

Pharmacological Management of Treatment-Resistant Depression

Alternative therapies often required to alleviate symptoms

by Casey Gallimore, PharmD

Treatment-resistant depression (TRD) is generally defined as the failure of at least two adequate trials of antidepressants from different pharmacological classes to produce significant improvement in depressive symptoms.^{1,2} This definition is left open to interpretation when considering what constitutes an “adequate trial” of an antidepressant. Although there are no set criteria, the most recent consensus suggests an adequate trial is an antidepressant prescribed at a maximally tolerated dose for a period of at least four weeks, and more likely for a duration of six to eight weeks or longer.¹⁻³ There is also some debate as to what describes a “significant improvement in depressive

It is estimated that only 30-40% of patients receiving adequate antidepressant therapy achieve remission. This suggests that a large percentage of patients are resistant to standard first-line antidepressant therapy. In these cases, alternative treatment regimens are required to alleviate depressive symptoms. Currently the three main treatment strategies employed in the management of TRD include: 1) switching current antidepressant therapy, 2) combining antidepressant agents, and 3) augmenting therapy with non-antidepressant agents.

AUGMENTATION

In an augmentation strategy, a separate pharmacological agent is added to enhance the therapeutic effect of the current antidepressant medication. The augmentation agent is not a standard antidepressant and often does not have an indication for depression. Advantages of augmentation include the maintenance of any gains achieved with the initial antidepressant, avoidance of possible discontinuation effects and need for medication tapering,

and utilization of a separate mechanism of action that may complement the current antidepressant or target specific troublesome symptoms such as anxiety or agitation. Several medications have been utilized and/or studied most frequently as augmentation agents in the management of TRD. These include lithium, thyroid



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hormone, buspirone, stimulants, and most recently atypical antipsychotics.

LITHIUM

Lithium is one of the oldest and most studied agents in the augmentation of depression treatment. Although the precise mechanism of action in the treatment of depression has not been completely described, it is hypothesized that lithium exerts its beneficial effects through enhancement of serotonergic neurotransmission and stimulation of the hypothalamic-pituitary-adrenocortical (HPA) system.^{4,5} While lithium trials have occasionally yielded conflicting results, a recent meta-analysis of 10 randomized, placebo-controlled trials found that lithium was significantly more effective than placebo when added to various antidepressants.⁶ Lithium has been studied most frequently in combination with tricyclic antidepressants (TCAs), although several more recent trials have included selective serotonin reuptake inhibitors (SSRIs). In one such trial, known as STAR*D, patients failing two previous antidepressant regimens could elect to have therapy augmented. A remission rate of 15.9% was observed with lithium augmentation.⁷

Significant treatment effects have been demonstrated at lithium doses of 600 to 800 mg/day and higher for a duration of at least 14 days.⁸ A maintenance plasma concentration of 0.5 to 0.8 mEq/L is recommended. Despite evidence supporting its efficacy, there are drawbacks to the initiation of lithium including the need for blood monitoring and an undesirable side effect profile. Lithium levels should be measured at least every two months once a stable dosing regimen has been established, and more frequently when first initiating therapy. The most common adverse effects associated with lithium use

Goal. Review the current drug therapy options for the management of treatment-resistant depression.

Objectives. 1) Describe current treatment strategies in the management of treatment-resistant depression; 2) Discuss potential advantages and disadvantages of each treatment strategy in the management of treatment-resistant depression; 3) Review the available evidence evaluating the efficacy and safety of augmentation therapy, combination therapy, and switching strategies in treatment-resistant depression; 4) Provide general recommendations to maximize the efficacy of depression treatment.

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symptoms.” Previously, antidepressant efficacy was evaluated in terms of ability to produce a response to treatment, which is defined as at least a 50% reduction in depressive symptoms. More recently, remission or the complete resolution of depressive symptoms has become the accepted treatment outcome.¹⁻³

are generally dose-related and include diabetes insipidus, tremor, weight gain, and gastrointestinal distress.

