Q/What's best when a patient doesn't respond to the maximum dose of an antidepressant?

Vincent Lo, MD

San Joaquin General Hospital Family Medicine Residency Program, French Camp, Calif

Lauren Maggio, MS(LIS), MA

Lane Library, Stanford University, Palo Alto, Calif

EVIDENCE-BASED ANSWER

A/ **FIRST, CONSIDER POSSIBLE CAUSES OF THE INADEQUATE RESPONSE,** then weigh treatment options in light of the characteristics of the individual patient and therapy. When managing a patient with nonpsychotic depression and inadequate response to the maximum dose of a single antidepressant, the physician should first identify factors that may contribute to the poor response, such as suboptimal dosage resulting from nonadherence, inadequate duration of therapy, and comorbid medical and psychiatric conditions (strength of recommendation [SOR]: **C**, expert opinion).

The literature supports several treatment alternatives, including augmentation with cognitive therapy, switch therapy, and combination-augmentation therapy; not enough studies exist to recommend the best treatment. All options reviewed produced a 20% to 50% remission rate (SOR: **B**, systematic reviews and randomized controlled trials [RCTs]).

Physicians should consider the patient's clinical history and preferences, along with drug toxicity, potential drug interactions, and cost when making treatment decisions (SOR: **C**, expert opinion).

The literature supports several treatment alternatives, but there is no single best option.

Evidence summary

A recent study randomized 158 patients who didn't respond to antidepressant therapy to either cognitive therapy with clinical management or clinical management alone.[1] The cognitive therapy group had a 29% cumulative relapse rate at 68 weeks, compared with 47% in the clinical management control group (number needed to treat [NNT]=6).

A crossover RCT compared 12 weeks of the cognitive behavioral analysis system of psychotherapy (CBASP) in 61 patients who had failed to respond to a 12-week course of nefazodone with 12 weeks of nefazodone treatment in 79 patients who hadn't responded to 12 weeks of CBASP.[2] Remission rates were comparable in the 2 crossover groups (28% for nefazodone vs 25% for CBASP; *P*=.92).

Drugs may produce a faster response

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial compared augmentation with as many as 16 sessions of cognitive therapy with pharmacologic augmentation and switch strategy among 65 patients who had failed to respond to 14 weeks of citalopram.[3]

The investigators concluded that augmentation with cognitive therapy or pharmacologic therapy was equally effective, but pharmacologic augmentation produced a more rapid response (mean time to first remission for cognitive therapy=53.3 days, compared with 40.1 days for pharmacologic therapy; *P*=.022). Patients who were switched to cognitive therapy had similar outcomes to patients who were switched to alternative antidepressants (remission rates=25% and 27.9%, respectively; *P*=.6881), but reported fewer adverse effects (0% vs 48%).

When an SSRI fails …

A recent systematic review of 8 RCTs (including STAR*D) and 23 open studies concluded

In 1 study, augmentation with cognitive therapy or medication worked equally well, but drugs produced a more rapid response.

that after a first failure of a selective serotonin reuptake inhibitor (SSRI), any switch within or between classes of antidepressant is legitimate and equally effective.[4]

Switching within the same class of antidepressant. The STAR*D study, an unblinded RCT, reported that patients (N=238; median age 41 years) who were switched to sertraline (as much as 200 mg per day for 14 weeks) when they didn't tolerate or respond adequately to citalopram had remission rates of 17.6% on the Hamilton Rating Scale for Depression (HAM-D) and 26.6% on the Quick Inventory of Depressive Symptomatology (QIDS).[5]

Switching to a different class of antidepressant. In a multisite study, outpatients who failed to respond to 12-week, double-blind treatment with either sertraline (n=117) or imipramine (n=51) were randomized to an additional 12 weeks of double-blinded treatment with the alternate medication. Investigators reported a 60% response rate in the sertraline switch group and a 44% response rate in the imipramine switch group.[6]

In the STAR*D study, patients who didn't tolerate or failed to respond to as many as 12 weeks of citalopram were switched to sustained-release (SR) bupropion, sertraline, or extended-release (ER) venlafaxine for as long as 14 weeks.[5] The bupropion-SR switch group (n=239, up to 400 mg per day) had remission rates of 21.3% (HAM-D) and 25.5% (QIDS); the sertraline switch group (n=238, up to 200 mg per day) had remission rates of 17.6% (HAM-D) and 26.6% (QIDS); and the venlafaxine-ER switch group (n=250, up to 375 mg per day) had remission rates of 24.8% (HAM-D) and 25% (QIDS). There were no clinically or statistically significant differences among the groups.

