

**Release date: December, 2007**

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**Expiration Date: December, 2008**

*WELCOME to the AMA's quarterly online CME newsletter, *Therapeutic Insights*. This issue of the newsletter is intended for primary care physicians and those physicians who treat patients with depression. Upon completion of this activity, participants should be able to:*

- *Utilize assessment tools to assist in the diagnosis of depression and to monitor the effects of therapy.*
- *Apply the treatment information from the STAR\*D trial to patients diagnosed with depression.*

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*It is estimated that it will take approximately 1 hour to review this material and answer the self-assessment questions. Record your answers to the evaluation and self-assessment questions online or by completing the answer sheet at the end of this newsletter and faxing or mailing according to instructions.*

## Educational Need

Every year, 26.2% of Americans aged 18 or older meet criteria for a mental health disorder,<sup>1</sup> while about 9.5% or 21 million adults<sup>2</sup> suffer from a mood disorder. Major depression, the most common mood disorder, will affect approximately 1 in 6 Americans during their lifetimes. Female gender, young adulthood, living alone, and low socioeconomic status are among the greatest risk factors.<sup>3</sup> Additional risk factors include a family history of mental illness, history of abuse, alcohol or drug abuse, negative life events, and medical illness.

Depression is the leading cause of disability in the US in individuals aged 15 to 44<sup>4</sup> and is predicted to be the second leading cause of disability worldwide by 2020, after cardiovascular disease.<sup>5</sup> Despite an increase in public awareness over the last decade, depression remains untreated for nearly half of those afflicted and is inadequately treated in over half of those who do seek treatment.<sup>3,5</sup>

Depression often goes undetected in primary care,<sup>3</sup> particularly in those who are non-Caucasian, elderly and male,<sup>7</sup> or who have multiple medical problems.<sup>8,9</sup> Even when properly diagnosed, only 25% of

depressed patients receive proper treatment.<sup>3</sup> A recent analysis of a large geographically diverse integrated administrative claims database projected to the US population indicated that approximately 50% of patients diagnosed with depression filled a prescription medication for their condition (**Figure 1**). Somatization, stigma, medical comorbidities, competing demands for physician time, and poor insurance reimbursement are often cited reasons.<sup>10</sup>

## Introduction

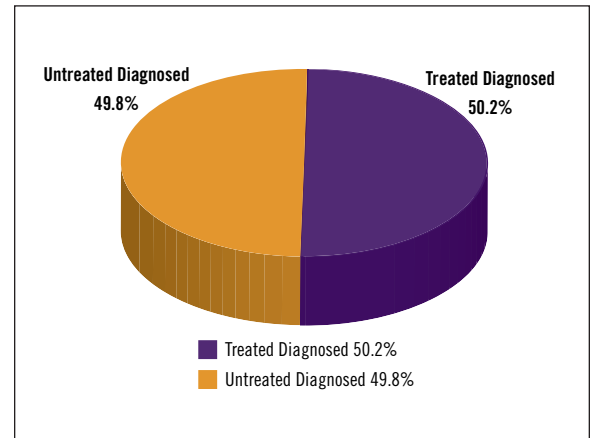
The majority of treatment for depression occurs in primary care, the “de facto” mental health care system in the US.<sup>11</sup> According to data recently analyzed by IMS Health, primary care physicians prescribe 62% of antidepressants, more than all other specialties (including psychiatry) combined (**Figure 2**).

Depression is even more prevalent in patients with medical illness,<sup>12</sup> including those with diabetes<sup>13</sup> and myocardial infarction.<sup>14</sup> Depression has been implicated as a risk factor for several medical disorders and is associated with poor outcomes in patients with diabetes, coronary artery disease, congestive heart failure, peripheral vascular disease, and stroke. Adverse outcomes in depressed patients are only partially explained by poor adherence to medications and lifestyle recommendations.<sup>15,16</sup> Other putative causes include dysregulation of the hypopituitary-adrenal axis, chronic inflammation, autonomic nervous system dysfunction, and alterations in platelet aggregation.<sup>17,18</sup> Data are emerging that suggest treatment of depression may substantially improve the outcomes of comorbid medical conditions.

The following case study is designed to update primary care physicians on approaches to the detection and management of major depressive disorder, and demonstrates the application of the recent findings of the National Institute of Mental Health (NIMH) funded Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) trial.

### Case Study

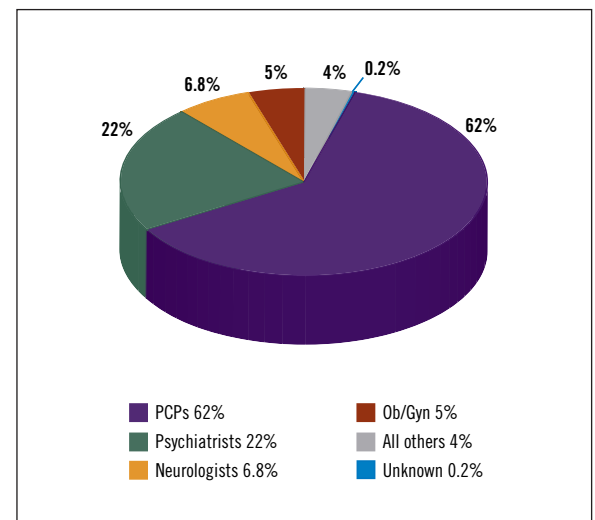
You are seeing Mr. Smith, a 67-year-old African American, for follow-up after a recent myocardial infarction. He complains of fatigue, headaches, and memory loss. He worries that he might have cancer. Past medical history includes hypertension and hyperlipidemia. Mr. Smith has been inconsistent in taking his medications, which include metoprolol 50 mg qd; lisinopril 40 mg qd; atorvastatin 20 mg qhs, and enteric coated aspirin, 81 mg qd. He is a former smoker and drinks one to two glasses of liquor daily. On examination, he has lost 10 lbs. since his last visit. Body mass index is 30.5. Blood pressure is 160/90. He has a flat affect. The remainder of his physical exam is unremarkable. You suspect Mr. Smith is depressed. What is your approach?



**Figure 1. Patients Diagnosed with Depression: Treated vs Untreated**

Source: IMS Health. Integrated Administrative Claims Data. Time period: 12 months ending December 2006.

Methods: The category of diagnosed/untreated is defined as patients with a diagnostic claim for depression between January 2005 and December 2006, who did not fill a prescription to treat their depression in the last 12 months of the study period. Treated and untreated refers to pharmacologic management and does not include psychotherapy or lifestyle and exercise recommendations.



**Figure 2. Treatment of Depression by Medical Specialty**

Source: IMS Health. Integrated Administrative Claims Data. Time period: 12 months ending December 2006.

Methods: Medical specialty treatment was derived by categorizing the top prescribing specialties based on the proportions of treated patients receiving agents with an FDA-approved label for depression.

## The Diagnostic Approach to Major Depressive Disorder

Over 50% of patients will present with somatic symptoms of depression, and while medical causes of depressive symptoms should be evaluated, delays in presumptive treatment should be avoided. Effective case-finding of depression can begin with two questions reflecting either mood disturbance or anhedonia:<sup>19</sup>

- (1) Over the past 2 weeks, have you felt down, depressed, or hopeless?
- (2) Over the past 2 weeks, have you felt little interest or pleasure in doing things?

If the patient responds “yes” to either question, further investigation is warranted. The DSM-IV criteria for major depression are listed in **Table 1**. The clinician might also choose one of the validated depression instruments to help diagnose, and even more importantly, monitor treatment. Examples of brief patient-administered questionnaires include the Beck Depression Inventory (BDI), the Zung Self-Assessment Depression Scale, the Geriatric Depression Scale (GDS), the Center for Epidemiologic Study Depression Scale (CES-D), and the Patient Health Questionnaire (PHQ-9). While all of these questionnaires are valid instruments, for the purposes of this case study, we will make use of the PHQ-9 (**Figure 3**). While patients should not be diagnosed solely on the basis of a PHQ-9 score, this instrument can help systematically assess the cardinal symptoms of depression, allow an assessment of severity, and provide a tool for monitoring treatment (**Table 2**).

When considering the diagnosis of depression, the clinician must evaluate for suicidal ideation, a history of mania or hypomania, alcohol or drug abuse, psychotic symptoms and psychiatric comorbidities. The presence of any of these phenomena increases the risk of suicide and will determine a different course of treatment.

