Adjunctive Therapy With Second-Generation Antipsychotics: The New Standard for Treatment-Resistant Depression?

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Depressive episodes that do not respond to at least several adequate courses of standard antidepressants account for a substantial proportion of the socioeconomic and medical burden associated with this common illness. As such, treatment-resistant depression represents both an important public health problem and a great unmet need in psychiatric therapeutics. Among the several "add-on" strategies with established efficacy for treatment-resistant depression, the second-generation antipsychotics have become the most commonly used in psychiatric settings. This article briefly examines the benefits and limitations of adjunctive therapy with second-generation antipsychotics to determine whether these medications are now the standard of comparison for new therapies for treatment-resistant depression.

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Treatment-resistant depression is not a diagnosis but rather a clinical description of a depressive episode that has not responded to adequate courses of antidepressant pharmacotherapy. It is not a rare condition; in fact, as many as 30%−40% of those who are prescribed antidepressants are considered treatment resistant within six months of initiating pharmacotherapy (1). Although several regulatory authorities require that patients have a history of nonresponse to at least two adequate courses of antidepressant monotherapy to enroll in studies of novel therapies for treatment-resistant depression, in practice, "treatment resistance" describes a broad spectrum of presentations and may be better viewed along a dimension rather than from a categorical (i.e., yes or no) perspective (2). A related term, "refractory depression," is sometimes used for patients with a history of nonresponse to numerous treatments. In my practice, I might only use this term if the patient had not responded to tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and electroconvulsive therapy (ECT) in addition to more contemporary first- and second-line interventions (2).

Any classification or staging of treatment-resistant depression should begin with a detailed assessment of various courses of therapy that have been tried during the current depressive episode and, if relevant, in past episodes. Although it is sometimes difficult to obtain an accurate history, and one must always keep in mind the possibility of occult nonadherence, the goal is to compile a list of medications that have been tried without the desired benefit, specifying both dose and duration as well as any dose-limiting side effects (2). At least six weeks of therapy at the minimum effective dose of a medication is usually required before it can be said that a patient is "resistant" to a particular antidepressant. In general, longer trials and higher doses allow for increased confidence in the adequacy of the treatment trial.

The staging system proposed by Thase and Rush (3) was hierarchical, beginning with nonresponse to adequate courses of first-line therapies (stage I treatment-resistant depression) and progressing to more advanced strategies, with nonresponse to ECT termed a stage V treatment-resistant depression. Today, the first stage or level of treatment-resistant depression is usually defined by nonresponse to either a selective serotonin reuptake inhibitor (SSRI) or a serotonin norepinephrine reuptake inhibitor, although a number of other medications, including some newer (e.g., vilazodone and vortioxetine) and some older (e.g., bupropion and mirtazapine) antidepressants, might count. As the number of therapeutic options has increased, however, it is less clear whether the hierarchical algorithm proposed by Thase and Rush, which culminated with sequential trials of TCAs, MAOIs, and ECT, is still the most reasonable way of gauging the degree of treatment resistance. For example, in the largest prospective study of treatment-resistant depression ever undertaken, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study (1), there was a small drop in remission rates from the initial to the second course of pharmacotherapy (from 37% to 31%) and then a more precipitous

drop in the likelihood of remission for the third and fourth steps of treatment (14% to 13%). This observation might suggest that more advanced strategies for treatment-resistant depression, including several adjunctive strategies and antidepressant combinations, might be even more valuable if used earlier in treatment algorithms. Whether treatment-resistant depression is viewed as a dichotomous process or along a continuum, the STAR*D data certainly illustrate that the chances for recovering from an episode of major depressive disorder become progressively smaller as the number of failed treatment trials mounts.