THYROID HORMONE

Thyroid hormone was first studied as an augmenting agent based on mood abnormalities observed with thyroid disease. While evidence supporting the use of thyroid hormone in TRD does exist, it is somewhat limited. To date, most studies have focused on the use of T_3 (L-triiodothyronine) in depression resistant to TCAs. A meta-analysis examining four randomized, double-blind studies did not find a significant difference in treatment response when T_3 was used to augment TCA therapy in euthyroid patients with refractory depression (relative response, 1.53; 95% CI, 0.70 to 3.35; $p=0.29$).⁹ However, this effect may have been largely due to the negative results from one single trial. Currently there are no placebo-controlled trials involving the use of thyroid hormone in SSRI-resistant depression; however, several small, uncontrolled trials demonstrating remission rates of 27-30% have been published.¹⁰⁻¹² In addition, T_3 augmentation produced a 24.7% remission rate in patients who had failed two previous antidepressant regimens in the STAR*D trial. This rate was not significantly different from patients augmented with lithium, however, T_3 augmentation was associated with a lower burden of side effects.⁷

A dosing range of 25-50 mg/day of T_3 is recommended. Therapy is generally well tolerated, although several adverse effects including palpitations, increased heart rate, sweating, nervousness, and headache have been reported.

ATYPICAL ANTIPSYCHOTICS

Aripiprazole is currently the only atypical antipsychotic with a FDA-labeled indication for the adjunctive treatment of major depressive disorder. However, atypical antipsychotics as a class are being prescribed off-label for TRD with increasing frequency. To date, double-blind, randomized, placebo-controlled trials have evaluated the use of olanzapine, risperidone, quetiapine, and aripiprazole as augmenting agents to standard antidepressants in TRD. A recent meta-analysis

of 10 such trials found that remission was more likely in patients randomized to an atypical antipsychotic agent versus placebo (RR=1.75; 95% CI=1.35 – 2.24; $p<0.0001$).¹³ Trials involving aripiprazole were not included in this analysis, however, its use as adjunctive therapy in patients unresponsive to at least one standard antidepressant agent have been evaluated in two identical, large, multicenter, randomized, double-blind, placebo-controlled trials.^{14,15} In both trials, aripiprazole treated patients demonstrated significantly greater response and remission rates (~32% and ~25% respectively). Evidence supporting the use of ziprasidone in TRD is limited. A recent randomized, open-label, pilot study of 64 patients with TRD failed to demonstrate a clinically significant difference in treatment effect with adjunctive ziprasidone versus continued sertraline monotherapy.¹⁶

As augmenting agents, atypical antipsychotics have generally been evaluated at doses lower than those utilized in schizophrenia: risperidone (0.5-2 mg/day); olanzapine (5-20 mg/day); quetiapine (50-300 mg/day); aripiprazole (10-30 mg/day); and ziprasidone (40-80 mg twice daily).^{17,18} Atypical agents may exert an antidepressant effect by facilitating noradrenergic neurotransmission through antagonism of 5-HT_{2A} receptors. Additional mechanisms including alpha₂-adrenergic antagonism, 5-HT_{1A} agonism, and monoamine reuptake inhibition may also play a role.¹⁹ Despite demonstrated efficacy, atypical antipsychotics do possess a considerable side effect profile that warrants close monitoring, especially with long-term use. Possible adverse effects include weight gain, metabolic changes (hypercholesterolemia, hyperglycemia), hyperprolactinemia, sedation, and extrapyramidal effects.

