What Alternatives to First-Line Therapy for Depression Are Effective?

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Depression is often a chronic illness that requires a methodical, long-term approach to manage it optimally. A single antidepressant trial is often insufficient for patients to achieve remission. Remission rates for selective serotonin reuptake inhibitors are about 30% to 35%. Using successive treatment steps with optimal medication dosing and making measurement-based treatment decisions can help patients achieve remission, but, at each step, remission is less likely than at the first step. Depression is considered treatment-resistant if 2 adequate trials of medication fail. Clinicians can use validated symptom checklists such as the 16-Item Quick Inventory of Depressive Symptomatology, 9-Item Patient Health Questionnaire, Global Assessment of Functioning, and Sheehan Disability Scale to identify patients with treatment-resistant depression. Treatment resistance is likely in patients with a history of depressive chronicity and concurrent psychiatric and medical disorders and may be mistakenly suspected in patients who have had an inadequate trial of medication or who have been misdiagnosed. Strategies that can be effective to combat treatment resistance include optimizing treatment, switching to another antidepressant, combining antidepressants, and augmenting antidepressants with nonantidepressant treatments such as buspirone, lithium, liothyronine, atypical antipsychotics, or other agents. In addition, clinicians need to cultivate strong therapeutic alliances with patients, use objective measurements, practice evidence-based medicine, and educate patients about the disease and its treatments.

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Evidence from years of increasing antidepressant use has highlighted a reality about depression treatments that was generally unanticipated by primary care clinicians at the outset. Antidepressant medications do not work as well as originally believed, or else depression is much harder to treat than clinicians' education on the topic led them to expect. Perhaps the reality is a combination of both of these factors.

Depression fits best into chronic illness models in terms of clinical approach, level of clinical challenge, and strength of therapeutic alliance and resources required for optimal management. Problems with treatment can result from both patient-related and physician-related factors. For example, patients may have health beliefs that negatively influence medication adherence and psychosocial contexts that do not support wellness. Clinicians may not approach diagnosis and treatment in a methodical, measurement-based, stepwise fashion because of limitations in medical education, practice setting, or mechanics.

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Remission rates for selective serotonin reuptake inhibitors (SSRIs) in clinical trials are about 30% to 35%. For instance, in the large Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial,[1] optimally dosed citalopram monotherapy yielded a remission rate of about one-third in the initial treatment step, according to the 16-item Quick Inventory of Depression Symptomatology–Self-Report ($QIDS\text{-}SR_{16}$). The STAR*D trial was unique in that it attempted to simulate real-life depression treatment outcomes in a broadly representative adult outpatient sample with nonpsychotic major depressive disorder (MDD) using successive acute treatment steps that incorporated optimized medication dosing and measurement-based treatment decisions.

Primary care physicians are often surprised to learn that most depressed patients exhibit at least some degree of treatment resistance (ie, failure to remit after 1 adequate antidepressant trial[2]). Many clinicians would be interested in proceeding with more advanced levels of intervention, despite the limitations of antidepressant efficacy, if they had access to sound and clear information on how to identify, assess, and care for the difficult-to-treat patient.

IDENTIFYING TREATMENT RESISTANCE

Robust (ie, complete) and sustained symptom remission is the goal of depression management. Complete remission is associated with a return to premorbid functioning and decreased risk of relapse. A study[3] of psychosocial functioning

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For Clinical Use

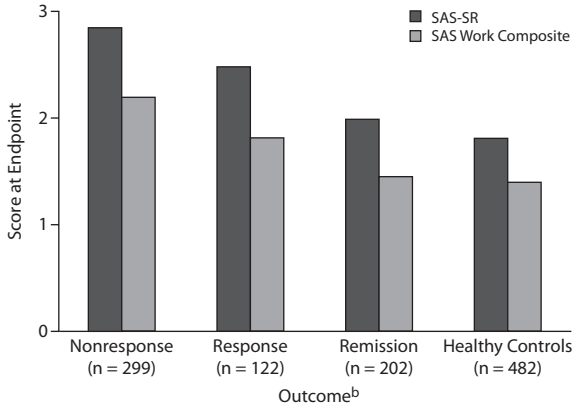
- Expect many patients with major depressive disorder to fail to achieve remission when treated with a single agent of adequate dose and duration.
- Identify those patients whose depression is truly treatment-resistant.
- To manage treatment-resistant depression, use alternative, evidence-based strategies such as drug switching, combination, and augmentation.