Suicidal ideation is a vital component of the assessment process; almost two-thirds of suicide victims have visited a health care provider in the four weeks prior to suicide.<sup>20</sup> Risk factors for suicide include the elderly, the unemployed, patients who live alone, those with legal or financial difficulties and individuals with terminal disease.

Helpful questions when assessing for suicide include:

- (1) Have you been so depressed that you’ve felt life is not worth living? Have you thoughts of harming yourself?
- (2) Have you thought about how you might take your own life?
- (3) Have you ever done anything to hurt yourself or come close to it?
- (4) What stops you from killing yourself?

Passive suicidal ideation (eg, “I wouldn’t mind if a truck ran over me”) should not, by itself, be alarming. Of greater concern is the patient who has thoughts of a specific method, particularly when means are readily available (eg, overdosing on insulin, shooting oneself with a firearm). Those with a prior suicide attempt or a family history of suicide are at high risk. The patient’s religious beliefs, reluctance to hurt family, and plans for the future can be reassuring.

**Table 1. DSM-IV Diagnostic Criteria for Major Depressive Episode**

**At least five of the following symptoms must be present most of the day, nearly every day, for at least two weeks. At least one of the first two bold symptoms must be present.**

- 1. Depressed mood**
- 2. Markedly diminished interest in usual activities**
3. Significant increase/loss of appetite/weight
4. Insomnia/hypersomnia
5. Psychomotor agitation/retardation
6. Fatigue or loss of energy
7. Feelings of worthlessness or guilt
8. Difficulty with thinking, concentrating or making decisions
9. Recurrent thoughts of death or suicide

Source: American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Washington, DC: American Psychiatric Association; 1994.

Patient Health Questionnaire — PHQ-9  
Nine Symptom Depression Checklist

Patient Name: \_\_\_\_\_ Date: \_\_\_\_\_

1. Over the *last 2 weeks*, how often have you been bothered by any of the following problems?

	Not at all	Several days	More than half the days	Nearly every day
	0	1	2	3
a. Little interest or pleasure in doing things	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b. Feeling down, depressed, or hopeless	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c. Trouble falling/staying asleep, sleeping too much	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
d. Feeling tired or having little energy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
e. Poor appetite or overeating	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
f. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
g. Trouble concentrating on things, such as reading the newspaper or watching television	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
h. Moving or speaking so slowly that other people could have noticed. Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
i. Thoughts that you would be better off dead or of hurting yourself in some way	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

2. If you checked off *any* problem on this questionnaire so far, how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all       Somewhat Difficult       Very Difficult       Extremely Difficult

Total # Symptoms: \_\_\_\_\_

Total Score: \_\_\_\_\_

This questionnaire may be photocopied for use in clinical practice.  
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Figure 3: Patient Health Questionnaire—PHQ-9

Using PHQ-9 for Diagnostic Assessment

Of the 9 items in question 1, include only those that are checked *at least* “More than half the days”, *except count the suicide item if present “at all.”*

At least one of item 1a or item 1b must be endorsed as more than half the days for a depression diagnosis. Also, question 2 for functional impairment must be answered *at least* “Somewhat difficult.”

Using PHQ-9 for Severity of Depression Measure

Of the 9 items in question 1, also include items checked “Several days.” Count one point for each item checked several days, two points for checked items more than half the days, three points for items checked nearly every day, and sum the total for a severity score.

**Table 2. Diagnostic Categories for Depression**

PHQ-9 Symptoms & Impairment	PHQ-9 Severity	Provisional Diagnosis	Treatment Recommendations**
1 to 4 symptoms, functional impairment	<10	Mild or Minimal Depressive Symptoms	- Reassurance and/or supportive counseling - Education to call if deteriorates
2 to 4 symptoms, question a or b +, functional impairment	10-14	Moderate Depressive Symptoms (Minor Depression)*	- Watchful waiting - Supportive counseling - If no improvement after one or more months, consider use of antidepressant or brief psychological counseling
≥5 symptoms, question a or b +, functional impairment	15-19	Moderately Severe Major Depression	- Patient preference for antidepressant and/or psychological counseling
≥5 symptoms, question a or b +, functional impairment	>20	Severe Major Depression	- Antidepressants alone or in combination with psychological counseling

\* If symptoms present for > 2 years, Chronic Depression, or functional impairment is severe, remission with watchful waiting is unlikely, immediate active treatment indicated for moderate depressive symptoms (minor depression).

\*\* Referral or co-management with mental health specialty clinician if patient is a high suicide risk or has bipolar disorder, an inadequate treatment response, or complex psychosocial needs and/or other active mental disorders.

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All patients with depressive symptoms should be screened for bipolar disorder (BPD). A national survey of 100,000 households detected a point prevalence for BPD of 3.4%, of which one-third had been misdiagnosed as having unipolar depression.<sup>21</sup> BPD represents the highest risk for suicide among psychiatric disorders. Incorrect diagnosis may lead to prescription of antidepressants, with attendant risks of nonresponse, relapse, mania, or rapid cycling.<sup>22</sup> Clinicians can screen for BPD using the mnemonic DIGFAST,<sup>23</sup> the self-administered Mood Disorders Questionnaire,<sup>24</sup> or by asking the following two questions:

- (1) Do you have days when you feel so good that you don't really need much sleep?
- (2) On your good days, do you have so much energy that people tell you to calm down?

Alcohol abuse may also be a consideration in this patient, as Mr. Smith could be minimizing his alcohol use. Screening for an alcohol use disorder can be accomplished by using the CAGE questions:<sup>25</sup>

- (1) Have you ever felt you ought to **C**ut down on your drinking?
- (2) Have people **A**nnoyed you by criticizing your drinking?
- (3) Have you ever felt bad or **G**uilty about your drinking?
- (4) Have you ever had an **E**ye-opener to steady nerves in the morning?

### Assessment of Patients for Bipolar Disorder: "DIGFAST" Mnemonic<sup>23</sup>

Are there periods of time when you experience:

- **D**istractibility—Poorly focused, multi-tasking
- **I**nsomnia—Decreased need for sleep
- **G**randiosity—Inflated self-esteem
- **F**light of Ideas—Complaints of racing thoughts
- **A**ctivities—Increased goal-directed activities
- **S**peech—Pressured or more talkative
- **T**houghtlessness—"Risk-taking" behaviors
  - Sexual, financial, travel, driving

A further diagnostic consideration is whether Mr. Smith is suffering from somatic delusions. He worries he may have cancer. The clinician can distinguish between a fear and a delusion by asking if cancer is a worry or a conviction.

Other questions to screen for psychosis include:

- (1) Does your mind ever play tricks on you; for example, have you heard voices when no one is around?
- (2) Do you feel that you are in any kind of danger?

Anxiety accompanies depression in up to 60% of cases.<sup>3</sup> Depressed patients with comorbid anxiety are more likely to abuse substances<sup>26</sup> and may have a higher risk of suicide attempt when compared to those with either disorder alone.<sup>27</sup> Two questions have a high sensitivity in the detection of anxiety disorders in primary care:<sup>28</sup> Over the last two weeks, how often have you been bothered by:

- (1) Feeling nervous, anxious or on edge?
- (2) Not being able to stop or control worrying?

*Mr. Smith relates the onset of his symptoms to his recent MI, which his wife corroborates. He is worried about his health and afraid of dying. A thorough medical evaluation reveals no cause for alarm. He scores 19 on the PHQ-9 (moderately severe depression). He readily admits he is depressed but doesn't endorse any symptoms suggestive of bipolar disorder, psychosis, or excessive drug or alcohol use. He is not suicidal. What treatment do you offer Mr. Smith?*

### Treatment of Depression

Evidence-based treatments for depression include nonpharmacologic interventions such as exercise, psychotherapy and support groups, and pharmacologic interventions. Aerobic exercise has intrinsic antidepressant effects<sup>29</sup>; two studies have shown efficacy equal to that of the antidepressant sertraline.<sup>30,31</sup> Depressed patients should be encouraged to participate in at least three 45-minute sessions of aerobic exercise per week. While many types of psychotherapy are practiced, problem-focused,<sup>32</sup> cognitive-behavioral,<sup>33</sup> and interpersonal therapies<sup>34</sup> have the most evidence of efficacy. Indeed, psychotherapy alone (without medication) is an appropriate option for patients with mild to moderate symptoms, an adjustment disorder, or “minor depression.”<sup>35</sup>

*You discuss the options of exercise, counseling, and medication with Mr. Smith. He says he is faithfully—with the encouragement of his wife—attending cardiac rehabilitation. Mrs. Smith wants to know which options are most effective and wonders if her husband might be more willing to take a medication rather than “endure” counseling (to which Mr. Smith readily assents).*

Mr. Smith's score of 19 on the PHQ-9 is consistent with a moderately severe depression. Antidepressant medication, with or without psychotherapy, should be recommended. Given Mr. Smith's preference for medication, you share that while there are currently numerous medications with FDA-approved labeling for depression in the US, the general consensus is that they are equally effective, regardless of mechanism of action.<sup>35</sup> The decision to use one drug over another should be based on:

- Personal or family history of response to a specific agent
- The drug's side effect profile
- Efficacy and safety in treating medical or psychiatric comorbidities
- Drug-drug interactions
- Cost
- Patient preference

For Mr. Smith, an antidepressant that is safe with comorbid cardiovascular disease, possesses few drug-drug reactions, and is unlikely to cause substantial weight gain would be preferable. The Smiths also want you to choose a first-tier medication from their health plan.