BUSPIRONE

As a partial 5-HT_{1A} receptor agonist, buspirone partially blocks the 5-HT_{1A} receptor at therapeutic doses. When acutely administered, SSRIs activate presynaptic 5-HT_{1A} receptors which in turn signal negative feedback that decreases the firing rate of the serotonergic neuron.¹⁹ By partially blocking 5-HT_{1A} receptors, buspirone could augment SSRI therapy by blunting the negative feedback loop and increas-

ing serotonergic transmission.¹⁸ Despite these speculated benefits, little evidence has emerged to unequivocally support the use of buspirone in TRD. Several small, open-label studies have yielded response rates of 59-68% following the addition of buspirone to TCA or SSRI therapy in patients previously unresponsive to standard antidepressant therapy.^{20,21} In the STAR*D trial, a response rate of 30.1% was achieved when patients who failed a 14-week trial of citalopram therapy were randomized to start buspirone.²² However, the only two available randomized, placebo-controlled trials failed to demonstrate a statistically significant benefit of buspirone augmentation over placebo in treatment-resistant patients.^{23,24} One of these trials did observe a statistically significant benefit of buspirone over placebo in a subset of patients with relatively severe depression, defined as an initial Montgomery-Ashberg Depression Rating Scale (MADRS) score >30.²⁴ Although interesting, further studies are required before conclusions can be drawn regarding the efficacy of buspirone in the augmentation of severe TRD.

Buspirone has been shown to be a relatively safe and well tolerated augmenting agent at daily doses of 10-30 mg twice daily. The most commonly observed side effects include nausea, dizziness, headache, and nervousness.

STIMULANTS

Prior to the introduction of monoamine oxidase inhibitors (MAOIs) and TCAs in the 1950s, stimulants were commonly used in the treatment of depressive disorders. Today stimulants are rarely used as first-line depression therapy due to an undesirable side effect profile, the potential for abuse, and the advent of safer treatment options. Stimulants are still occasionally prescribed as augmentation therapy in TRD, and interest in this use was renewed with the introduction of modafinil. Although broadly classified as a stimulant, modafinil is thought to have a unique mechanism of action compared to amphetamine-like drugs, and does not appear to cause norepinephrine or dopamine release.^{25,26} Special interest has focused on patients with the depressive symptoms of fatigue and hypersomnia. However, despite continued use, evidence is still sparse

for the efficacy of modafinil and stimulants in depression. A recent Cochrane review of available randomized, controlled trials did not find a significant difference in mean depression score or clinical response when stimulants, including methylphenidate and modafinil, were used as adjunctive antidepressant treatment versus placebo.²⁷ In addition there did not appear to be any significant difference between treatment and control groups in fatigue or hypersomnia scores.²⁷ A recent double-blind, randomized, placebo-controlled trial of methylphenidate augmentation of antidepressant monotherapy, not included in the Cochrane review, did demonstrate a significant improvement in apathy and fatigue as secondary outcome measures in the augmentation versus control group. There was however, no significant difference in the primary outcome measure of MADRS depression score.²⁸

Dosing in TRD has ranged from 10-54 mg daily for methylphenidate and 100-400 mg daily for modafinil.²⁷ For both medications, doses are generally started low and titrated upwards as needed and tolerated. Stimulants do carry the risk of modestly elevating blood pressure and heart rate. While this is generally not problematic in otherwise healthy patients, these effects can prove dangerous in patients with pre-existing hypertension or underlying heart conditions. This risk prompted the American Heart Association (AHA) to recently recommend a baseline ECG in all children and adolescents prior to the initiation of ADHD stimulant medications.²⁹ No specific recommendation exists for adult patients, but a detailed patient history to screen for cardiac abnormalities should be conducted in all patients, and blood pressure and heart rate should be closely monitored at baseline and throughout therapy. Other possible side effects include decreased appetite, abdominal pain, weight loss, anxiety, and insomnia or restlessness. The combined use of amphetamine-like stimulants and MAOIs is contraindicated due to the potentially fatal risk of hypertensive crisis.

COMBINATION THERAPY

Combination therapy refers to the concurrent use of two or more antidepressant medications. Combination therapy may be employed when a trial of antidepres-

sant monotherapy produces a partial response, but does not induce full remission. Adding a second antidepressant with a unique mechanism of action would theoretically maintain the beneficial effects produced by the first antidepressant, while furthering the likelihood of remission. Although this treatment strategy is often utilized in clinical practice, evidence supporting safety and efficacy is still limited. Very few randomized trials have evaluated the use of antidepressant combination therapy in TRD, and those few available trials have primarily focused on the combination of a SSRI and a TCA. A single trial by Carpenter et al. and the STAR*D trial have provided some insight into the combined use of second-generation antidepressants.