in patients taking sertraline or imipramine, in a 12-week acute treatment trial, compared Social Adjustment Scale–Self Report scores of nonresponders and partial responders with scores of individuals who achieved symptom remission. Results demonstrated that only patients with remission of depressive illness functioned at a level comparable to that of healthy control subjects, according to work and interpersonal functioning measures (Figure 1).[4] The STAR*D study[5] confirmed that patients whose depressive symptoms had remitted at entry to follow-up were less likely to experience relapse than patients whose symptoms had only responded to treatment at entry to follow-up. Additionally, the children of mothers who failed to remit were found to have a greater depressive symptom burden than those whose mothers achieved episode remission. In children whose mothers' depression failed to remit, the rate of depressive disorders from baseline to 3 months increased from 7% to 11%, while in children whose mothers achieved episode remission, the rate of depressive disorders decreased from 18% to 9%.[6] Therefore, the presence of persistent residual symptoms, even minor ones, should be routinely assessed so that treatment resistance can be identified.

The use of well-researched symptom checklists, such as the self-reported QIDS-SR_{16},[7] the 9-item Patient Health Questionnaire (PHQ-9),[8] the Hamilton Depression Rating Scale (HDRS),[9] the Global Assessment of Functioning (GAF),[10] or the Sheehan Disability Scale (SDS),[11] can help clinicians identify treatment-resistant depression and help patients achieve full remission of symptoms. For an in-depth review of assessing treatment response and remission, see the article in this supplement, "When Should You Move Beyond First-Line Therapy for Depression?" by Roger S. McIntyre, MD, FRCPC.[12]

Other useful indications of treatment resistance include persistent high utilization of telephone triage, emergency services, and work-in appointments. Missed work days, frequent use of sick leave, and a persistence of the physical symptoms that often accompany depression (eg, headache, back pain, bowel complaints) can also arouse clinicians' suspicion of a less-than-robust response to antidepressant treatment.[13]

Figure 1. Impaired Functioning Normalizes Only With Remission of Depression[a]



[a]Reprinted with permission from Thase.[4]
[b]Significant differences ($P \leq .05$) existed in SAS work composite scores between response vs nonresponse, remission vs nonresponse, and remission vs response.
Abbreviation: SAS-SR = Social Adjustment Scale–Self-Report.

CAUSES OF TREATMENT RESISTANCE

Several factors are associated with treatment resistance. The STAR*D trial[5] found that a large number of treatment steps was needed for participants with chronic depressive illness, early onset of depression (at < 18 years of age), concurrent psychiatric disorders (including substance use/abuse), and general medical disorders, all of which are associated with failure to achieve symptomatic remission. Other factors associated with treatment resistance included difficult psychosocial contexts and comorbid melancholic and anxious features.[5]

Biologic heterogeneity very likely plays a role in treatment resistance, although little is known about the specific types of heterogeneity that may be actively involved.[1] Chronicity of depression may produce brain changes that negatively impact treatment response. Pharmacogenetic and other studies may help to determine which treatments are more likely to achieve remission in certain patients, but the multiple potential sources of treatment resistance underline the importance of the availability of a broad repertoire of treatment options and data about efficacy and effectiveness.

The appearance (but not the true presence) of treatment resistance is associated with medication nonadherence and with 2 problems that STAR*D specifically addressed: inadequate dose and inadequate duration of treatment.[14] A lack of diagnostic precision is also a potential source of what can appear to be treatment resistance.[15] Bipolar disorder, in particular, is a predominately depressive mood disorder, which makes differential diagnosis challenging. Bipolar disorder requires a specific treatment approach for acute depressive episodes that is different from that of MDD, and antidepressant interventions may be counterproductive for bipolar disorder.