STRATEGIES OF TREATMENT-RESISTANT DEPRESSION: OPTIMIZING, SWITCHING, AND ADDING

Before starting a new treatment for a patient with treatment-resistant depression, one must review the accuracy of the diagnosis, ensure that the patient has been adherent to the current treatment and has not been surreptitiously using large amounts of alcohol or drugs, and confirm that the past trials have been adequate in terms of both duration and dose. Although many of the newer antidepressants do not have crisply delineated dose-response relationships, it is generally a good idea to optimize the index course of therapy by titrating the dose up to the maximum approved dose, if tolerability permits. When the adequacy of the current course of therapy is in doubt, a conservative yet very reasonable strategy is to extend the treatment trial by two more weeks.

When a course of antidepressant therapy has been optimized but is still not effective, the tolerability of the index antidepressant is one of the keys to deciding what to do next. If tolerability is marginal or worse, the decision is easy: Switch to a dissimilar antidepressant. When the index therapy is well tolerated and there has been some improvement, many psychiatrists opt for adding an adjunct rather than switching. Using an adjunct in this context not only conveys the advantage of building on top of an established therapy but avoids any worsening that might result from tapering and cross-titration (2). STAR*D studied five "add-on" strategies, including three medications that are not classified as antidepressants (buspirone, lithium, and the T_3 form of thyroid hormone) and two antidepressants (bupropion and mirtazapine). The use of two antidepressants together is usually called a combination treatment rather than an adjunctive strategy, although this distinction is largely semantic. Although the research design used in STAR*D did not permit a strict comparison of the adjunctive and switching strategies, it did seem across all three randomized levels that the patients who received adjunctive therapies were more likely to remit than those who were switched to another course of antidepressant monotherapy (1). However, because the patients who opted to switch strategies reported higher levels of depressive symptoms and more side effects with the index medication, it is possible that the apparent disadvantage of the switching strategy was an epiphenomenon. That said, it is also true that it is faster to implement an adjunctive strategy than it is to orchestrate a switch, even when an accelerated cross-titration schedule is used.

SECOND-GENERATION ANTIPSYCHOTICS: THE NEW STANDARD FOR THERAPY OF TREATMENT-RESISTANT DEPRESSION?

Arguably the oldest adjunctive strategy—namely, adding an antipsychotic medication to a TCA or MAOI—was widely used in the 1960s but largely had fallen out of favor by the early 1980s, in part because the risk of tardive dyskinesia associated with therapy with the first generation of antipsychotic medications was thought to be particularly high for people with mood disorders. Moreover, other strategies were introduced that did not convey such a risk—including lithium augmentation, in the 1980s, and combining SSRIs with TCAs, in the 1990s (2). The perception that it was inappropriate to use antipsychotic medications to treat patients with nonpsychotic depressive disorders began to change shortly after the introduction of the first members of a newer or so-called second generation of antipsychotics, particularly following publication of the small but very influential study of Shelton and colleagues (4). Across the next ten years, the adjunctive use of second-generation antipsychotics for antidepressant nonresponders skyrocketed (5), and, although exact data are lacking, the second-generation antipsychotics now seem to be the most widely used form of adjunctive therapy for antidepressant nonresponders. As Nelson and Papakostas (6) reviewed, multiple positive, placebo-controlled studies have been conducted for four second-generation antipsychotics, including the three drugs that have been approved by the Food and Drug Administration (FDA) for a specific indication (aripiprazole, quetiapine, and olanzapine) and a fourth (risperidone) that was studied but not evaluated by the FDA for this indication. Recently, a fifth second-generation antipsychotic (brexpiprazole) was approved by the FDA on the basis of two positive studies (7, 8).

With so many members of the second-generation antipsychotic class showing such positive findings, including drugs as dissimilar as risperidone and quetiapine or olanzapine and aripiprazole, it is very likely that antidepressant effects are common across the whole class. In practice, all four of these medications show relatively rapid clinical benefits, which almost invariably are observed within one to two weeks (2). Moreover, the adjunctive efficacy of all four drugs that distinguish this adjunctive strategy is typically observed at doses that are only one-fourth to one-half those used to treat acute schizophrenia or mania (2). Thus, in this clinical context, it seems that the antidepressant effects of these medications are not directly tied to their antipsychotic effects.