Despite the described deficit of trial evidence, certain antidepressant combinations are favored in clinical practice based on potential advantages and disadvantages.¹⁸ One such combination is a SSRI with bupropion. This combination has the advantage of impacting multiple neurotransmitter systems including dopamine, serotonin, and norepinephrine. The addition of bupropion may also improve SSRI-induced sexual dysfunction.³⁰ In the STAR*D trial, a remission rate of 29.7% was observed following randomization to combination therapy with bupropion SR in depressed patients who had not achieved remission after 14 weeks of citalopram monotherapy. This remission rate was not significantly different from that of patients randomized to augmentation therapy with buspirone.²² Based on available evidence, bupropion and SSRIs can be prescribed together safely, but close monitoring is recommended, as side effects similar to those associated with each monotherapy are possible.^{22,31}

Another favorable antidepressant combination is mirtazapine with a SSRI or serotonin / norepinephrine reuptake inhibitor (SNRI) such as venlafaxine. While mirtazapine also increases noradrenergic and serotonergic transmission, it does so through a mechanism that does not involve inhibition of the reuptake transporter. Mirtazapine increases release of norepinephrine and serotonin by antagonizing presynaptic α_2 -adrenergic inhibitory receptors. Mirtazapine is also an antagonist at 5-HT₂ and 5-HT₃ receptors, which

could theoretically diminish some of the adverse effects produced by SSRI agents. The Carpenter et al. study randomized patients currently receiving a SSRI, venlafaxine or bupropion to combination therapy with mirtazapine or placebo. After four weeks, the mirtazapine group had experienced a significantly greater response rate (64% versus 20%, $p=0.043$), but only a numerically greater remission rate (45.5% versus 13.3%, $p=0.068$).³² In this case, the short trial duration may have limited the ability of some patients to reach remission. In addition, the STAR*D trial produced a remission rate of 13.7% when patients failing three previous 14-week trials of various antidepressant regimens were randomized to combination therapy with venlafaxine and mirtazapine. This was not significantly different from the remission rate observed in patients switched to the MAOI tranylcypromine.³³ Drawbacks to combination therapy with mirtazapine include an increased risk of sedation and weight gain.³²

Although commonly seen in clinical practice, the combined use of TCAs and SSRIs is not recommended as first-line combination therapy, and if utilized together, caution should be exercised. As a class the SSRIs have the potential to inhibit CYP450 enzymes for which numerous TCAs are substrates. When used concurrently, TCA metabolism can be significantly reduced, resulting in an increased risk of toxicities including dry mouth, urinary retention, sedation, and cardiotoxicity. Additionally the results from randomized trials evaluating the efficacy of combined TCA and SSRI therapy in TRD have been conflicting.³⁴

SWITCHING THERAPY

When an antidepressant regimen fails to produce an adequate treatment response, a clinician may elect to switch a patient to an entirely different therapy. This option is often appealing because it avoids the polypharmacy and subsequent increased risk of drug-drug interactions and adverse effects that may occur with augmentation or combination therapy. However, there are some drawbacks to simply switching antidepressant therapy. First of all, this strategy prompts the question of which antidepressant to switch to, and unfortunately, at this time there is limited

data to direct clinicians in this important decision. In addition, evidence suggests that the likelihood of achieving remission decreases substantially after two adequate medication trials. Therefore, in patients who are truly treatment resistant, a more complicated regimen that involves combination or augmentation may be required.³