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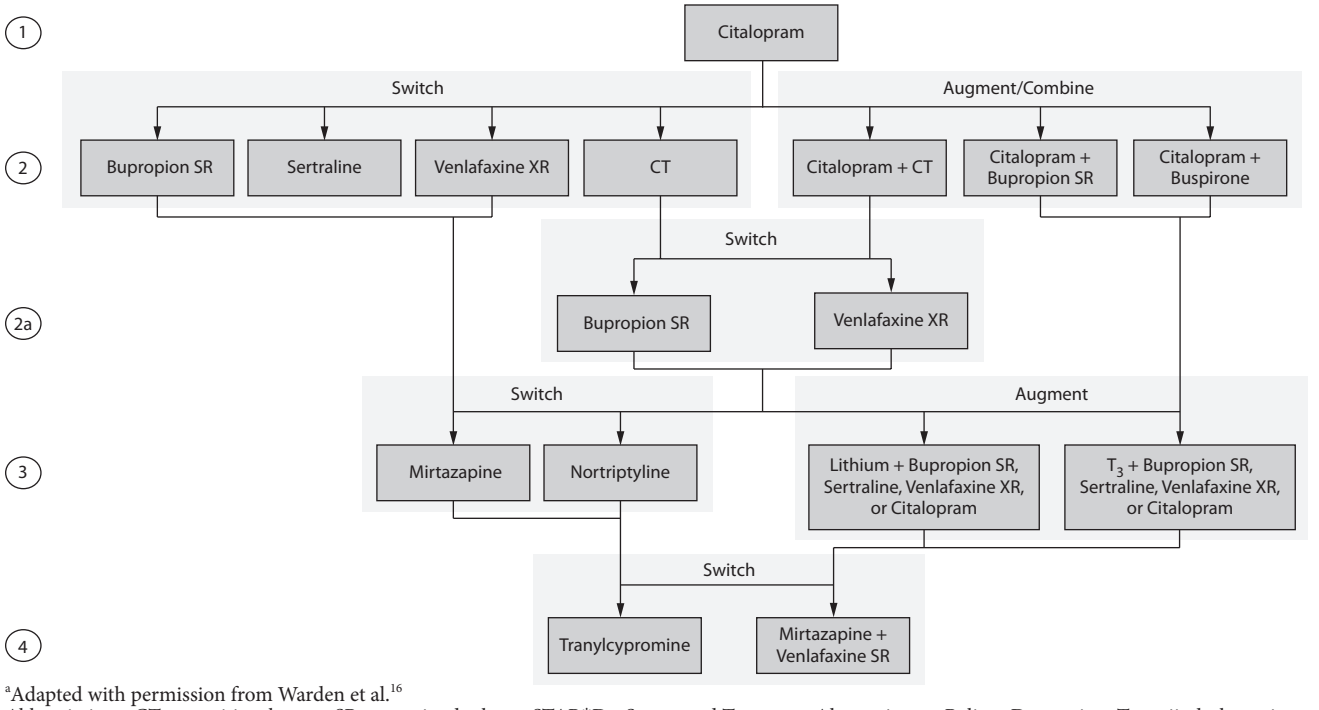
Figure 2. Treatment Switches and Augmentations/Combinations in the 4 Levels of the STAR*D Trial[a]



[a]Adapted with permission from Warden et al.[16]
Abbreviations: CT = cognitive therapy, SR = sustained release, STAR*D = Sequenced Treatment Alternatives to Relieve Depression, T_3 = triiodothyronine (liothyronine), XR = extended release.

SOMATIC STRATEGIES FOR TREATMENT-RESISTANT DEPRESSION IN STAR*D

Several strategies are available to clinicians when treating patients whose depression has failed to respond to previous treatment. The STAR*D trial[16] described the efficacy of a number of options, including psychosocial treatment (cognitive therapy). The study[16] had 4 levels of treatment, and patients who did not reach remission following an optimized, adequate trial of citalopram moved through subsequent steps that involved switching, combining, or augmenting treatment (Figure 2).

