpatients studied the efficacy of augmenting standard antidepressants with atypical antipsychotic agents to treat resistant major depressive disorder.[6] Across the trials, the pooled risk ratio (RR) for remission was 1.75 (95% CI, 1.36-2.24) and for response rates was 1.35 (95% CI, 1.13-1.63). Pooled rates for remission and response were 47.4% vs 22.3% (NNT=4) and 57.2% vs 35.4% (NNT=4.6), respectively.

Although the meta-analysis found no difference in overall discontinuation rates (P=.929), the rate of discontinuation because of adverse events was lower among placebo-treated patients (RR=3.38, P<.0001). These results suggest a role for atypical antipsychotic agents in augmenting standard antidepressants for treatment-resistant major depressive disorder.

Recommendations

Both the American Psychiatric Association[7] and the Institute for Clinical Systems Improvement[8] recommend considering a trial of lithium or thyroid augmentation for patients who respond only partially to initial antidepressant therapy. Many experienced clinicians consider lithium to be the most effective adjunct. The APA cautions, however, that its Major Depressive Disorder Practice Guideline, published in 2000, is no longer current.[9] An update is expected by the end of the year.

Other options include maximizing the initial treatment, switching to another agent, or augmenting initial treatment with another antidepressant agent or psychotherapy. Before prescribing any additional treatments for patients who fail to respond to initial antidepressant therapy, however, primary care physicians need to be mindful of the fact that empirical data regarding the relative effectiveness of these strategies are limited—and that they should consider whether the patients they're treating have bipolar—rather than unipolar—depression. JFP

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