The question of which antidepressant agent to switch to was evaluated in the STAR*D trial and more recently, in a meta-analysis by Papakostas et al. In the STAR*D trial patients electing to switch therapy after treatment failure with citalopram were randomized to therapy with bupropion SR, venlafaxine XR, or sertraline. There was no significant or clinical difference in the remission rates observed for the three drugs (21.3% bupropion SR, 24.8% venlafaxine XR, sertraline 17.6%).³⁵ This suggests that following a failed trial with a SSRI, a within-class switch to another SSRI and an across-class switch to an agent with a different mechanism of action are both effective strategies. This trial further evaluated switching strategies when patients failing two antidepressant regimens were randomized to monotherapy with mirtazapine or nortriptyline. Once again remission rates for the two drugs did not differ significantly (12.3% mirtazapine, 19.8% nortriptyline).³⁶ It is important to note that in the STAR*D trial, overall remission rates were low and trended downwards following each subsequent treatment failure.³ Therefore, the likelihood of achieving complete remission is decreased in those patients who are very treatment resistant and have failed multiple antidepressant treatment regimens.

The meta-analysis by Papakostas et al. also evaluated within- versus across-class switches in TRD. The results of four randomized, placebo-controlled trials were pooled to compare switching to a second SSRI versus a non-SSRI antidepressant in patients who had not experienced a sufficient improvement in depressive symptoms following initial SSRI treatment. Non-SSRI antidepressants included mirtazapine, venlafaxine, and bupropion, and the SSRIs evaluated were paroxetine, citalopram, and sertraline. Overall, remission was more likely in patients randomized to switch to a non-SSRI versus a second SSRI (remission rates= 28% and 23.5%, respectively; $p=0.007$).³⁷ The authors did

note that the overall difference in remission rate was small at 4.5%, and although this is statistically significant, it may not be of clinical significance to make an impact in actual practice.

There is also speculation that antidepressant agents that possess a combined serotonergic and noradrenergic mechanism of action may be more efficacious than SSRIs in TRD. This is supported by a recent meta-analysis of randomized, double-blind clinical trials that found response rates were significantly greater in patients treated with antidepressants that increase both serotonergic and noradrenergic neurotransmission versus SSRIs (63.6% and 59.3%, respectively; $p=0.003$).³⁸ Once again, although this difference was statistically significant, it is unclear whether a 4.3% difference in response rate is clinically significant. In addition, this meta-analysis was not focused on patients with TRD. Further research is needed to determine if these results translate to the treatment-resistant population.

Overall, switching antidepressant therapy can produce remission in TRD. However, the preferred sequence through which this should be accomplished is still unclear. The available evidence is largely limited to evaluating switching strategies following treatment failure with a SSRI. To date, research has not focused on patients experiencing an inadequate response from an antidepressant trial with a non-SSRI. At this time it can be surmised that when switching therapy there is not a clear advantage of one antidepressant over another in terms of efficacy. The same considerations that govern initial antidepressant selection (patient preference, tolerability, cost, ease of administration, etc.) should be applied when selecting a specific switching strategy.

SUMMARY

In summary, TRD is complicated to treat, and the probability of experiencing a complete remission from depressive symptoms decreases each time a patient fails another antidepressant treatment regimen.³ This being said, remission or a complete recovery from a depressive episode is possible with persistent and aggressive treatment, and should be the goal of therapy. Regardless of the treatment strategy utilized, there are several general recommendations

that can help maximize the efficacy of depression treatment. First, a therapeutic and sometimes vigorous dose of an antidepressant should be utilized. Patients should be initiated on an appropriately low starting dose, but it is prudent to titrate the dose into the target dosing range as tolerated. Too often this does not occur and patients are maintained on doses that do not allow for maximum antidepressant effect. In addition, if a patient experiences a response or a partial response to an average antidepressant dose, additional benefit or possible remission may occur if the dose is further maximized as tolerated.^{1,2} It is also crucial that antidepressants are given an adequately long trial duration. It was previously thought that a clinically significant improvement in depressive symptoms should be seen after four to six weeks of antidepressant therapy, but results from the STAR*D trial have since challenged this notion. Patients in the STAR*D trial required an average of seven weeks to reach remission, and 40% of those entering remission did so after eight or more weeks.³ Thus, at least an eight-week trial with an antidepressant at a maximally tolerated dose is recommended before treatment failure is declared.³ It is very important to educate patients about this long duration so they do not become frustrated and discontinue treatment prematurely.