Dose Optimization and Adequate Length of Treatment Trial

Optimizing the antidepressant dose is essential for success in treating depression. Optimization means using maximally tolerated doses within the usual dosing range. Most antidepressants have starting doses that are lower than the average dose required for full response, so the target dose has to be reached over time until therapeutic efficacy and patient tolerance are balanced. Extending the duration of the acute phase of treatment beyond the 8-week period that is typical for randomized controlled trials is also often necessary in clinical practice. In fact, the STAR*D trial[16] found that a substantial number of patients required 12 to 14 weeks of treatment to reach remission with the initial treatment. When a patient's response to a single antidepressant agent falls short of remission, options include switching to a different antidepressant, combining the existing antidepressant with a second antidepressant, or augmenting the antidepressant with a nonantidepressant agent.

Antidepressant Switches

Antidepressant switches are often, but not always, accomplished by cross-titration, which is a gradual reduction in dose of the primary agent combined with a gradual introduction of its replacement. (In STAR*D, bupropion and buspirone were discontinued without tapering at level 2.) Switches were allowed from citalopram monotherapy to bupropion sustained release (SR), sertraline, or venlafaxine extended release (XR) monotherapy in level 2. The study allowed switches from these antidepressants to either mirtazapine or nortriptyline monotherapy in level 3. In level 4, patients could switch to the monoamine oxidase inhibitor tranylcypromine or mirtazapine combined with venlafaxine XR.

Only about one-third of patients reached remission with citalopram monotherapy in level 1 of the STAR*D study (Figure 3).[16] In level 2, the switches from citalopram to sertraline, venlafaxine XR, or bupropion SR were equivalently effective; remission rates were about 25%. Remission rates for monotherapy switch strategies at levels 3 and 4 were substantially less (8.0%–13.8%) than at level 2.

Antidepressant Combinations

Combinations of antidepressants have been widely used to treat adverse effects of the primary agent. For example,

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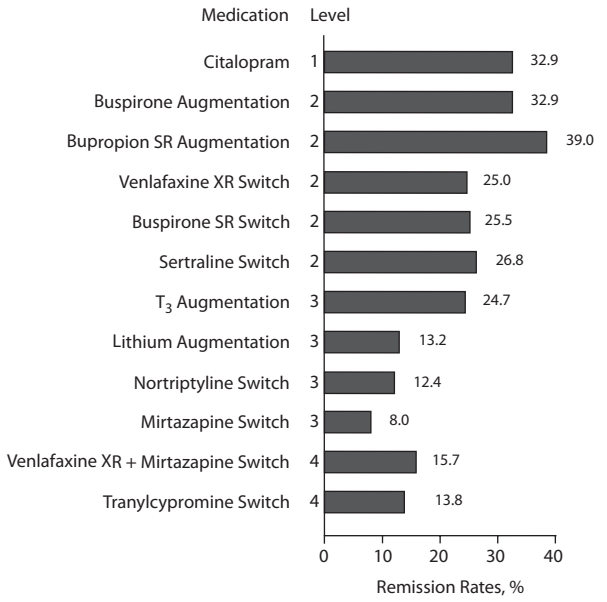
Figure 3. Remission Rates for Pharmacotherapy Treatment at Exit From Each Level of the STAR*D Trial[a]



[a]Adapted with permission from Warden et al.[16] Remission was defined as a score ≤ 5 on the 16-item Quick Inventory of Depressive Symptomatology–Self-Report at exit.
Abbreviations: SR = sustained release, STAR*D = Sequenced Treatment Alternatives to Relieve Depression, T_3 = triiodothyronine (liothyronine), XR = extended release.

trazodone has been used to manage insomnia, and bupropion has been used for SSRI-related sexual dysfunction. Most antidepressant combinations for treatment-resistant depression focus on the therapeutic synergy of synaptic effects afforded by this strategy. For instance, a combination of an SSRI plus a low dose of the tricyclic antidepressants desipramine or nortriptyline is an attempt to achieve dual monoamine (serotonin [5-HT] plus norepinephrine [NE]) reuptake inhibition. Other combinations and augmentations seek to add α_2 antagonism (eg, mirtazapine) or 5-HT_{1A} antagonism (eg, buspirone, an atypical anxiolytic).

