Easing the Burden of Treatment-Resistant Depression

This ACADEMIC HIGHLIGHTS *section of* The Journal of Clinical Psychiatry *presents the highlights of the planning teleconference series "Easing the Burden of Treatment-Resistant Depression," which was held in July 2008. This report was prepared by the CME Institute of Physicians Postgraduate Press, Inc., and was supported by an educational grant from Bristol-Myers Squibb Company and Otsuka America Pharmaceutical, Inc.*

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Depression is one of the leading causes of disability worldwide and affects 121 million people.[1] Individuals with depression experience significant cognitive, behavioral, and physical impairments related to this disorder.[2] Although depression is a highly treatable illness,[3] the majority of patients with depression do not receive adequate treatment, and few patients who do receive adequate treatment achieve full symptomatic remission.

In this ACADEMIC HIGHLIGHTS, experts in the treatment of depression presented topics such as how to use measurement-based care as well as switching, augmentation, and combination strategies to help patients fully recover from depression.

The Importance of Treating Depression to Full Remission

The goal for the treatment of major depressive disorder (MDD) is achieving and sustaining remission—complete resolution of symptoms and restoration of presymptomatic levels of functioning.[4,5] Madhukar H. Trivedi, MD, explained how to use measurement-based care and research-based, sequenced treatment strategies to reach this goal.

Lack of complete remission from an acute episode of MDD (especially the first one) is associated with adverse consequences such as a high risk of relapse,[6,7] more severe depressive episodes,[7] and increased all-cause mortality.[8] Dr. Trivedi explained that, although remission rates in clinical trials are low and patients with chronic forms of MDD may be less likely than others to achieve full symptomatic remission, clinicians can strive for remission by measuring patients' symptoms throughout treatment so that appropriate changes in strategy can be made when necessary.[5]

Measurement-Based Care

The use of measurement-based care will help clinicians to assess symptom severity, medication side effects, and adherence to treatment. Dr. Trivedi described a number of assessment tools that are available to determine whether or not patients' emotional and physical symptoms have resolved (Table 1). Of these tools, the most commonly used in clinical research are the Hamilton Rating Scale for Depression[9,10] and the Montgomery-Asberg Depression Rating Scale.[11] Dr. Trivedi stated that these scales may be difficult to use in everyday clinical practice, and neither incorporates all 9 diagnostic criteria defined in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR)[12] for MDD.

Dr. Trivedi remarked that other scales are being used more often in clinical practice because of their practicality. For example, The Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR)[13] takes less than 10 minutes for patients to complete and does include the 9 criteria of MDD.[12]

For defining remission, explained Dr. Trivedi, the QIDS-SR and 2 other self-rated scales—the Patient Health Questionnaire[14] and the Beck Depression Inventory[15]—may be comparable. However, for making measurement-based clinical decisions, the QIDS-SR may have advantages, as it has well-defined anchors of severity, frequency, and dysfunction that guide treatment for individual symptoms.

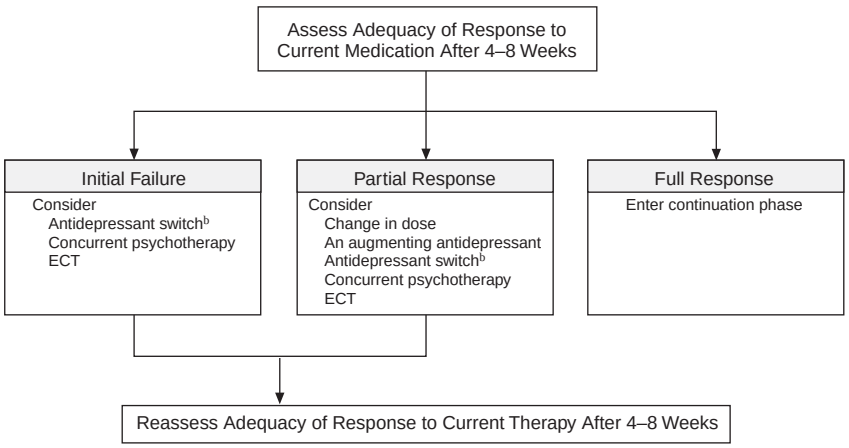
FOR CLINICAL USE

- Use measurement-based care to ensure the patient's progress toward remission.
- Consider switching, augmenting, or combining medications when patients only partially or do not respond to first-line antidepressant monotherapy.
- For antidepressant-resistant depression, consider tolerability and safety when switching to another antidepressant or adding antipsychotics or other types of agents.