At this point, there is no question about the efficacy of adjunctive second-generation antipsychotic therapy for patients with treatment-resistant depression; rather, the remaining concerns center on three issues: When effective,

how long should the second-generation antipsychotic be continued? What is the relative efficacy of adjunctive second-generation antipsychotic therapy compared with older standards, such as lithium or thyroid hormone, or various antidepressant combinations? Can the second-generation antipsychotics be considered a truly cost-effective option for treatment-resistant depression, especially when issues pertaining to longer term safety are taken into account?

When Effective, How Long Should a Second-Generation Antipsychotic Be Continued?

Research has not yet established the optimal duration of therapy with a second-generation antipsychotic after successful adjunctive treatment. Most experts agree that, in contrast to the standard of practice for antidepressants, clinicians should not assume that a six- to nine-month course of continuation phase will be necessary after a successful course of adjunctive therapy. Similarly, the package inserts for each of the FDA-approved second-generation antipsychotics offer vague recommendations about the duration of therapy, advising a "minimum necessary" course of treatment. Given that there is good evidence from the schizophrenia literature that the risks of tardive dyskinesia, weight gain, and other metabolic side effects increase over time, it is generally a good idea to try to taper the adjunctive second-generation antipsychotic within two or three months if clinically feasible. Few longer-term studies permit more precise estimates of relapse to be gauged, although one study (9) suggested that the absolute hazard of discontinuing olanzapine after stabilization on a combination of olanzapine and fluoxetine was about 20% across six months (which was about twice the relative hazard of relapse on combined treatment). Obviously, if the patient relapses shortly after tapering the second-generation antipsychotic, a longer course of therapy may prove to be necessary, although—to date—there are no reliable clinical or laboratory markers of the need for ongoing therapy. When it is clinically necessary to extend the adjunctive second-generation antipsychotic for longer than a few months, careful monitoring of weight and metabolic status is warranted, as is documentation of the lack of dyskinetic or other abnormal involuntary movements.

What Is the Relative Efficacy of Adjunctive Second-Generation Antipsychotic Therapy?

The data on the comparative efficacy of adjunctive second-generation antipsychotic therapy are sparse, and it is unfortunate that STAR*D was designed just a few years too early—that is, before there was sufficient evidence to justify inclusion of an adjunctive second-generation antipsychotic arm in the second or third level of the experiment. In the absence of data from adequately controlled studies, one must make do with indirect comparisons. For example, if the results of the adjunctive arms of STAR*D (1) are placed side by side with the meta-analytic findings of Nelson and Papakostas (5), one might conclude that the benefits of adjunctive therapy with second-generation antipsychotics are not "heads above" those of buspirone or bupropion (level 2) or those of lithium or thyroid hormone (level 3). However, it is wise to be cautious about comparisons across studies. In this case, an interpretive bias may favor the STAR*D findings, because an open-label study that does not have a placebo control group is likely to obtain "better" results than a study that uses a more rigorous double-blind, placebo-controlled design.

To date, only two adequately powered studies have prospectively addressed the important topic of comparative efficacy (10, 11), and results of one these studies are not yet known. In the first of these two larger scale, pragmatic trials (10), Bauer and colleagues randomly assigned 460 patients to receive six weeks of open-label adjunctive therapy with either extended-release quetiapine (300 mg/day; N=231) or lithium therapy (.6–1.2 mEq/L; N=229). An additional 228 patients were randomly assigned to receive extended-release quetiapine as monotherapy (300 mg/day). Results did not reveal a clear winner with respect to treatment effectiveness at study end point or tolerability: Because the study was conceived as a noninferiority trial, the primary analyses indicated that adjunctive quetiapine therapy was not inferior to adjunctive lithium therapy. Secondary analyses did favor the adjunctive quetiapine arm with respect to symptom reduction during the first three weeks of therapy, but after six weeks of therapy that difference was no longer statistically significant after adjustment for multiple comparisons.