The STAR*D study[16] made use of combination strategies in levels 2 and 4 of the trial. As shown in Figure 3, bupropion SR combination with citalopram yielded a remission rate of 39.0%. At level 4, in which the sample comprised highly treatment-resistant patients, the combination of venlafaxine XR and mirtazapine yielded a remission rate of 15.7%.[16]

Antidepressant Augmentation

The STAR*D trial[16] used a few augmentation strategies. In level 2, citalopram could be augmented with buspirone. In level 3, both liothyronine (T_3) and lithium could be used to augment sertraline, bupropion SR, venlafaxine XR, or citalopram. Remission rates varied for individual augmentations (see Figure 3).

Prior to the STAR*D trial, lithium had been one of the best-studied antidepressant augmentation agents for treatment-resistant depression. At low doses, lithium augmentation may provide rapid improvement in some patients, but a plasma level of at least 0.7 mEq/L should be maintained before assessing therapeutic effects. Disadvantages of lithium include negative stigma for some patients; the need for plasma drug level, renal, and thyroid monitoring; and annoying adverse effects. Augmentation with lithium also has potential for drug-drug interactions, for example, with nonsteroidal anti-inflammatory drugs and angiotensin-converting enzyme inhibitors, that increase plasma lithium levels. Lithium-induced thyroid dysfunction and lithium toxicity can also occur. Lithium augmentation remission rates theoretically may have been reduced in STAR*D by the dosing limit of 900 mg/d.[5] Liothyronine was better tolerated than lithium as an augmenting agent in the STAR*D trial.

STAR*D and the Challenge of Treatment Resistance

The results of the STAR*D trial illustrated the difficulties in reaching the goal of sustained remission of MDD and the need for more treatment options for treatment resistance. This trial was the largest prospective study of sequential treatments ever conducted, and remission rates declined at every level of intervention. Substantial decreases in remission rates were seen at steps 3 and 4 (see Figure 3).[16] Relapse rates, even for those reaching remission, were high.[1] The methodology of STAR*D prevented comparing the value of switch versus combination strategies.[5]

ANTIDEPRESSANT AUGMENTATION BEYOND STAR*D

Psychostimulants

Psychostimulants have been used as monotherapy or as adjunct therapy for treatment-resistant depression, but a recent systematic review in the Cochrane Database[17] found only modest support for their use. Dexamphetamine, methylphenidate, methylamphetamine, pemoline, and modafinil were included in 24 randomized controlled trials. Modafinil was evaluated separately because of its distinct pharmacology. Only 3 small trials (62 total participants) in that review found significant short-term benefit of psychostimulants versus placebo for depressive symptoms and fatigue; the improvement in depressive symptoms was of questionable clinical significance. Modafinil did not show significant difference from placebo for depressive symptoms.

Other Agents

Other agents, for example, pindolol, L-methylfolate, and estrogens, have been proposed as antidepressant augmentation or facilitation, ie, enhancing the speed of antidepressant response. Although some of these agents have been evaluated, they cannot be recommended for widespread clinical adoption because data for these approaches are from trials that were small, poorly controlled, or negative.[18]