Table 1. Selected Assessment Tools for Depression

Tool	Clinician- or Self-Rated	Description	Remission Score
Hamilton Rating Scale for Depression (HAM-D)[9,10]	Clinician-rated	Rating scales that measure the severity of depression	≤ 7 on the HAM-D-17; ≤ 8 on the HAM-D-21
Montgomery-Asberg Depression Rating Scale (MADRS)[11]	Clinician-rated	10-item rating scale that measures the severity of depression	≤ 10
Quick Inventory of Depressive Symptomatology (QIDS)[13]	Clinician- or self-rated	16-item rating scales that identify signs and symptoms of depression	≤ 5
Patient Health Questionnaire (PHQ-9)[14]	Self-rated	9-item rating scale that measures the frequency of symptoms of depression during the past 2 weeks	≤ 4
Beck Depression Inventory (BDI)[15]	Self-rated	21-item rating scale that measures depressive attitudes	≤ 9

Figure 1. APA Practice Guidelines: Active Phase Treatment of MDD[a]



[a]Adapted with permission from the American Psychiatric Association (APA).[18]
[b]When considering changing antidepressants, choose either another antidepressant from the same class or, if 2 previous medication trials from the same class were ineffective, an antidepressant from a different class.
Abbreviations: ECT = electroconvulsive therapy, MDD = major depressive disorder.

Treatment Strategies for Achieving Remission

Choosing an effective antidepressant is crucial to helping patients reach remission of MDD. However, Dr. Trivedi stressed that factors besides effectiveness should be considered when selecting among agents; these factors include mechanism of action, tolerability, safety, ease of use, and cost (direct and indirect), as well as the treatment history of the patient and his or her family. Some of these factors may result in treatment nonadherence, which can be a factor in what is perceived to be treatment resistance.[16,17] True treatment resistance may be associated with chronic depression, severe illness, or comorbid psychiatric disorders.[16]

Dr. Trivedi recommended that, to achieve remission, clinicians should take the following steps:

- Carefully select first-line antidepressants with patient education in mind
- Sequence or combine agents if first-line treatment is unsuccessful
- Use caution when modifying treatment
- Closely monitor the patient's symptomatic and functional status using measurement-based care to ensure progress and adherence

Dr. Trivedi also recommended that clinicians refer to the treatment steps for the acute phase of depression that were published by the American Psychiatric Association (APA)[18] (Figure 1).

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study—the largest depression treatment trial conducted in actual practice settings and the first to study remission as a predefined primary outcome measure[19]—was also discussed by Dr. Trivedi. The study used a measurement-based care approach via QIDS-SR administration.

The first step of the study[20] was treatment with the selective serotonin reuptake inhibitor (SSRI) citalopram for up to 14 weeks. Among patients who responded to treatment, 56% did not respond until week 8 or later, and among patients whose MDD remitted, 40% did not experience remission until week 8 or after. About half of patients who completed treatment with citalopram and did not remit continued to have mild or moderate symptoms. Patients who did not achieve remission went on to choose successive steps in the treatment sequence.

The STAR*D study found that remission rates decreased with each treatment step. Further, patients who achieved response but not remission in each acute phase step had steadily increasing rates of relapse. Overall, remission rates were higher for patients who chose combination therapy as a second step than for those who chose monotherapy.[19]

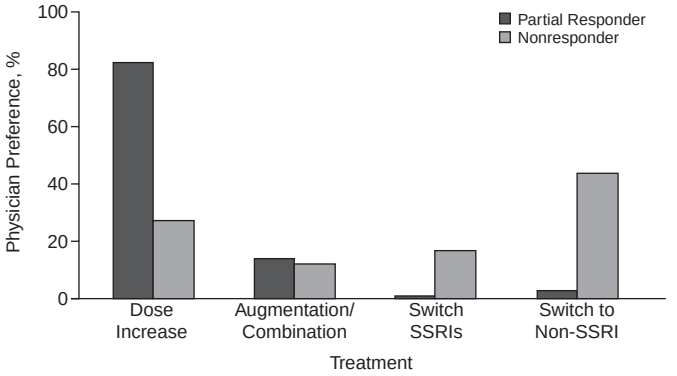
Conclusion

Dr. Trivedi concluded that clinicians should strive for remission when treating patients with depression, because patients who do not achieve remission are at risk for further impairment in mental and physical health. Using measurement-based care is essential to determine whether or not patients have achieved complete remission. In addition, consulting evidence-based guidelines and clinical trials in which remission is the main goal of treatment may aid in improving patients' outcomes.