The second large-scale study, known by the acronym VAST-D (11), was completed in 2015, although the results are not yet known. This trial, which was conducted at Veterans Affairs medical centers in the United States, compared adjunctive therapy with aripiprazole against bupropion therapy, including both switching and adjunctive options. Given the nature of the study population, the results of this trial will expand the literature by including a relatively high proportion of patients with treatment-resistant depression and comorbid substance abuse or dependence or posttraumatic stress disorder.

Are Adjunctive Second-Generation Antipsychotics Cost-Effective?

As yet, there have been no adequately controlled studies of the cost-effectiveness of adjunctive second-generation antipsychotic therapy. Nevertheless, given the greater retail cost of these medications (compared with, say, switching to a generic form of venlafaxine, adjunctive therapy with lithium, or combined therapy with bupropion and an SSRI), one can conclude that—if benefit is comparable—cost-effectiveness in all likelihood favors the older strategies. This difference will, of course, dissipate as the members of the second-generation antipsychotic class become generically available and progressively greater numbers of generic alternatives are introduced. However, if the longer term costs could take into account the negative impact of weight gain, dyslipidemia, or more uncommon adverse outcomes (e.g., development of diabetes mellitus or tardive dyskinesia), it seems certain that the cost-benefit ratio would shift even

further toward the older strategies (12). Therefore, it is prudent to delimit use of adjunctive second-generation antipsychotic therapy to cases in which the clinical urgency of a rapid onset of therapeutic effects might justify the higher costs.

CONCLUSIONS

Adjunctive therapy with second-generation antipsychotics has become one of the most widely used strategies for patients who have not obtained an adequate response from antidepressant medications. At present, there is no better proven strategy for treatment-resistant depression, given that multiple positive, placebo-controlled studies have been conducted for adjunctive therapy with five second-generation antipsychotics: aripiprazole, brexpiprazole, olanzapine, risperidone, and quetiapine. When effective, these medications tend to work quickly, often producing meaningful symptom relief in one to two weeks. The second-generation antipsychotics are, however, more costly than most other pharmacological options, and the cost of these medications is further amplified when the impact of frequent (e.g., weight gain) and infrequent (e.g., diabetes and tardive dyskinesia) side effects is taken into account. Cost-effectiveness estimates are further limited by a dearth of data on the longer term use of adjunctive therapy with second-generation antipsychotics. As a result, although the second-generation antipsychotics should indeed be thought of as one of the gold standards for treating antidepressant nonresponders, the potential benefits must be carefully balanced against both the higher cost of these medications and the several manageable but real risks. When symptom severity and the urgency for rapid benefit are sufficient to justify the costs and potential risks, the second-generation antipsychotics can indeed be considered the standard of care for patients who have not responded to several courses of antidepressant monotherapy.

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During the past three years, Dr. Thase reports that he has been a consultant to or received research funding from Alkermes, AstraZeneca, Avenir, Eli Lilly & Co., Forest Laboratories, GlaxoSmithKline, Janssen (Johnson & Johnson), Otsuka, Roche Inc., and Takeda. In addition, he has been a consultant to Allergan, Aventis, Bristol-Myers Squibb, Cerecor, Gerson Lehman Group, Guidepoint Global, H. Lundbeck A/S, MedAvante Inc., Merck, Naurex, Neuronetics Inc., Novartis, Nestle (PamLab), Pfizer, Shire, and Sunovion, and he has received additional research funding from the Agency for Healthcare Research and Quality, Assurex, National Institute of Mental Health, and Pharmaneuroboost. Dr. Thase reports that his spouse is an employee of PelotonAdvantage, which does business with a number of pharmaceutical companies.

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