## Therapeutic Insights • Management of Major Depressive Disorder in Primary Care

Common medications used for depression are summarized in **Table 3**. Selective serotonin reuptake inhibitors (SSRIs) are the most common class of antidepressants prescribed (**Figures 4a & 4b**). Many SSRIs are also FDA-approved for anxiety disorders, making them “broad spectrum” agents. Common side effects may be remembered by the mnemonic SSRI (**S**tomach upset, **S**exual side effects, **R**estlessness (akathisia), **I**nsomnia or hypersomnolence). Some side effects (GI distress and akathisia) can be minimized by starting at a low dose and slowly titrating the dose upward. Nausea may be less common with controlled-release preparations (eg, paroxetine CR).

**Table 3. Overview of Commonly Used Antidepressants**

Antidepressant*	Starting Dose (mg/d)	Therapeutic Dose Range (mg/d)	Maximum Dose* (mg/d)	Comments
<b>Serotonin Reuptake Inhibitors (SSRIs)</b>				
<b>Citalopram</b>	10	20-60	60	Few drug interactions
<b>Escitalopram</b>	5	10-20	20	Few drug interactions; also has FDA-approved indication for GAD.
<b>Fluoxetine</b>	10	20-60	80	Long-acting metabolite (half-life up to 2 weeks); drug-drug interactions; also FDA-approved indication for PMDD, panic disorder, OCD and bulimia. Once-weekly formulation available.
<b>Paroxetine</b>	10	20-50	60	High discontinuation syndrome; 2D6 inhibition; weight gain; anticholinergic side effects. Congenital atrial septal defects in the first trimester exposure. Also has FDA-approved indication for PMDD, panic disorder, PTSD, GAD, and OCD.
<b>Paroxetine CR</b>	12.5	25-62.5	75	
<b>Sertraline</b>	25	50-200	200	Few drug interactions; also has FDA-approved indication for PMDD, panic disorder, OCD and social phobia.
<b>Other Antidepressants</b>				
<b>Venlafaxine IR</b>	25	50-200	375	High-risk discontinuation syndrome; monitor blood pressure. May be more dangerous in overdose than SSRIs. Also has FDA-approved indication for GAD, panic disorder and social phobia; effective for hot flashes.
<b>Venlafaxine XR (SNRI)</b>	37.5	75-225	225	
<b>Duloxetine (SNRI)</b>	20	40-60	120	Potent 2D6 inhibitor; monitor blood pressure; hepatotoxicity in patients with pre-existing liver disease. FDA-approved indication for GAD and neuropathic pain. Effective for stress incontinence.
<b>Mirtazapine</b> ( $\alpha_2$ -adrenergic blocker with 5-HT <sub>2A</sub> and 5-HT <sub>3</sub> inhibition)	7.5	15-45	45	Weight gain and sedation. Rare neutropenia. Few drug interactions. Low risk of sexual side effects. Commonly used to augment other antidepressants.

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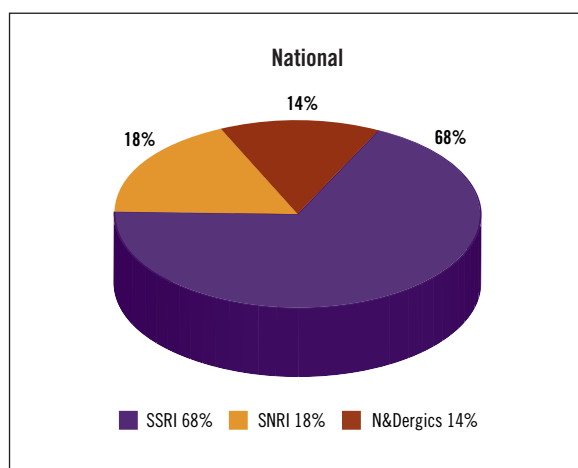
**Table 3. Overview of Commonly Used Antidepressants (continued)**

Antidepressant*	Starting Dose (mg/d)	Therapeutic Dose Range (mg/d)	Maximum Dose* (mg/d)	Comments
<b>Other Antidepressants (continued)</b>				
<b>Bupropion IR</b>	75	225-300	300	Seizure precautions; may cause agitation.
<b>Bupropion SR</b>	100	200-400	400	Ineffective for anxiety disorders. Immediate and sustained-release formulations must be given in divided doses. Also has FDA-approved indication for nicotine dependence; effective in adult ADHD. Low risk of sexual side effects or weight gain. No discontinuation syndrome; common augmentation agent.
<b>Bupropion XL (DNRI)</b>	150	300-450	450	
<b>Nefazodone (SSRI with 5-HT<sub>2A</sub> inhibition)</b>	150	300-600	600	Potent 3A4 inhibitor; sedation; hepatotoxicity. Sedation may help with insomnia (dosed at night). Low risk of sexual side effects or weight gain.
<b>Selegiline Transdermal (MAO inhibitor)</b>	6 mg/24 hr patch	6-12 mg/24 hr patch	12 mg/24 hr patch	Hypertensive crises; serotonin syndrome may occur with contraindicated drugs at any dose of selegiline. Must wait 2 weeks (5 weeks with fluoxetine) after discontinuation of other antidepressants before initiating selegiline. Dietary restrictions at 9 and 12 mg/24 hr dose. Skin irritation at the application site.

OCD=obsessive compulsive disorder PTSD=post-traumatic stress disorder GAD=generalized anxiety disorder PMDD=premenstrual depressive disorder ADHD=attention deficit hyperactivity disorder

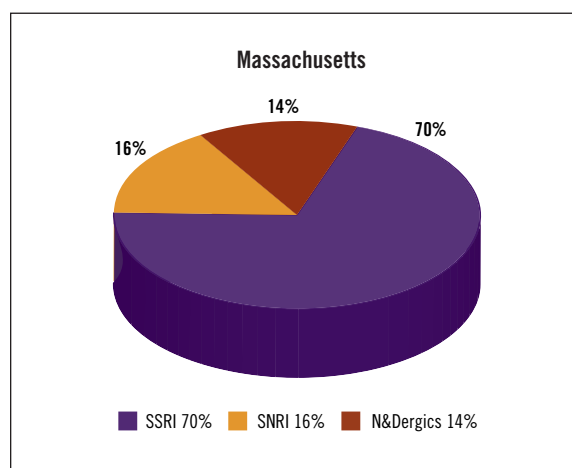
SNRI=serotonin norepinephrine reuptake inhibitor DNRI=dopamine norepinephrine reuptake inhibitor 5HT=serotonin.

\*Maximum doses for any indication. (Source: *Physicians' Desk Reference (PDR)*. 61st ed. Montvale, NJ:Thomson PDR;2007) Lower starting doses may be necessary in the elderly, those with renal or hepatic insufficiency, or slow 2D6 metabolizers. Higher doses may be needed in some patients, particularly those with OCD, refractory symptoms, or ultra-rapid 2D6 metabolizers.



**Figure 4a: Proportion of Prescriptions Dispensed at Retail Pharmacies Nationally. N&Dergics (NDRIs) include bupropion.**

Source: IMS Health. National Retail Prescription Data. Time period: 12 months ending June 2007.



**Figure 4b: Proportion of Prescriptions Dispensed at Retail Pharmacies in the state of Massachusetts. N&Dergics (NDRIs) include bupropion.**

Source: IMS Health. National Retail Prescription Data. Time period: 12 months ending June 2007.