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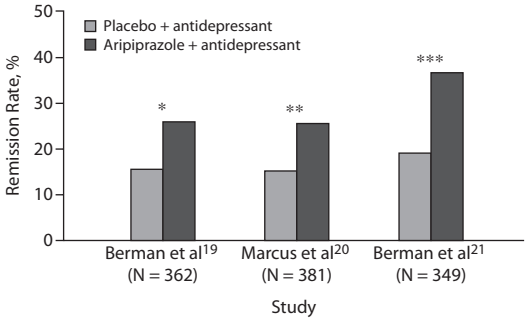
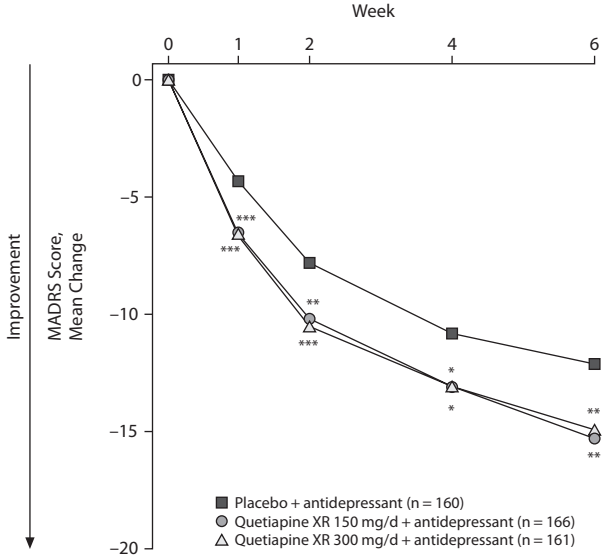
Figure 4. Remission Rates in 3 Studies of Depressed Patients Treated With Antidepressants Plus Aripiprazole or Placebo[a]



[a]Remission was defined as a score ≤ 10 on the Montgomery-Asberg Depression Rating Scale.
*P = .011.
**P = .016.
***P < .001.

Figure 5. Change in MADRS Total Score in Patients Treated With an Antidepressant Plus Quetiapine XR or Placebo[a]



[a]Reprinted with permission from Bauer et al.[24]
*P < .05.
**P < .01.
***P < .001.
Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, XR = extended release.

Atypical Antipsychotics

The development and execution of the STAR*D trial predated the emergence of atypical antipsychotics as useful psychopharmacologic agents in the management of depressive episodes. Two atypical antipsychotics—aripiprazole and quetiapine—have received US Food and Drug Administration approval for the adjunctive management of MDD that has inadequately responded to antidepressant monotherapy. Also, the olanzapine-fluoxetine combination is approved for treatment-resistant depression in adult patients.

Aripiprazole. Aripiprazole, the first atypical antipsychotic approved as add-on therapy for patients failing to remit when taking antidepressant monotherapy, has been evaluated in large, placebo-controlled studies.[19–21] As shown in Figure 4, remission rates were significantly greater for adjunctive aripiprazole versus adjunctive placebo, according to scores ≤ 10 on the Montgomery-Asberg Depression Rating Scale (MADRS). A pooled analysis of 2 of those studies,[20,21] conducted by Nelson and colleagues,[22] found a large effect size (1.1 to 1.3) on subscales of the 17-item HDRS that evaluate core depression symptoms, including depressed mood, interest in work and activities, guilt, and psychic anxiety. Effect size for change in the composite score was large for drive (0.91) and moderate for anxiety (0.75) and insomnia (0.49) in patients who received adjunctive aripiprazole compared with those who received placebo. Adjunctive aripiprazole was generally well tolerated. The most common adverse effects were akathisia, headache, and restlessness.[19,20] The dose range for adjunctive aripiprazole was 2 mg/d to 15 mg/d for patients taking fluoxetine or paroxetine controlled release but up to 20 mg/d for those taking escitalopram, venlafaxine XR, or sertraline.[22]

Quetiapine. Quetiapine XR as adjunctive therapy in 493 patients with MDD with an inadequate response to an antidepressant was studied in a 6-week randomized controlled trial.[23] Doses of 150 mg/d or 300 mg/d of quetiapine XR yielded a significant reduction in mean MADRS total scores as early as week 1 (P < .001) (Figure 5).[23] Although response rates (defined as a ≥ 50% reduction in MADRS score from baseline) at week 6 for both quetiapine XR doses were higher than that for placebo, only the 300-mg/d quetiapine XR dose was associated with significantly higher response rates than placebo (P < .05). However, when remission rates (defined as a MADRS total score ≤ 8) at week 6 were compared, the remission rate for the 150-mg/d dose of quetiapine XR was significant versus placebo (36.1%, P < .05), whereas the 300-mg/d dose remission rate was not significant (31.1%, P = .126) compared with that of placebo (23.8%). A post hoc analysis using a remission rate of a MADRS score ≤ 10 yielded remission rates of 41.6% (P < .05) for the 150-mg/d dose and 40.4% (P = .073) for the 300-mg/d dose versus placebo (31.3%). The most common adverse effects were dry mouth and somnolence.