Switching Strategies for Partial Responders to Antidepressant Treatment

Antidepressant monotherapy is modestly effective in the treatment of depression, as evidenced in the STAR*D trial.[20] For patients who do not achieve an adequate response to the initial monotherapy, explained Maurizio Fava, MD, switching to a different antidepressant may be the best next step.

Figure 2. Physicians' Next-Step Preferences After 8 Weeks of Unsuccessful Treatment[a]



[a]Adapted with permission from Fredman et al.[21]
Abbreviation: SSRI = selective serotonin reuptake inhibitor.

Next-Step Preferences

A survey of more than 400 psychiatrists[21] found that switching was physicians' last choice in the context of partial response (Figure 2). According to Dr. Fava, this finding indicates a reluctance to jeopardize patients' partial symptomatic improvement; rather, switching for partial responders is often chosen because of a marked intolerance of the initial medication. Similarly, in the STAR*D trial,[22] subjects who did not remit after initial treatment were given a choice between switching or adding a treatment; most who chose to switch either had no response to citalopram or could not tolerate side effects.

Switching Within or Outside SSRI Class

When switching antidepressants, a clinician and patient may choose to stay within the original medication class or to change classes. Dr. Fava explained that the rationale for switching within a class is that some pharmacologic properties may differ between agents in the same class. Conversely, switching to a medication in another class may yield a different neurochemical effect. In addition, specific depressive subtypes may be more responsive to one antidepressant class than another.

Switching within SSRI class. Studies[23,24] of patients who failed to respond to an initial SSRI have reported response rates of 50% or greater after switching to another SSRI. A within-class switch is advantageous, stated Dr. Fava, because it can be done immediately; patients typically tolerate the switch to another SSRI without a washout period. However, the pharmacologic actions of a second SSRI may be too similar to those of the first SSRI to provide any greater efficacy. Therefore, a switch from an SSRI to an agent in another class may be preferred.

Switching to SNRIs. Dr. Fava said that serotonin-norepinephrine reuptake inhibitors (SNRIs) may be a better switch option for some patients than a second SSRI. These dual-action agents are hypothesized to be more effective in certain depressive subtypes than single-action agents, perhaps due to the distinctive roles and potential synergistic effects of serotonin and norepinephrine.

One study[25] of subjects who had failed to respond in 2 or more antidepressant (typically SSRI) trials found that response and remission rates were about 20% higher with the SNRI (venlafaxine) than with the SSRI (paroxetine). Another study[26] found that after being switched to the SNRI duloxetine, subjects who had had poor response or tolerability to an SSRI or venlafaxine responded at a similar rate as previously untreated patients. While not

conclusive, stated Dr. Fava, evidence suggests a potential role for SNRIs in SSRI-resistant patients.

Switching to TCAs. One study[27] found that 40% of subjects with treatment-resistant depression (who had mainly been treated with SSRIs) responded and 12% achieved remission when switched to the tricyclic antidepressant (TCA) nortriptyline. Dr. Fava noted that benefits associated with TCAs include a lower cost compared with some other medications and the potential usefulness of these agents in certain depressive subtypes, such as melancholic depression.[28]

Switching to MAOIs. Monoamine oxidase inhibitors (MAOIs) may be particularly useful in treatment-resistant patients who have atypical depression[29] or anergic bipolar depression.[30] However, added Dr. Fava, disadvantages of MAOI treatment include dietary restrictions and the need for a washout period before starting and after ending treatment.

Switching to other non-SSRI classes. Patients who either did not respond to or could not tolerate SSRIs had a response rate of 48% when switched to mirtazapine in an open-label study.[31] Another open-label trial[32] showed that switching to bupropion led to a 60% full or partial response rate in subjects who had not previously responded to the SSRI fluoxetine.

STAR*D Switch Results

In the STAR*D trial, subjects who chose the pharmacologic switch option for the second level of treatment were randomly assigned to take another SSRI (sertraline), bupropion, or venlafaxine.[33] Those switched to venlafaxine experienced a nonsignificantly greater remission rate compared with those taking bupropion or sertraline according to the 17-item Hamilton Rating Scale for Depression (HAM-D-17), but QIDS-SR scores showed almost identical remission rates for all 3 groups.[34]

In the third treatment stage of STAR*D, subjects who chose to switch antidepressants were randomly assigned to take mirtazapine or nortriptyline.[35] Nortriptyline had a nonsignificant advantage over mirtazapine based on HAM-D-17 scores, but, again, QIDS-SR remission rates were comparable between groups.