Sleep disturbance can be managed by adjusting the time of day in which the medication is administered or by adding a hypnotic. Paroxetine tends to be the most sedating of SSRIs and should be dosed initially at night. While SSRIs' effect on weight is variable, a prospective randomized study of 3 SSRIs found that 25% of patients taking paroxetine gained more than 7% of initial body weight after 6 months.<sup>36</sup> Serious medical complications that can occur with SSRIs include the serotonin syndrome, gastrointestinal bleeding (particularly when combined with NSAIDs), and the syndrome of inappropriate antidiuretic hormone secretion.<sup>37</sup> Congenital abnormalities and neonatal complications have been found in babies exposed to SSRIs in utero.<sup>38</sup> SSRIs have also been linked to osteoporosis and an increased risk of fracture.<sup>39</sup>

SSRIs with short half-lives, such as paroxetine, may be more likely to cause a discontinuation syndrome (a flu-like illness that can be accompanied by emotional volatility and vague neurologic complaints), while long half-life drugs (such as fluoxetine) may enhance adherence, but be a problem if side effects are encountered.

SSRIs are metabolized by the cytochrome P450 system in the liver, and may inhibit the metabolism of other drugs through the same system. Sertraline, citalopram, and escitalopram have the fewest drug-drug interactions among SSRIs. Large randomized controlled trials have demonstrated efficacy and safety for both sertraline<sup>40</sup> and citalopram<sup>41</sup> in cardiac patients, and either would be acceptable first-line choices for this patient.

Bupropion, a dopamine-norepinephrine reuptake inhibitor, has a low risk of weight gain, sexual dysfunction, or hypersomnolence. Side effects include dry mouth, agitation and insomnia, minor increase in blood pressure, and rare drug-drug interactions. Bupropion is associated with a dose-dependent risk of seizures and is contraindicated in patients at risk. This includes patients with an eating disorder, or history of CNS disease (including seizures) and those who abuse alcohol or other sedatives. It has demonstrable safety in cardiac patients and would be another reasonable option for treating Mr. Smith.

Serotonin-norepinephrine reuptake inhibitors (SNRIs) include venlafaxine and duloxetine. At low doses, venlafaxine acts as a serotonin reuptake inhibitor; at higher doses (*ie*, greater than 225 mg), it blocks reuptake of norepinephrine and is associated with a dose-dependent increase in diastolic blood pressure.<sup>42</sup> Venlafaxine has a short half-life and may be more dangerous in overdose,<sup>43,44</sup> particularly when coingested with alcohol or other sedatives. Duloxetine is another SNRI that is also associated with mild increases in pulse and blood pressure<sup>45,46</sup> and, may inhibit the metabolism of beta-blockers. Thus, the SNRIs are probably not the best choice for Mr. Smith.

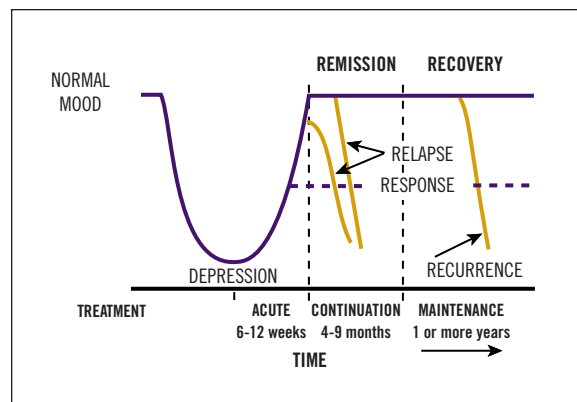
Mirtazapine blocks alpha 2 adrenergic auto- and heteroreceptors, leading to increases in noradrenergic and serotonergic transmission. Data support its efficacy in anxiety disorders. It is well tolerated by the elderly, and is safe in patients with heart disease.<sup>47</sup> Displacement of clonidine from alpha 2 receptors has been associated with rebound hypertension in at least two cases.<sup>48,49</sup> Mirtazapine blocks serotonin receptors 2A and 3, conferring a low incidence of sexual and gastrointestinal side effects, respectively; however, its antihistaminic properties often lead to sedation and significant weight gain (*ie*, 20%), which is undesirable for Mr. Smith.

*You discuss the pros and cons of each medication and offer Mr. Smith treatment with generic citalopram beginning at 10 mg, which is first tier with his managed care insurer. He is advised to increase citalopram in one week, to 20 mg, if tolerated. How do you follow Mr. Smith?*

Depression care is conceptualized in three stages: acute, continuation, and maintenance (**Figure 5**). In the acute stage, the goal of therapy is remission, or abolition of depressive symptoms. An effective way to gauge the effects of treatment, including initial response, is to do a baseline PHQ and follow-up ratings.<sup>50</sup> A 50% reduction of PHQ-9 score corresponds to a response, while a score below 5 indicates remission. An alternative is to use an analog scale. The patient is asked to rate his mood from 1 to 10, where 1 is severely depressed and 10 represents “the best you’ve ever felt.” An increase of 3 or more points represents response, and a score of 8 or above indicates remission.

After remission is achieved, continuation of medication is recommended for an additional 6 to 12 months.<sup>35</sup> Maintenance treatment is advised for patients with severe, difficult to treat, or recurrent depression. A recent four-phase trial, the STAR\*D, offers important insights into the follow-up and treatment of major depressive disorder.

The STAR\*D trial enrolled patients with recurrent and moderately severe depression (probably more seriously depressed patients than encountered in typical primary care settings). Over 4000 patients were enrolled and started on flexibly dosed citalopram (chosen for its presumed safety and tolerability), starting at 20 mg/d. Dosage was gradually titrated to a maximum of 60 mg/d. Patients were monitored and assessed quite carefully, but otherwise the study was developed to mirror the typical conditions of practice. Patients who had not tolerated citalopram or were not in remission could choose one or more options from four treatment arms: a *switch medication strategy* (change to a new medication), an *augmentation medication strategy* (add an additional medication), a *switch strategy that included medication or cognitive therapy*, or an *augmentation strategy that included medication or cognitive behavioral therapy* (**Table 4**). As in the real world, people were given choices about acceptable treatment options; for example, a patient who deemed psychotherapy unacceptable would be randomized to treatment arms that included only medication. A patient who had achieved partial response to citalopram might choose to be randomized only to an augmentation strategy that included either medication or psychotherapy. As might be expected, only 21 participants (out of 1439 entering phase 2) were agreeable to *any* phase 2 treatment. By giving patients choices STAR\*D was designed to mirror real world practice and the preferences of patients.



**Figure 5: Stages and Outcomes of Antidepressant Therapy**

Adapted from Stahl SM. *Essential Psychopharmacology of Depression and Bipolar Disorder*. New York. Cambridge University Press, 2001.

**Table 4: STAR\*D Treatment Levels**

**Level 1** All patients treated with the SSRI citalopram

**Level 2** Patients randomized to one of the following arms:\*

- Switch from citalopram to another antidepressant (sertraline, venlafaxine XR, or bupropion CR)
- Switch from citalopram to cognitive therapy
- Augmentation of citalopram with a second medication (bupropion SR or buspirone)
- Augmentation of citalopram with cognitive therapy

**Level 3** Patients randomized to one of the following arms:\*

- Switch from previous medication(s) to another antidepressant (mirtazapine or nortriptyline)
- Augmentation from previous medication(s) with another medication (lithium or T<sub>3</sub> thyroid hormone)

**Level 4** Patients randomized to one of the following:\*

- Switch from previous medication(s) to tranylcypromine
- Switch from previous medication(s) to combination of mirtazapine and venlafaxine XR

\*Equipose stratified randomization allowed patients to select out treatment arms but not individual medications

STAR\*D=Sequenced Treatment Alternatives to Relieve Depression; SSRI=Selective Serotonin Reuptake Inhibitor; XR=extended release; SR=sustained release; T<sub>3</sub>=triiodothyronine  
Reprinted with permission from Ziffra MS, Gilmer WS. STAR\*D: Lessons Learned for Primary Care. *Primary Psych*. 2007;14:51-58.

Those who could not tolerate phase 2 treatment, or remained symptomatic, entered into the next phase of the study. Phase 3 involved a choice between a second *medication switch* or another *augmentation strategy*. Again, patients could choose which strategy but were randomized to individual medications. The final phase was entered by those unable to tolerate or who were refractory to phase 3 treatment. In phase 4, patients were randomized to monotherapy with tranylcypromine (an MAO inhibitor) or to a combination of venlafaxine plus mirtazapine.