In another randomized placebo-controlled trial[24] of quetiapine XR as adjunctive therapy in patients with MDD who had had an inadequate response to an antidepressant (N = 446), the 300-mg/d quetiapine dose, but not the 150-mg/d dose, was found to be significantly superior to placebo for response and remission. The response rates (≥ 50% reduction in MADRS score) were 58.9% for 300 mg/d of quetiapine and 46.2% for placebo (P < .05), and remission rates (MADRS score ≤ 8) were 42.5% and 24.5%, respectively (P < .01).

Olanzapine-fluoxetine combination. The olanzapine-fluoxetine combination is the only pharmacologic strategy containing an atypical antipsychotic that has been studied in patients with inadequate response to at least 2 antidepressant

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trials. A post hoc integrated analysis[25] of 1,146 patients with MDD in 5 studies for which 1 of the entry criteria was failure to respond to 2 different antidepressants in the current episode found a significantly higher remission rate (defined as a MADRS score ≤ 10) for the olanzapine-fluoxetine combination (25.5%) versus fluoxetine (17.3%, $P = .006$) and olanzapine (14.0%, $P < .001$). The most common adverse events experienced with the combination treatment were weight gain, increased appetite, dry mouth, and somnolence.

CONCLUSION

Major depression is often difficult to treat. A majority of patients fail to achieve remission when taking a single agent at an adequate dose and duration. Switch and combination strategies with other antidepressant treatments may be effective options for single antidepressant failures. Augmentation strategies with nonantidepressant treatments such as atypical antipsychotics, buspirone, liothyronine, and lithium, among other treatments, may also be effective in helping patients achieve remission.

Clinicians who manage depression should be prepared to use long-term strategies in a chronic illness paradigm. This treatment model seeks to enhance therapeutic alliances, uses measurement-based and evidence-based decisions, and involves the patient in disease-state education and familiarization with various treatment approaches.

Beneficial treatments will continue to emerge in the future. Many of these treatments will have novel mechanisms of action and require clinicians to be open to learning to use new agents. The benefits of such learning are relief for patients from a debilitating illness, better functional status for patients, and enhanced physician satisfaction with clinical practice.

Drug names: aripiprazole (Abilify), bupropion (Aplenzin, Wellbutrin, and others), buspirone (BuSpar and others), citalopram (Celexa and others), desipramine (Norpramin and others), escitalopram (Lexapro and others), estrogens (Premarin, Enjuvia, and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), liothyronine (Cytomel and others), lithium (Lithobid and others), methylphenidate (Ritalin, Metadate, and others), mirtazapine (Remeron and others), modafinil (Provigil), nortriptyline (Pamelor, Aventyl, and others), olanzapine-fluoxetine (Symbyax), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), sertraline (Zoloft and others), tranylcypromine (Parnate and others), trazodone (Oleptro and others), venlafaxine (Effexor and others).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, bupropion, buspirone, desipramine, estrogens, liothyronine, lithium, methylphenidate, mirtazapine, modafinil, nortriptyline, trazodone, dexamphetamine, L-methylfolate, methylamphetamine, pemoline, and pindolol are not approved by the US Food and Drug Administration for adjunctive use in major depressive episodes.