At level 4 of STAR*D, patients had the option of switching to either tranylcypromine monotherapy or a venlafaxine-mirtazapine combination.[36] The MAOI tranylcypromine led to very low remission rates, and the combination treatment was only slightly more effective.

Advantages and Disadvantages of Switching

From a clinical perspective, explained Dr. Fava, switching is a relatively well-tolerated and effective strategy that may be more cost-effective for the patient than other treatment approaches. The main disadvantage of switching is that, if the patient has benefited from the initial drug, switching risks losing that benefit, which may not be regained.

The second drug may have a more acceptable side effect profile than the first medication; however, warned Dr. Fava, clinicians tend to gradually taper the initial drug and slowly titrate the second drug, so the second agent may intensify the initial drug's side effects, but an immediate switch may be necessary. Also, side effects may be different but not more tolerable, and switching from one class to another will not always result in a significant reduction of side effects. When switching between classes, patients may experience discontinuation reactions to withdrawal of the first drug that could affect their desire to stay on the second agent. Of course, emphasized Dr. Fava, starting or stopping MAOI treatment always requires a washout period.

Conclusion

Switching medications is a reasonable strategy not only for nonresponders but also for partial responders to antidepressant treatment. Although many patients and clinicians prefer dose optimization or adding over switching after partial response, intolerable side effects from the initial antidepressant may make switching a favorable option. However, if the switch is not to a drug with substantially different pharmacologic actions, the same side effects may occur. Therefore, Dr. Fava advised, switching within or outside of the initial antidepressant class should be considered with a focus on the individual circumstances and desired outcomes of each patient.

Augmentation and Combination Strategies in Resistant Depression

After having no response or partial response, patients with MDD are often given an additional medication to augment the effects of the current antidepressant. According to J. Craig Nelson, MD, augmentation strategies involve adding an agent that is not approved by the US Food and Drug Administration (FDA) for use as an antidepressant, while combination strategies involve adding another FDA-approved antidepressant. A potential advantage of augmentation or combination strategies is the maintenance of improvements achieved with the initial antidepressant treatment while aiming for further recovery.

Augmentation Strategies

A meta-analysis[37] found that lithium augmentation is effective, but Dr. Nelson noted that the majority of included studies were small, used TCAs rather than SSRIs, and did not clearly define resistant depression. In addition, the STAR*D study found that lithium was not well tolerated.

The addition of triiodothyronine (T_3) to a TCA hastened clinical response in a sample of patients without treatment resistance significantly more than placebo in 5 of 6 studies in a meta-analysis and review ($P < .002$).[38] However, added Dr. Nelson, another meta-analysis[39] of 4 placebo-controlled trials using T_3 to augment TCAs in

treatment-resistant patients failed to find efficacy. Placebo-controlled trials of T_3 augmentation of SSRIs in resistant depression have not been reported, but STAR*D[40] found that the addition of T_3 to existing medication was effective and resulted in significantly lower discontinuation rates than lithium augmentation.

Dr. Nelson continued that the use of stimulants to augment TCAs or monoamine oxidase inhibitors has a long history, but no placebo-controlled studies have been reported. Recently, a controlled trial[41] of extended release methylphenidate augmentation of an SSRI in 60 patients was reported. While response rates appeared to favor methylphenidate (40% vs. 23%), the difference was not significant.

A multicenter, controlled study[42] of partial responders to SSRI monotherapy with excessive fatigue and sleepiness found that modafinil-treated patients were more likely to be very much improved and have greater overall improvement on the Clinical Global Impressions-Improvement (CGI-I) scale than placebo-treated patients. A subsequent extension study[43] reported sustained response in responders and improvement in sleepiness, fatigue, and mood in initial nonresponders.

Dr. Nelson stated that, when added at the beginning of treatment, pindolol augmentation of SSRIs may result in more rapid improvement in patients with depression.[44] However, when added later in treatment for refractory depression, pindolol augmentation did not appear to elicit a significant response compared with placebo.[45]

Dr. Nelson explained that low folic acid levels are associated with depression.[46] Low folate also predicts reduced response to treatment[47] and increased risk of relapse.[48] One randomized, double-blind study[49] found that adding folate to fluoxetine therapy enhanced response in women, but not in men. Higher doses of folate may be needed in men.