So what were the results of STAR\*D? In phase 1 of the STAR\*D trial,<sup>51</sup> patients received flexible doses of citalopram, 20 to 60 mg adjusted at 2 to 3 week intervals, for up to 14 weeks. Response, defined as a 50% reduction in depression scores, occurred in 49% of patients, while remission (becoming symptom free) was achieved in only 37% of patients. It took an average of six weeks of treatment for patients to respond and nearly seven weeks to achieve a remission. More than half of those who responded did so after six weeks. Participants were more likely to achieve remission if they were Caucasian, female, of higher socioeconomic status, married or living with someone, had mild to moderate depressive symptoms, few comorbidities, and a brief episode of depression. Age was not an independent predictor of remission.<sup>51</sup> The implication for our patient: it will take up to 6-8 weeks for a less than 50% chance of response and a less than one-third chance of remission. A family history of response to antidepressant therapy confers an additional prognostic indicator.<sup>52-54</sup>

In Phase 2 of the STAR\*D trial, cognitive therapy was as effective as switching to a second medication in achieving remission.<sup>55</sup> Though cognitive behavioral therapy is effective in the elderly,<sup>56</sup> recent studies suggest that pharmacotherapy is more effective than counseling in maintaining remission in this population.<sup>57,58</sup>

Monitoring the patient, particularly early in the course of therapy, is important. In May 2007, on the basis of an analysis of nearly 400 trials covering 100,000 adults, the black box warning (previously limited to children and adolescents) was expanded to include an increased suicide risk for young adults aged 18 to 24. The revised label acknowledged no increase of risk in individuals ages 25 to 64 and a decreased risk of suicidal behavior in individuals over the age of 65. While epidemiologic data suggest a decreased risk of suicide associated with the use of antidepressants,<sup>59</sup> the risk of suicide attempt is probably highest one month before and one month after the initiation of treatment.<sup>60,61</sup> In addition, the risk of mania appears to emerge early after the initiation of therapy. Thus, follow-up by phone or in the office is prudent within the first few weeks of antidepressant treatment.

*You advise the patient: “Although this medication is designed to help you feel better, in very rare circumstances it can lead to thoughts of hurting oneself or can give people too much energy. Please contact me if you find you have thoughts of harming yourself or you have racing thoughts and increased difficulty sleeping.”*

*You call Mr. Smith after one week, and while he doesn’t note any side effects, he sees no change in his depression. You encourage him to increase the dose of citalopram to 20 mg. After 4 weeks, Mr. Smith returns and notes some improvement, but continues to suffer from residual depressive symptoms, including fatigue and anhedonia. His PHQ-9 score is 12. You elect to increase his citalopram to 40 mg. After another two weeks his PHQ score is 9, and he has residual symptoms. What do you recommend?*

The goal for our patient is the elimination of depressive symptoms, corresponding to a PHQ-9 score of less than 5. Mr. Smith’s PHQ-9 score has dropped from 19 to 9, indicating response but not remission. Premature discontinuation will lead both clinician and patient to conclude that a potentially helpful medication is ineffective. Lack of response or remission should prompt exploring the four “Ds” (drug, dosage, duration, diagnosis):

- **Is the patient taking the drug as prescribed?**

In the “real-world” experience of the STAR\*D trial, 26% of patients dropped out of the study in the first three months. Younger age, lower levels of education, African American race, and first episode of depression predicted dropouts.<sup>62</sup> In a large geographically diverse integrated administrative claims database, projected to the US population, less than half of patients were taking their medication after 6 months (Figure 6) and only 21% of patients filled their prescriptions for a full year. The proportion of patients persistent at 1 year was higher than among those greater than and equal to 45 years of age. Similarly, there was a slight increase in persistence among those with at least 1 comorbidity. Phone calls, frequent visits, and patient education have been shown to enhance patient compliance.

- **Has the dosage been adequate?**

The patient should be titrated to the maximum dose tolerable. The rate of increase will depend upon the patient’s age, medical comorbidities, side effects, and prior history of response. In general, dosage increases should be slower in the elderly or those with hepatic and renal disease.

- **Has the patient taken the medication for a proper duration?**

Fifty-four percent of patients in the STAR\*D trial required more than 6 weeks to achieve a response, and one-third of remitters took 10 weeks or more to achieve remission.<sup>51</sup>

- **Is the diagnosis correct?**

Commonly missed diagnoses that predict poor antidepressant response include bipolar disorder, alcohol or substance abuse, personality disorders, psychotic depression, iatrogenic symptoms, and sleep disorder.

Mr. Smith has shown an initial response to treatment, but still has significant residual symptoms. The clinician has three choices: increase the dose of citalopram, augment with a second agent, or switch to another antidepressant. Increasing the dose may exacerbate side effects or require the addition of another medication to treat side effects. Augmentation increases out-of-pocket costs, increases risk of drug-drug interactions, and may reduce compliance. Switching antidepressants risks forfeiting the response obtained with the original medication.

In the second phase of the STAR\*D trial, 727 patients who had side effects or had not remitted after 14 weeks of treatment with an SSRI (citalopram, max dose 60 mg/d) were randomly switched to either sustained-release bupropion (max 400 mg/d), a second SSRI (sertraline, max 200 mg/d), or extended-release venlafaxine (max 375 mg/d). Regardless of assignment, about one-fourth of the participants achieved remission and another quarter had a response.<sup>63</sup> There were no significant differences in time to achieve remission (median 4 to 6 weeks) or tolerability between the three groups. Switching to another SSRI was equally effective and as well tolerated as switching to a drug from a different class. Another set of 565 adults agreed to have their SSRI augmented randomly with sustained-release bupropion (max 400 mg/d)

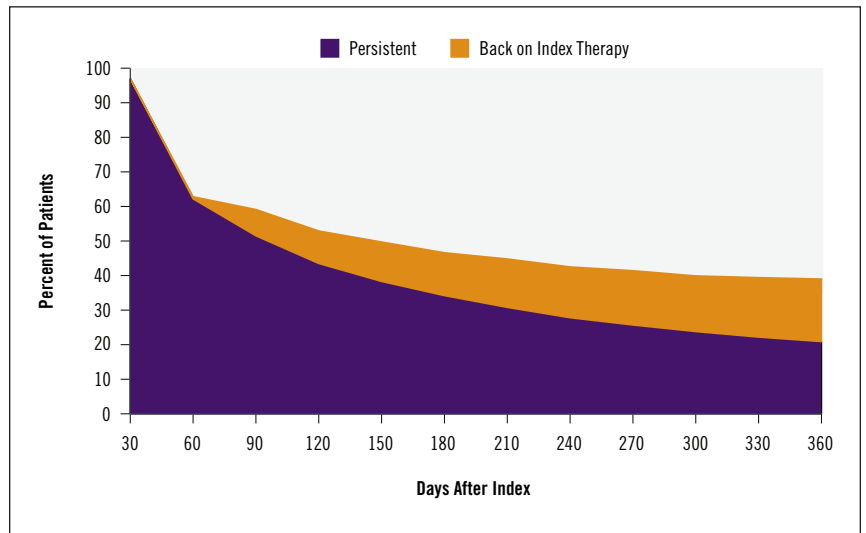


Figure 6. Persistence and Back On Therapy Percentage by Treatment Duration

Source: IMS Health. Integrated Administrative Claims Data. Time period: 12 months ending December 2006.

**Methods**

- **Persistent:** A measure referring to how long a new patient remains on therapy. Persistence was calculated by dividing the number of new patients remaining on therapy (drug class) by the total patient population new to therapy during the timeframe of this analysis.
- **Back on Therapy:** This metric reflects the number of patients with a gap in treatment history (patients starting a treatment, stopping the treatment and returning to treatment within a specified drug class).
- **Index:** Index refers to the time drug therapy was initiated with the prescribed drug class.

or buspirone (max 60 mg/d). In the augmentation group, 35% of the patients became symptom free.<sup>64</sup> Bupropion was slightly more effective and slightly better tolerated than buspirone. A much smaller third group of patients in phase 2 of STAR\*D agreed to be randomized to a strategy that included psychotherapy. One hundred eighty-two participants were randomly switched from citalopram to an alternate medication or cognitive therapy (CT); 122 patients agreed to be randomized to augmentation with medication or CT. Switching or augmenting with CT resulted in outcomes equivalent to switching or augmenting with medication; augmentation with medication achieved remission faster than augmentation with CT (median difference of 20 days), whereas switching to CT was better tolerated than switching to a second medication.<sup>55</sup>

In a recent meta-analysis of four trials involving 1496 subjects who had not responded to an SSRI, patients randomly switched to a non-SSRI antidepressant (bupropion, mirtazapine, or venlafaxine) were equally likely to respond, but slightly more likely to remit, than patients switched to a second SSRI. Pooled remission rates were comparable to those found in the second phase of STAR\*D: 28% for non-SSRIs and 23.5% for SSRIs.<sup>65</sup> Whether this difference is clinically significant remains debatable.

