How should you manage a depressed patient unresponsive to an SSRI?

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EVIDENCE-BASED ANSWER

The best approach among studied alternatives to manage a patient with treatment-resistant depression is not clear from the evidence. All of the options reviewed seem to have about a 25% to 30% success rate.

Switching to other antidepressants or augmenting with non-antidepressant drugs has the best supporting evidence (strength of recommendation [SOR]: **B**).[1] Adding additional antidepressants (SOR: **B**), using psychotherapy (SOR: **B**), and initiating electroconvulsive therapy (ECT) (SOR: **C**) are options. Various antidepressants are used as add-on therapy. Psychotherapy is often recommended, though the evidence of benefit after a failed course of initial therapy is sparse. The evidence supporting use of ECT in treatment-resistant depression is weak.

Comparison among the options is based on expert opinion (SOR: **C**). Additional reports from the STAR*D trial may improve the quality of the evidence in the near future.

CLINICAL COMMENTARY

Optimize initial drug dose and duration, then change to a different medication if needed

Although "epidemics" of obesity and avian influenza steal headlines, depression remains an American scourge, with a lifetime prevalence of 13% and rising. Major depressive disorder is often a chronic or relapsing illness, with recurrence rates of more than 40% at 2 years. Treatment resistance may be associated with pain (which is a presenting symptom in two thirds of depressed patients), psychosocial factors, psychiatric comorbidities, or the presence of bipolar disorder rather than unipolar depression.

Various forms of counseling and psychotherapy, alone or in combination with medications, are effective in treating depression, and I recommend them liberally when resources permit. Like the authors of this review, I first optimize initial drug dose and duration, then change to a different medication if needed. Some evidence suggests benefit from a combined serotonin and norepinephrine agent, such as venlafaxine (Effexor) or imipramine (Tofranil), which may also alleviate pain. I often add a noradrenergic tricyclic antidepressant, such as nortriptyline or desipramine, or the newer agent mirtazapine (Remeron), to a selective serotonin reuptake inhibitor (SSRI) for augmentation. I encourage physicians not to fear tricyclics, although I am hesitant to use lithium, thyroxine, or atypical antipsychotics in depression because of their hazards.

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FAST TRACK

First optimize the initial drug dose and duration; then change to a different medication if needed

Evidence summary

In general, strategies for addressing treatment-resistant depression have not been compared in head-to-head studies. Guidelines at this time are based mainly on expert opinion[2,3] and gradually accumulating data from a few randomized controlled studies or low-quality cohort studies.

While it makes sense, as the question implies, to first optimize the dose and duration of SSRI treatment in treatment-resistant depression, it is not clear which strategy to employ next. Switch, augmentation, and combination strategies may each improve clinical outcomes, but which strategy is best is based on expert opinion at this time.

Optimize. The first step in treatment-resistant depression should be optimizing dose and duration of therapy.[4] For fluoxetine (Prozac), based on a nonrandomized open trial, patients should receive 8 weeks of treatment before the SSRI course is deemed adequate. Only 23% of patients who have not responded to 8 weeks of fluoxetine respond to a still longer course of fluoxetine.

Switch. The strongest evidence is from the recent STAR*D trial, a randomized study that assigned patients in one arm of the study who had no relief from (or did not tolerate) therapy with citalopram (Celexa) to 1 of 3 drugs—sustained-release bupropion (Wellbutrin SR), sertraline (Zoloft), or extended-release venlafaxine (Effexor XR). The study concluded that approximately 1 in 4 patients have remission after switching to an antidepressant from another drug class.[1] Further switches in antidepressant monotherapy have a low success rate (10%–20%).[5]

Add/combine. Mixed evidence supports combining different antidepressants. There is cohort study evidence that combining citalopram and bupropion is more effective than switching to the alternate antidepressant,[6] but other cohort studies did not find a significant difference between switching and augmenting. An arm of the STAR*D trial added either sustained-release bupropion or buspirone (Buspar) to the failed citalopram therapy. Thirty percent of patients with depression unresponsive to citalopram had remission when bupropion-SR or buspirone was added.[7] The STAR*D reports do not compare the 2 strategies of switching or combining drugs directly.

Augment. Evidence from a meta-analysis with aggregate data from 3 studies representing a total of 110 patients showed that augmentation of various antidepressants with lithium leads to improved outcomes (number needed to treat [NNT]=3.7).[8] A cohort study of augmentation with an atypical antipsychotic agent such as aripiprazole (Abilify) suggest improved outcomes, but similar studies found no benefit.[9] A small (23-patient) randomized trial of lamotrigine (Lamictal) suggests that it may augment the effect of fluoxetine.[10]

Psychotherapy. A systematic review of psychological therapies in treatment-resistant depression found 2 controlled studies (of cognitive therapy and cognitive behavioral therapy) out of 12 total studies meeting their inclusion criteria that demonstrated improved scores on the Hamilton Rating Scale for Depression. Further study of these therapies was recommended.[11]

ECT. The evidence supporting use of ECT for treatment-resistant depression comes from studies following failure of treatment with tricyclic antidepressants and monoamine oxidase (MAO) inhibitors. Methodological problems in these older studies do not permit an estimate of response rate.[12]

Recommendations by others

The American Psychiatric Association treatment guideline recommends changing antidepressant, adding or changing to psychotherapy, or ECT if no response to 4 to 8 weeks of the initial therapy in depression.[13] A guideline from the University of Michigan recommends referral to a psychiatrist if patients have treatment refractory depression (defined in their guideline as failure of 2 successive trials of antidepressants).[14] The Institute for Clinical Systems

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Improvement guideline recommends considering switch, augmentation, or other therapies (including adding or modifying psychotherapy).[15]

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FAST TRACK

Psychotherapy is often recommended, though evidence of benefit after a failed course of medication is sparse