Response declines with multiple switches

Patients who didn't respond to this treatment arm and were switched again to either mirtazapine (n=114, as much as 60 mg per day) or nortriptyline (n=121, as much as 200 mg per day) had a much less favorable response (mirtazapine 12.3% vs nortriptyline 19.8%; NNT nortriptyline-mirtazapine=13).[7]

Patients who failed to respond to this treatment arm were randomized to either tranylcypromine (n=58, mean 36.9 mg per day) or venlafaxine plus mirtazapine (n=51, mean 210.3 and 35.7 mg per day, respectively). Both groups had low remission rates (tranylcypromine 6.9%, venlafaxine plus mirtazapine 13.7%; NNT venlafaxine plus mirtazapine-tranylcypromine=15).[8]

Lithium and T3 augmentation both work

A 1999 systematic review of 9 double-blind RCTs (N=234) reported that patients treated with lithium augmentation (250-1200 mg per day, or a serum level of ≥0.5 mmol/L for ≥2 weeks) had a 45% improvement in depressive symptoms (HAM-D), whereas the placebo group showed 18% improvement (NNT=3.7; 95% confidence interval [CI], 2.6-6.6).[9] An updated meta-analysis of 10 RCTs confirmed the efficacy of lithium augmentation compared with placebo (41% vs 14.4% improvement; NNT=5).[10]

Recently, the STAR*D study (N=142) reported that augmentation with either lithium or triiodothyronine (T_3) after 2 antidepressant failures was equally effective (lithium response 15.9%; T_3 response 24.7%; NNT T_3-lithium=11; *P*=.43). However, lithium was more often associated with side effects (number needed to harm [NNH]=7; *P*=.045).[11]

Bupropion and buspirone augmentation are comparable

An unblinded RCT found that patients who failed to respond to citalopram responded when augmented with either bupropion-SR or buspirone.[12] After 8 weeks of treatment, the bupropion-SR group (n=565, as much as 400 mg per day) had remission rates of 29.7% (HAM-D) and 39.9% (QIDS); the buspirone group (n=286, as much as 60 mg per day) had remission rates of 30.1% (HAM-D) and 26.9% (QIDS) (NNT buspirone-bupropion-SR=10). However, the bupropion-SR group had a lower dropout rate because of intolerance (12.5% vs 20.6%; NNH=12; *P*<.009).

Augmentation with atypical antipsychotics works

A recent meta-analysis of 10 RCTs (N=1500 outpatients) assessed the effectiveness of augmenting various antidepressants with atypical antipsychotic agents (olanzapine, risperidone,

and quetiapine) for treatment-resistant major depressive disorder.[13] The pooled remission and response rates favored augmentation with atypical antipsychotics over adjunctive placebo (47% vs 22.3% and 67.2% vs 35.4%, respectively).

Another randomized study of 362 patients with incomplete response to standard antidepressant treatment found adjunctive aripiprazole was effective and well tolerated (mean change in Montgomery-Åsberg Depression Rating Scale score: –8.8 in the aripiprazole group vs –5.8 in the placebo group; $P<.001$).[14]

Agents that aren't recommended

Expert review doesn't recommend routine use of other agents that have been studied for augmentation therapy, including dopaminergic drugs, pyschostimulants, modafinil, anticonvulsants, inositol, opiates, estrogen, dehydroepiandrosterone, folate and S-adenosylmethionine, tryptophan, omega-3 fatty acid, pindolol, and monoamine oxidase inhibitors.[15]

Recommendations

The Institute for Clinical Systems Improvement[16] and the American Psychiatric Association[17] recommend evaluating the dose and duration of medication, the patient's adherence to medication, and the accuracy of diagnosis or impact of comorbidities for patients who don't respond adequately to treatment. Physicians also may consider other strategies, including switch therapy, augmentation therapies, psychotherapy, and electroconvulsive therapy. JFP

In a recent meta-analysis, pooled remission rates favored augmentation with atypical antipsychotics over adjunctive placebo.

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