*Mr. Smith is offered either an increase in medication, a switch, or an augmentation strategy. He prefers to see if augmentation will work. You elect to start bupropion XL, 150 mg/d. You discuss potential side effects, including agitation, dry mouth, insomnia, and a 0.1% risk of seizure.*

Bupropion is a reasonable choice for augmentation in this patient, given its salutary effects on weight, safety in cardiac disease, and few drug/drug interactions. Despite its lack of indication for anxiety disorders, bupropion can be effective in reducing anxiety in depressed patients with subsyndromal anxiety.

*Over the next three weeks you speak with Mr. Smith several times, and while he initially tolerated the addition of bupropion, his self-scored PHQ has started to increase from 9 to 13. An increase to 300 mg of bupropion was not tolerated. Likewise, an increase of citalopram to 60 mg was limited by nausea. What do you try next?*

In the third phase of the STAR\*D trial, 142 patients who had failed to achieve remission after two antidepressants were randomized to receive augmentation with either lithium or triiodothyronine ( $T_3$ ). After 14 weeks of treatment, remission rates with lithium (max dose, 900 mg) and  $T_3$  (max dose, 50 mcg) were 15% and 26%, respectively. Average time to achieve remission was approximately 7 weeks. No statistically significant differences were found between the two groups in efficacy; however,  $T_3$  was better tolerated.<sup>66</sup> Another 235 patients who entered phase 3 were randomized to switch to nortriptyline or mirtazapine. Twelve percent of patients assigned to nortriptyline and 8% of those assigned to mirtazapine achieved remission; there were no significant differences between response, remission, or side effects. The mean time to remission was about 6 weeks. Finally, 109 patients who did not remit during the first three phases entered the fourth phase. In phase 4, patients were randomized to receive either the MAO-I tranylcypromine (max dose, 60 mg) or mirtazapine (max dose, 45 mg) plus venlafaxine (max dose, 300 mg) for 12 weeks. Remission rates were 14% and 16%, respectively, after a mean of about 8 weeks. There were no significant differences between groups in response or remission rates; however, more patients discontinued tranylcypromine due to side effects than did patients assigned to mirtazapine plus venlafaxine.<sup>67</sup>

While the design of STAR\*D does not allow comparison among the switch and augmentation groups, one trend is clear. Patients who advanced through the four phases of treatment had a lower rate of response or remission with each successive trial of treatment. The response rates were 49%, 29%, 17%, and 16%, for the first, second, third, and fourth phases, respectively, and the remission rates were 37%, 31%, 14%, and 13%. The cumulative remission rate was 67%. Remission rates using the standardized step care approach of STAR\*D were equivalent in primary care and mental health settings.<sup>68</sup>

*Given these data, you elect to switch citalopram to sertraline. Bupropion is discontinued. Sertraline is initiated at 50 mg and increased to 100 mg after 4 weeks. In follow-up, Mr. Smith's PHQ-9 score is 5 and he and his wife are grateful. How long should the patient remain on antidepressants? What is the risk of relapse?*

Current guidelines recommend continuing antidepressant therapy for 6-12 months following remission from a single major depressive episode. For those who have had two or more depressive episodes, the risk of relapse is over 70%, sufficiently high to warrant indefinite treatment. In the STAR\*D trial, patients were encouraged to continue their medications at the previously effective dose, and were followed for 12 months. Relapse rates ranged from 33% in the phase 1 remitters to 50% in the phase 4 remitters. Patients who had improved but not remitted (responders) and those who entered more phases of treatment (ie, were more treatment refractory) had higher rates of relapse. The mean time to relapse for those who did relapse was shorter for those who required two or more steps<sup>68</sup> compared with those who went into remission in phase 1. Thus, while Mr. Smith has a better than 50% chance to remain symptom free in the ensuing 12 months, close follow-ups are recommended. Both patient and physician must consider the risks and benefits of continuing medication beyond the first year.

*You see Mr. Smith in follow-up one month after remission and he continues to do well. You follow up for his routine care every three months. At one-year follow-up, Mr. Smith continues to be depression free and wants to go off his medication. What do you counsel?*

When a decision is made to stop a serotonergic antidepressant, care must be taken to avoid the SSRI discontinuation syndrome. More common with agents that have short half-lives (eg, paroxetine or venlafaxine), the severity of symptoms range from mild nuisance to extremely disabling. Patients report flu-like symptoms, emotional lability, and neurologic complaints such as blurred vision, shock-like sensations, paresthesias, and vertigo.<sup>69</sup> The incidence of discontinuation syndrome is over 20% in some studies.<sup>70,71</sup> In the STAR\*D trial, citalopram was discontinued without washout when patients were switched to a second drug. The investigators noted that all three replacement drugs—bupropion, venlafaxine and sertraline—had equal tolerability, but discontinuation symptoms were not reported. When present, discontinuation symptoms begin within the first few days of drug cessation, persist up to three weeks after discontinuation, and resolve within 24 hours of resuming the precipitating agent.<sup>69</sup> There is little risk of discontinuation syndrome when switching between one SSRI/SNRI and another. Doses of the second SSRI/SNRI may be initiated at a level comparable to the dosage of the discontinued agent. An exception is when switching from fluoxetine to another serotonergic agent. A 2D6 inhibitor with a long half-life, fluoxetine may raise blood levels of the substituted drug. On the other hand, when an SSRI/SNRI is discontinued, it is recommended to taper the SSRI/SNRI over several weeks. If a faster taper is required or the taper is poorly tolerated, a five-day supply of fluoxetine can be prescribed. Instructions are given for the patient to take fluoxetine, 10 mg, as needed for discontinuation symptoms. Its long half-life makes discontinuation symptoms unlikely.

*Mr. Smith returns one month after discontinuing sertraline. While initially he felt a bit achy and was concerned his depression was coming back, he now feels fine. He thanks you for your help. You make sure to regularly monitor Mr. Smith for signs of depression and enlist his wife to let you know if she notices any problems.*

## Conclusion

In this newsletter, we have reviewed the diagnosis and management of depression in an elderly man with comorbid medical illness. The monitoring of treatment, along with switch and augmentation strategies, was discussed. An evidence-based approach to treatment was reviewed drawing recent lessons from STAR\*D:

- (1) After four phases of treatment, only two-thirds of patients can be expected to achieve remission.
- (2) Switching from one SSRI to another SSRI yields response and remission rates equal to switching to another class of antidepressant.
- (3) Time to response or remission is more than six weeks in over half of patients.
- (4) Relapse is common within the first year of treatment (occurring in between one-third and one-half of all patients) and is more common in patients who have achieved partial response rather than remission. Those who have failed more than one antidepressant have a higher risk of relapse compared to those who have remitted with the first agent.

## Self-Assessment Questions

You may receive your CME certificate online by going to [www.ama-assn.org/go/therapeuticinsights](http://www.ama-assn.org/go/therapeuticinsights) and completing the self-assessment and program evaluation. Alternatively, you may use the answer sheet provided with the AMA Therapeutic Insights newsletter to record your answers, and either fax to 312-464-4849 or mail to:

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American Medical Association  
515 N State Street  
Chicago, IL 60610

If completing online, you will be able to print your CME certificate.  
If faxing or mailing, you will receive your CME certificate in 3-4 weeks.