A preliminary study[50] of antidepressant augmentation with an omega-3 fatty acid in patients with breakthrough depression showed significant benefits versus placebo augmentation ($P <$ .001). In addition, a meta-analysis[51] found efficacy for omega-3 fatty acid in depression, but the reviewed studies included patients with bipolar disorder and monotherapy as well as augmentation trials.

No existing controlled studies have observed significant results with buspirone or testosterone augmentation; however, Dr. Nelson noted, studies with large sample sizes and clearly defined treatment resistance are needed. Dr. Nelson added that results of estrogen augmentation trials have been inconsistent and have not clearly shown efficacy; the doses and preparations of estrogen and the patient samples have varied among trials.

Newer agents that have selective norepinephrine reuptake inhibition have been tried as augmentation to SSRIs. Dr. Nelson explained that the idea was to use drugs that act on norepinephrine and serotonin together to increase efficacy. No controlled trials have been reported for augmentation therapy with an SSRI and reboxetine. The addition of atomoxetine to an SSRI failed to demonstrate efficacy in a controlled study.[52]

Combination Strategies

One of the first antidepressant combination strategies for treatment-resistant depression was with TCAs and SSRIs. A randomized, double-blind study[53] found that combination treatment with desipramine and fluoxetine was significantly more likely to result in remission than monotherapy with either drug (P = .001). However, another study[54] observed higher (but nonsignificant) response rates with high-dose fluoxetine monotherapy than with either a desipramine-fluoxetine combination or lithium augmentation of fluoxetine in nonresponders and partial responders. Dr. Nelson noted that the lower doses and blood levels in this study[54] may explain the differing results.

Dr. Nelson stated that one of the most popular strategies is the combination of SSRIs with bupropion. The idea is to combine agents acting on serotonin with an agent acting on catecholamines, but no placebo-controlled studies have been reported.

The combination of SSRIs and mirtazapine has received some attention, continued Dr. Nelson. A double-blind, placebo-controlled study[55] of the addition of mirtazapine to another antidepressant (mostly SSRIs) found the active combination to be significantly more effective than the addition of placebo in patients with inadequate response to antidepressant monotherapy. Another double-blind study[56] found that combination treatment with mirtazapine and paroxetine was significantly more effective than either monotherapy. In addition, a STAR*D report[36] stated that the combination of mirtazapine and venlafaxine had equivalent efficacy to tranylcypromine in extremely treatment-resistant patients, but the combination was better tolerated.

Conclusion

Of the augmentation and combination strategies described, several are supported by evidence; however, few are supported by well-designed, large studies with clearly defined treatment resistance, concluded Dr. Nelson. Also, few studies directly compared treatment strategies, identified predictors of response to particular strategies, or discussed how long to continue combination or augmentation strategies in patients who respond to them. More research is needed to address these deficiencies in the existing literature.

Evidence-Based Evaluation of Atypical Antipsychotics for Treating Refractory Depression

Although an increasing number of antidepressant agents are available for treating depression, about half of patients do not respond and as many as

Table 2. Variables to Check Before Considering a Patient Treatment Resistant

Nonadherence to treatment (because of poor tolerability or other factors) may result in nonresponse to the initial drug(s)
Correct diagnosis (including subtype of depression and presence of comorbidity) to inform the selection of alternate treatments
Adequate dose and duration of initial treatment, because some patients experience delayed response and remission
Factors that delay response to treatment (older age, illness chronicity, co-occurring psychiatric or medical disorders, and severe symptomatology)

Table 3. Questions Concerning Atypical Antipsychotic Augmentation of Antidepressants for Treatment-Resistant Depression

Are the benefits of antipsychotic agents due to an antidepressant effect of the antipsychotics themselves or a therapeutic synergy achieved through adjunctive use?
Given the potentially serious long-term side effects of antipsychotics, how long should augmenting medications be continued?
How effective are antipsychotic agents in preventing depressive relapse?
Should the antidepressant be tapered when an antipsychotic is added?
What are the differences in efficacy and effectiveness among the atypical antipsychotics for syndromal indications such as anxiety, agitation, insomnia, and neurovegetative symptoms?

two thirds of patients do not achieve remission after an adequate trial of the first-line treatment.[20] Michael E. Thase, MD, explained that alternative treatments are needed for the many patients with resistant depression.