In practice, the ideal method for managing TRD is still unknown. While evidence exists to support augmenting, combination, and switching strategies, there is no clear cut recommendation for the use of one over the other. A good starting point when considering the next step in the management of TRD is to obtain an accurate and detailed treatment history including drug, dose, duration, adherence, tolerability and efficacy. Once a good history is documented, there are some general advantages and disadvantages to the use of each strategy that should be considered when developing a treatment plan for each individual patient. Switching to an entirely different antidepressant regimen may be preferred when a patient has experienced little or no response to an antidepressant following a sufficient dose and trial duration or if a patient has experienced unacceptable adverse effects. Drawbacks to completely switching

therapy include the potential need for titration when discontinuing an antidepressant, the complete loss of any benefit the antidepressant may have produced, and a possibly long window before clinical improvement with the new regimen is expected. Combination and augmentation strategies are useful if a patient has experienced a response, but not complete remission with the current antidepressant and wishes to continue on it. In this instance, combination therapy may be preferred if there are available antidepressants the patient has not yet tried. However, if the patient has failed or has not tolerated multiple antidepressant agents in the past, it may be more prudent to add an augmenting agent. Clear disadvantages to the combined use of multiple antidepressants or antidepressants with augmenting agents is an increased pill burden, increased cost, and increased potential for drug-drug interactions and adverse effects. Finally, it is crucial to involve the individual patient in treatment decisions and take into account patient preferences. What are the patient's goals of therapy? What possible adverse effects is the patient willing to tolerate? What dosing schedule, monitoring and cost is the patient willing to incur? Which medications is the patient willing to take? These answers become valuable tools for a clinician when designing a safe and effective treatment regimen for resistant depression. ●

Casey Gallimore is clinical assistant professor and pharmacotherapy lab coordinator at the UW School of Pharmacy.

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Pharmacological Management of Treatment-Resistant Depression