- Each of the following factors increases the risk of suicide in a depressed patient EXCEPT:
  - History of hypomania
  - Alcohol and drug abuse
  - Age less than 25
  - Terminal disease
  - Family history of suicide
- Which of the following statements taken from the STAR\*D trial results are FALSE regarding remission with antidepressive therapy?
  - Greater chance of remission in patients with mild-to-moderate depression.
  - Approximately one in three patients will achieve remission with initial treatment (lasting up to 14 weeks) with an antidepressant.
  - After 4 phases of treatment, described in the STAR\*D trial, approximately two-thirds of patients can be expected to achieve remission.
  - Rates of remission are the same whether switching to another antidepressant in the same class or to an antidepressant from a different class.
  - The risk of relapse is similar in patients who achieved remission with a single agent compared to patients who failed on more than one agent before achieving remission.
- In a patient who has failed a 6 week trial of a single SSRI, all of the following are reasonable options EXCEPT:
  - Increase the dose of the initial agent
  - Add bupropion for augmentation
  - Switch to another SSRI
  - Add lithium for augmentation
  - Continue the current antidepressant for an additional 2-4 weeks before considering treatment change
- Which of the following agents is most likely to be associated with flu-like symptoms if stopped abruptly?
  - Paroxetine
  - Bupropion
  - Sertraline
  - Fluoxetine
  - Mirtazapine
- Based upon the findings from STAR\*D, which of the following statements are TRUE?
  - Cognitive therapy is less efficacious than switching to a second drug in patients who have failed an initial course of antidepressant medication.
  - Relapse occurs sooner in patients whose depression responds, but does not remit, after an adequate trial of antidepressant therapy.
  - Nearly two-thirds of patients will respond to a second antidepressant after failure of response to an initial course of therapy.
  - Dual-acting agents (eg, SNRIs) are more effective in achieving remission than are agents acting only on the serotonergic system.
  - Augmentation strategies (eg, combining two antidepressants) yield higher remission rates as compared to strategies that involve monotherapy.

## Program Evaluation

- The program provided useful information on the assessment and monitoring of major depressive disorder.
- The program provided an approach to improve the use of antidepressant therapy (dosage, medication switching, and augmentation) by applying the treatment information from the STAR\*D trial to patients diagnosed with depression.
- The program provided an overview of how to utilize assessment tools to assist in the diagnosis of depression and to monitor the effects of therapy.
- The program provided me with adequate information on patient follow up.
- The format of the program met my educational needs.
- Did you perceive commercial bias in this activity?
- Based on the information in this AMA *Therapeutic Insights* newsletter, what likely changes do you anticipate in your practice?

## Self-Assessment Responses

*(Please circle your response, one response per question)*

- |     |   |   |   |   |   |
|-----|---|---|---|---|---|
| Q.1 | a | b | c | d | e |
| Q.2 | a | b | c | d | e |
| Q.3 | a | b | c | d | e |
| Q.4 | a | b | c | d | e |
| Q.5 | a | b | c | d | e |

Name: \_\_\_\_\_

Address: \_\_\_\_\_

\_\_\_\_\_

City/State/Zip \_\_\_\_\_

Phone: \_\_\_\_\_ Fax: \_\_\_\_\_

E-mail address: \_\_\_\_\_

## Evaluation Responses *(Please circle)*

- |     | <i>Strongly<br/>Agree</i> | <i>Agree</i> | <i>Disagree</i> | <i>Strongly<br/>Disagree</i> |
|-----|---------------------------|--------------|-----------------|------------------------------|
| Q.1 | 1                         | 2            | 3               | 4                            |
| Q.2 | 1                         | 2            | 3               | 4                            |
| Q.3 | 1                         | 2            | 3               | 4                            |
| Q.4 | 1                         | 2            | 3               | 4                            |
| Q.5 | 1                         | 2            | 3               | 4                            |
| Q.6 | 1                         | 2            | 3               | 4                            |
| Q.7 | _____                     |              |                 |                              |

\*M.E.# \_\_\_\_\_

\*The Medical Education (ME) number is an 11-digit number assigned to every physician in the US by the AMA for identification and recording of basic information. If you are an AMA member, this number is found on your AMA membership card. If you do not have your ME number, you can obtain this number by calling the AMA at 1-800-262-3211. If this is not possible, please identify your date of birth, medical school, and year of graduation so that AMA staff can look up your ME number and accurately record credits.

Date of Birth: \_\_\_\_\_  
Mo/day/year

Medical School: \_\_\_\_\_

Yr. Graduation: \_\_\_\_\_

Hours of participation claimed (not to exceed 1): \_\_\_\_\_

Signature: \_\_\_\_\_

When completed, please fax to 312.464.4849 or mail to:

Additional Comments \_\_\_\_\_

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## References

- Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62(6):617-627.
- USA Statistics in Brief—Population by Sex, Age, and Region. <http://www.census.gov/compendia/statab/files/pop.html>. Accessed October 29, 2007.
- Kessler RC, Berglund P, Demler O, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA*. 2003;289(23):3095-3105.
- The World Health Report*. WHO; 2004.
- Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. *Lancet*. 1997;349(9064):1498-1504.
- Wang PS, Lane M, Olfson M, Pincus HA, Wells KB, Kessler RC. Twelve-month use of mental health services in the United States: results from the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62(6):629-640.
- Koenig HG. Recognition of depression in medical patients with heart failure. *Psychosomatics*. 2007;48(4):338-347.
- Bogner HR, Ford DE, Gallo JJ. The role of cardiovascular disease in the identification and management of depression by primary care physicians. *Am J Geriatr Psychiatry*. 2006;14(1):71-78.
- Nuyen J, Spreeuwenberg PM, Van Dijk L, den Bos GA, Groenewegen PP, Schellevis FG. The influence of specific chronic somatic conditions on the care for co-morbid depression in general practice. *Psychol Med*. 2007;1-13.
- Goldman LS, Nielsen NH, Champion HC. Awareness, diagnosis, and treatment of depression. *J Gen Intern Med*. 1999;14(9):569-580.
- Regier DA, Goldberg ID, Taube CA. The de facto US mental health services system: a public health perspective. *Arch Gen Psychiatry*. 1978;35(6):685-693.
- Dantz B, Ashton AK, D'Mello DA, et al. The scope of the problem: physical symptoms of depression. *J Fam Pract*. 2003;Suppl:S6-8.
- Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. *Diabetes Care*. 2001;24(6):1069-1078.
- Carney RM, Freedland KE, Sheline YI, Weiss ES. Depression and coronary heart disease: a review for cardiologists. *Clin Cardiol*. 1997;20(3):196-200.
- Gonzalez JS, Safren SA, Cagliero E, et al. Depression, self-care, and medication adherence in type 2 diabetes: relationships across the full range of symptom severity. *Diabetes Care*. 2007;30(9):2222-2227.
- DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Arch Intern Med*. 2000;160(14):2101-2107.
- Lett HS, Blumenthal JA, Babyak MA, et al. Depression as a risk factor for coronary artery disease: evidence, mechanisms, and treatment. *Psychosom Med*. 2004;66(3):305-315.
- Whooley MA. Depression and cardiovascular disease: healing the broken-hearted. *JAMA*. 2006;295(24):2874-2881.
- Whooley MA, Avins AL, Miranda J, Browner WS. Case-finding instruments for depression. Two questions are as good as many. *J Gen Intern Med*. 1997;12(7):439-445.
- Jurrlink DN, Herrman N, Szalai JP, Kopp A, Redelmeier DA. Medical illness and the risk of suicide in the elderly. *Arch Intern Med*. 2004;164(11):1179-1184.
- Hirschfeld RM, Calabrese JR, Weissman MM, et al. Screening for bipolar disorder in the community. *J Clin Psychiatry*. 2003;64(1):53-59.
- Ghaemi SN, Rosenquist KJ, Ko JY, Baldassano CF, Kontos NJ, Baldessarini RJ. Antidepressant treatment in bipolar versus unipolar depression. *Am J Psychiatry*. 2004;161(1):163-165.
- Ghaemi SN. Bipolar disorder and antidepressants: An ongoing controversy. *Prim Psychiatry*. 2001;8:28-34.
- Hirschfeld RM. The Mood Disorder Questionnaire: a simple, patient-rated screening instrument for bipolar disorder. *Prim Care Companion J Clin Psychiatry*. 2002;4(1):9-11.
- Ewing JA. Detecting alcoholism—the CAGE questionnaire. *JAMA*. 1984;252:1905-1907.
- Rush AJ, Zimmerman M, Wisniewski SR, et al. Comorbid psychiatric disorders in depressed outpatients: demographic and clinical features. *J Affect Disord*. 2005;87(1):43-55.
- Pilowsky DJ, Olfson M, Gameroff MJ, et al. Panic disorder and suicidal ideation in primary care. *Depress Anxiety*. 2006;23(1):11-16.
- Kroenke K, Spitzer RL, Williams JB, Monahan PO, Lowe B. Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection. *Ann Intern Med*. 2007;146(5):317-325.
- Mather AS, Rodriguez C, Guthrie MF, McHarg AM, Reid IC, McMurdo ME. Effects of exercise on depressive symptoms in older adults with poorly responsive depressive disorder: randomised controlled trial. *Br J Psychiatry*. 2002;180:411-415.
- Blumenthal JA, Babyak MA, Moore KA, et al. Effects of exercise training on older patients with major depression. *Arch Intern Med*. 1999;159(19):2349-2356.
- Blumenthal JA, Babyak MA, Doraiswamy PM, et al. Exercise and pharmacotherapy in the treatment of major depressive disorder. *Psychosom Med*. 2007;69(7):587-596.
- Mynors-Wallis LM, Gath DH, Lloyd-Thomas AR, Tomlinson D. Randomised controlled trial comparing problem solving treatment with amitriptyline and placebo for major depression in primary care. *BMJ*. 1995;310(6977):441-445.