Before determining whether a patient truly has treatment-resistant depression, several variables that can make a patient falsely appear to be resistant to treatment must be considered, said Dr. Thase (Table 2). For example, nonresponse may be caused by nonadherence to treatment.

Augmentation With Atypical Antipsychotics

Dr. Thase continued that atypical antipsychotics are increasingly being chosen for augmentation of antidepressants in treatment-resistant patients because of both the growing number of studies demonstrating their usefulness and their clinical reputation for rapid benefits.

The use of antipsychotic agents is not limited to depressions within the bipolar spectrum or to depressions with psychotic features, explained Dr. Thase, although these are among the reasons that patients do not respond to antidepressant treatment. He also reported that the atypical antipsychotic agents are now more commonly used than the older, typical agents.

Some atypical antipsychotic agents have evidence of efficacy as augmentation of antidepressants in at least 2 published studies of treatment-resistant depression. A meta-analysis[57] examined 10 double-blind, randomized, placebo-controlled clinical trials of the olanzapine, risperidone, or quetiapine in addition to an antidepressant for patients with treatment-resistant depression. Subjects receiving adjunctive antipsychotic treatment had about 25% greater rates of remission and response than those receiving antidepressant treatment plus placebo. However, patients receiving augmentation with atypical antipsychotics had significantly higher discontinuation rates due to adverse effects than those who received placebo augmentation ($P = .0001$). Dr. Thase noted that a limitation of this meta-analysis was that studies of only 3 of the atypical agents were included.

The olanzapine-fluoxetine combination agent has been found to be more efficacious than either fluoxetine or olanzapine monotherapy in patients with nonpsychotic, treatment-resistant unipolar depression.[58] Risperidone has also been found to have short-term effiacacy,[59,60] but a relapse-prevention study[61] using risperidone augmentation of citalopram did not show significantly different results than placebo augmentation.

Placebo-controlled studies of adjunctive ziprasidone for treatment-resistant depression are needed. However, small trials[62,63] have suggested ziprasidone is safe and potentially efficacious as augmentation.

One atypical antipsychotic, aripiprazole, is FDA-approved as an add-on treatment for antidepressant-resistant depression. Two randomized, double-blind, placebo-controlled studies[64,65] evaluated the efficacy of adding aripiprazole for patients with treatment-resistant depression and found that remission and response rates were significantly greater with the addition of aripiprazole than placebo ($P = .001$ and $P = .027$, respectively, for the first study, and $P = .016$ and $P < .001$, respectively, for the second study). The studies showed a relatively rapid onset of benefit. However, about 25% of patients taking aripiprazole in each study experienced akathisia, versus about 4% with placebo. Dr. Thase added that lower dosages of aripiprazole should be used in treating resistant depression than schizophrenia or mania.

Augmentation with atypical antipsychotics appears to be efficacious across the class, but more research is needed on between-drug differences and long-term efficacy, said Dr. Thase. Several questions need to be answered in relation to augmentation therapy with atypical antipsychotics for treatment-resistant depression (Table 3).

Conclusion

Atypical antipsychotic augmentation can lead to depression remission in some patients who have not fully responded to standard antidepressants, but additional studies are needed to determine if efficacy can be sustained, said Dr. Thase. Adverse effects with atypical antipsychotics may include weight gain, movement disorders, and other potentially long-term effects, and the specific agents should be compared in terms of tolerability as well as efficacy. These agents should also be compared in treating specific residual symptoms and, finally, should be compared against other adjunctive strategies,

such as lithium or thyroid hormone augmentation.

Drug names: aripiprazole (Abilify), atomoxetine (Strattera), bupropion (Wellbutrin, Aplenzin, and others), buspirone (BuSpar and others), citalopram (Celexa and others), desipramine (Norpramin and others), duloxetine (Cymbalta), fluoxetine (Prozac and others), lithium (Eskalith, Lithobid, and others), methylphenidate (Ritalin, Concerta, and others), mirtazapine (Remeron and others), modafinil (Provigil), nortriptyline (Pamelor, Aventyl, and others), olanzapine (Zyprexa), olanzapine-fluoxetine (Symbyax), paroxetine (Paxil, Pexeva, others), quetiapine (Seroquel), risperidone (Risperdal and others), sertraline (Zoloft and others), tranylcypromine (Parnate and others), venlafaxine (Effexor and others), ziprasidone (Geodon).

Disclosure of off-label usage: The chair has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside US Food and Drug Administration–approved labeling has been presented in this article.

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