- Which of the following most accurately defines “treatment resistant depression?”
 - Failure of a selective serotonin reuptake inhibitor to produce a significant improvement in depressive symptoms.
 - Failure to produce a significant improvement in depressive symptoms with combination antidepressant therapy.
 - Failure of at least two adequate trials of antidepressants from different pharmacological classes to produce a significant improvement in depressive symptoms.
 - Failure to produce a significant improvement in depressive symptoms following at least two weeks of antidepressant drug therapy.
- This should be the goal of therapy for the treatment of a depressive episode.
 - Remission
 - Response
 - Partial response
 - Maintenance
- Lithium has been studied most extensively as an augmenting agent to this class of antidepressants.
 - SSRIs
 - SNRIs
 - MOAIs
 - TCAAs
- Which of the following statements is true regarding the comparison of lithium augmentation versus T_3 augmentation in the STAR*D Trial?
 - Lithium was associated with a lower side effect burden.
 - T_3 was associated with a lower side effect burden.
 - Lithium was associated with a significantly greater remission rate.
 - T_3 was associated with a significantly greater remission rate.
- This atypical antipsychotic agent has not yet been studied as an augmenting agent for treatment resistant depression in a double-blind, randomized, placebo-controlled trial.
 - Aripiprazole
 - Olanzapine
 - Quetiapine
 - Ziprasidone
- As augmenting agents in TRD, atypical antipsychotic agents are generally used at doses that are _____ the doses prescribed in the treatment of schizophrenia.
 - Lower than
 - Equivalent to
 - Higher than
- It is hypothesized that this partial 5-HT_{1A} receptor agonist is able to augment SSRI therapy by blunting the negative feedback loop that normally decreases serotonergic transmission.
 - Aripiprazole
 - Bupropion
 - Lithium
 - Modafinil
- Due to safety concerns, the following items should be monitored prior to initiating methylphenidate as an augmenting agent in treatment-resistant depression.
 - EEG, neurologic exam
 - BP, HR, history of cardiac abnormalities
 - SCr, BUN
 - All of the above
- Which of the following describes a potential benefit to the use of combination therapy in treatment-resistant depression?
 - Decreased risk of drug-drug interactions
 - Lower incidence of adverse drug effects
 - Avoidance of possible discontinuation effects
 - Increased patient compliance
- Which of the following statements is true regarding the combined use of bupropion and a SSRI in the treatment of resistant depression?
 - Remission rates are significantly greater than those achieved with bupropion augmentation therapy.
 - The combined use of bupropion with a SSRI is contraindicated.
 - Adding bupropion to a SSRI increases the risk of sexual dysfunction.
 - Multiple neurotransmitter systems including serotonin, dopamine, and norepinephrine are impacted.
- Which of the following is a benefit of starting mirtazapine in patient who failed to achieve remission with venlafaxine monotherapy?
 - Additive inhibition of the serotonin reuptake transporter.
 - Increased noradrenergic and serotonergic transmission via a novel mechanism of action.
 - Decreased risk of weight gain and sedation.
 - Expected remission rates of 60-70%.
- This agent has the potential to inhibit the metabolism of tricyclic antidepressants, thus increasing the risk of toxicities.
 - Bupropion
 - Fluoxetine
 - Lithium
 - Mirtazapine
- Based on the results of the STAR*D Trial, which of the following statements regarding patients who failed an initial trial with a SSRI is correct?
 - A within class switch to another SSRI is likely to be more effective than an across-class switch to a non-SSRI antidepressant.
 - An across-class switch to non-SSRI antidepressant is likely to be more effective than a within-class switch to another SSRI.

- c. A within-class switch to another SSRI and an across-class switch to a non-SSRI antidepressant are both effective treatment options.
 - d. The STAR*D Trial did not evaluate switching options following the failure of an initial trial with a SSRI.
14. A patient calls your pharmacy and states that she does not feel that the citalopram she has been taking is helping her depression. She would like you to contact her prescriber to request a switch to a different antidepressant. Before it can be determined that the patient has failed therapy with citalopram, what additional information should be assessed?
- a. Duration of citalopram therapy
 - b. Citalopram dosing
 - c. Patient adherence with citalopram therapy
 - d. All of the above should be assessed
15. You are the clinical pharmacist in a family medicine clinic. One of the medical residents sees a patient for a follow-up depression visit and consults you regarding the patient's antidepressant drug regimen. The patient was started on citalopram 20 mg daily 8 weeks ago. No improvement in symptoms was noted after four weeks of therapy and the

- dose was increased to 40 mg daily. Today it is four weeks later and the patient has still not noticed any improvement in her symptoms. Based on the available information, which of the following represents the best treatment recommendation?
- a. Continue citalopram at the current dose for four additional weeks
 - b. Continue citalopram at the current dose and start imipramine 50 mg daily
 - c. Discontinue citalopram and start buspirone 5 mg three times daily
 - d. Discontinue citalopram and start venlafaxine XR 75 mg daily
16. How do you rate this lesson?
- a. Very Good
 - b. Good
 - c. Poor
17. Did it meet the learning objectives?
- a. Yes
 - b. No
18. How long did it take you to complete this lesson?



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QUIZ ANSWER FORM circle one answer per question

- | | | |
|------------|-------------|-------------|
| 1) a b c d | 7) a b c d | 13) a b c d |
| 2) a b c d | 8) a b c d | 14) a b c d |
| 3) a b c d | 9) a b c d | 15) a b c d |
| 4) a b c d | 10) a b c d | 16) a b c |
| 5) a b c d | 11) a b c d | 17) a b |
| 6) a b c | 12) a b c d | 18) _____ |



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November/December 2008

Pharmacological Management of Treatment-Resistant Depression

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