REFERENCES

1. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry.* 2006;163(11):1905–1917.
2. Souery D, Amsterdam J, de Montigny C, et al. Treatment resistant depression: methodological overview and operational criteria. *Eur Neuropsychopharmacol.* 1999;9(1–2):83–91.
3. Miller IW, Keitner GI, Schatzberg AF, et al. The treatment of chronic depression, pt 3: psychosocial functioning before and after treatment with sertraline or imipramine. *J Clin Psychiatry.* 1998;59(11):608–619.
4. Thase ME. Update on partial response in depression. *J Clin Psychiatry.* 2009;70(suppl 6):4–9.
5. Rush AJ, Warden D, Wisniewski SR, et al. STAR*D: revising conventional wisdom. *CNS Drugs.* 2009;23(8):627–647.
6. Weissman MM, Pilowsky DJ, Wickramaratne PJ, et al for the STAR*D-Child Team. Remissions in maternal depression and child psychopathology: a STAR*D-child report. *JAMA.* 2006;295(12):1389–1398.
7. Rush AJ, Trivedi MH, Ibrahim HM, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry.* 2003;54(5):573–583.
8. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med.* 2001;16(9):606–613.
9. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry.* 1960;23(1):56–62.
10. American Psychiatric Association. Global Assessment of Functioning (GAF) Scale. In: *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000:34.
11. Leon AC, Olfson M, Portera L, et al. Assessing psychiatric impairment in primary care with the Sheehan Disability Scale. *Int J Psychiatry Med.* 1997;27(2):93–105.
12. McIntyre RS. When should you move beyond first-line therapy for depression? *J Clin Psychiatry.* 2010;71(suppl 1):16–20.
13. Maes M. "Functional" or "psychosomatic" symptoms, eg a flu-like malaise, aches and pain and fatigue, are major features of major and in particular of melancholic depression. *Neuroendocrinol Lett.* 2009;30(5):564–573.
14. Trivedi MH, Rush AJ, Gaynes BN, et al. Maximizing the adequacy of medication treatment in controlled trials and clinical practice: STAR*D measurement-based care. *Neuropsychopharmacology.* 2007;32(12): 2479–2489.
15. Gaynes BN. Identifying difficult-to-treat depression: differential diagnosis, subtypes, and comorbidities. *J Clin Psychiatry.* 2009; 70(suppl 6):10–15.
16. Warden D, Rush AJ, Trivedi MH, et al. The STAR*D Project results: a comprehensive review of findings. *Curr Psychiatry Rep.* 2007;9(6): 449–459.
17. Candy B, Jones L, Williams R, et al. Psychostimulants for depression. *Cochrane Database Syst Rev.* 2008;(2):CD006722.
18. Shelton RC, Osuntokun O, Heinloth AN, et al. Therapeutic options for treatment-resistant depression. *CNS Drugs.* 2010;24(2):131–161.
19. Berman RM, Marcus RN, Swanink R, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry.* 2007;68(6):843–853.
20. Marcus RN, McQuade RD, Carson WH, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol.* 2008;28(2):156–165.
21. Berman RM, Fava M, Thase ME, et al. Aripiprazole augmentation in major depressive disorder: a double-blind, placebo-controlled study in patients with inadequate response to antidepressants. *CNS Spectr.* 2009; 14(4):197–206.
22. Nelson JC, Mankoski R, Baker RA, et al. Effects of aripiprazole adjunctive to standard antidepressant treatment on the core symptoms of depression: a post-hoc, pooled analysis of two large, placebo-controlled studies. *J Affect Disord.* 2010;120(1–3):133–140.
23. Bauer M, Pretorius HW, Constant EL, et al. Extended-release quetiapine as adjunct to an antidepressant in patients with major depressive disorder: results of a randomized, placebo-controlled, double-blind study. *J Clin Psychiatry.* 2009;70(4):540–549.
24. El-Khalili N, Joyce M, Atkinson S, et al. Extended-release quetiapine fumarate (quetiapine XR) as adjunctive therapy in major depressive disorder (MDD) in patients with an inadequate response to ongoing antidepressant treatment: a multicentre, randomized, double-blind, placebo-controlled study (published online ahead of print Feb 23, 2010). *Int J Neuropsychopharmacol.*
25. Trivedi MH, Thase ME, Osuntokun O, et al. An integrated analysis of olanzapine/fluoxetine combination in clinical trials of treatment-resistant depression. *J Clin Psychiatry.* 2009;70(3):387–396.

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