33. DeRubeis RJ, Gelfand LA, Tang TZ, Simons AD. Medications versus cognitive behavior therapy for severely depressed outpatients: mega-analysis of four randomized comparisons. *Am J Psychiatry*. 1999;156(7):1007-1013.
34. de Mello MF, de Jesus Mari J, Bacaltchuk J, Verdelli H, Neugebauer R. A systematic review of research findings on the efficacy of interpersonal therapy for depressive disorders. *Eur Arch Psychiatry Clin Neurosci*. 2005;255(2):75-82.
35. Practice guideline for the treatment of patients with major depressive disorder (revision). [http://www.psych.org/psych\\_pract/treat/pg/prac\\_guide.cfm](http://www.psych.org/psych_pract/treat/pg/prac_guide.cfm). Accessed October 29, 2007.
36. Fava M, Judge R, Hoog SL, Nilsson ME, Koke SC. Fluoxetine versus sertraline and paroxetine in major depressive disorder: changes in weight with long-term treatment. *J Clin Psychiatry*. 2000;61(11):863-867.
37. Looper KJ. Potential medical and surgical complications of serotonergic antidepressant medications. *Psychosomatics*. 2007;48(1):1-9.
38. Louik C, Lin AE, Werler MM, Hernandez-Diaz S, Mitchell AA. First-trimester use of selective serotonin-reuptake inhibitors and the risk of birth defects. *N Engl J Med*. 2007;356(26):2675-2683.
39. Richards JB, Papaioannou A, Adachi JD, et al. Effect of selective serotonin reuptake inhibitors on the risk of fracture. *Arch Intern Med*. 2007;167(2):188-194.
40. Carney RM, Jaffe AS. Treatment of depression following acute myocardial infarction. *JAMA*. 2002;288(6):750-751.
41. Lesperance F, Frasura-Smith N, Koszycki D, et al. Effects of citalopram and interpersonal psychotherapy on depression in patients with coronary artery disease: the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial. *JAMA*. 2007;297(4):367-379.
42. Thase ME. Effects of venlafaxine on blood pressure: a meta-analysis of original data from 3744 depressed patients. *J Clin Psychiatry*. 1998;59(10):502-508.
43. Buckley NA, McManus PR. Fatal toxicity of serotonergic and other antidepressant drugs: analysis of United Kingdom mortality data. *BMJ*. 2002;325(7376):1332-1333.
44. Koski A, Vuori E, Ojanpera I. Newer antidepressants: evaluation of fatal toxicity index and interaction with alcohol based on Finnish postmortem data. *Int J Legal Med*. 2005;119(6):344-348.
45. Wernicke J, Lledo A, Raskin J, Kajdasz DK, Wang F. An evaluation of the cardiovascular safety profile of duloxetine: findings from 42 placebo-controlled studies. *Drug Saf*. 2007;30(5):437-455.
46. Perahia DG, Gilaberte I, Wang F, et al. Duloxetine in the prevention of relapse of major depressive disorder: double-blind placebo-controlled study. *Br J Psychiatry*. 2006;188:346-353.
47. Honig A, Kuyper AM, Schene AH, et al. Treatment of post-myocardial infarction depressive disorder: a randomized, placebo-controlled trial with mirtazapine. *Psychosom Med*. 2007;69(7):606-613.
48. Abo-Zena RA, Bobek MB, Dweik RA. Hypertensive urgency induced by an interaction of mirtazapine and clonidine. *Pharmacotherapy*. 2000;20(4):476-478.
49. Troncoso AL, Gill T. Hypertensive urgency with clonidine and mirtazapine. *Psychosomatics*. 2004;45(5):449-450.
50. Lowe B, Unutzer J, Callahan CM, Perkins AJ, Kroenke K. Monitoring depression treatment outcomes with the patient health questionnaire-9. *Med Care*. 2004;42(12):1194-1201.
51. Trivedi MH, Rush AJ, Wisniewski SR, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR\*D: implications for clinical practice. *Am J Psychiatry*. 2006;163(1):28-40.
52. O'Reilly RL, Bogue L, Singh SM. Pharmacogenetic response to antidepressants in a multigenerational family with affective disorder. *Biol Psychiatry*. 1994;36(7):467-471.
53. Grof P, Duffy A, Cavazzoni P, et al. Is response to prophylactic lithium a familial trait? *J Clin Psychiatry*. 2002;63(10):942-947.
54. Franchini L, Serretti A, Gasperini M, Smeraldi E. Familial concordance of fluvoxamine response as a tool for differentiating mood disorder pedigrees. *J Psychiatr Res*. 1998;32(5):255-259.
55. Thase ME, Friedman ES, Biggs MM, et al. Cognitive therapy versus medication in augmentation and switch strategies as second-step treatments: a STAR\*D report. *Am J Psychiatry*. 2007;164(5):739-752.
56. NIH consensus conference. Diagnosis and treatment of depression in late life. *JAMA*. 1992;268(8):1018-1024.
57. Reynolds CF, 3rd, Dew MA, Pollock BG, et al. Maintenance treatment of major depression in old age. *N Engl J Med*. 2006;354(11):1130-1138.
58. Dombrowski AY, Lenze EJ, Dew MA, et al. Maintenance treatment for old-age depression preserves health-related quality of life: a randomized, controlled trial of paroxetine and interpersonal psychotherapy. *J Am Geriatr Soc*. 2007;55(9):1325-1332.
59. Gibbons RD, Brown CH, Hur K, et al. Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents. *Am J Psychiatry*. 2007;164(9):1356-1363.
60. Gibbons RD, Brown CH, Hur K, Marcus SM, Bhaumik DK, Mann JJ. Relationship between antidepressants and suicide attempts: an analysis of the Veterans Health Administration data sets. *Am J Psychiatry*. 2007;164(7):1044-1049.
61. Simon GE, Savarino J, Operskalski B, Wang PS. Suicide risk during antidepressant treatment. *Am J Psychiatry*. 2006;163(1):41-47.
62. Warden D, Trivedi MH, Wisniewski SR, et al. Predictors of attrition during initial (citalopram) treatment for depression: a STAR\*D report. *Am J Psychiatry*. 2007;164(8):1189-1197.
63. Rush AJ, Trivedi MH, Wisniewski SR, et al. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. *N Engl J Med*. 2006;354(12):1231-1242.

64. Trivedi MH, Fava M, Wisniewski SR, et al. Medication augmentation after the failure of SSRIs for depression. *N Engl J Med*. 2006; 354(12):1243-1252.
65. Papakostas GI, Fava M, Thase ME. Treatment of SSRI-resistant depression: a meta-analysis comparing within- versus across-class switches. *Biol Psychiatry*. 2007.
66. Nierenberg AA, Fava M, Trivedi MH, et al. A comparison of lithium and T(3) augmentation following two failed medication treatments for depression: a STAR\*D report. *Am J Psychiatry*. 2006;163(9):1519-1530.
67. McGrath PJ, Stewart JW, Fava M, et al. Tranylcypromine versus venlafaxine plus mirtazapine following three failed antidepressant medication trials for depression: a STAR\*D report. *Am J Psychiatry*. 2006;163(9):1531-1541.
68. 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.
69. Black K, Shea C, Dursun S, Kutcher S. Selective serotonin reuptake inhibitor discontinuation syndrome: proposed diagnostic criteria. *J Psychiatry Neurosci*. 2000;25(3):255-261.
70. Coupland NJ, Bell CJ, Potokar JP. Serotonin reuptake inhibitor withdrawal. *J Clin Psychopharmacol*. 1996;16(5):356-362.
71. Bogetto F, Bellino S, Revello RB, Patria L. Discontinuation syndrome in dysthymic patients treated with selective serotonin reuptake inhibitors: a clinical investigation. *CNS Drugs*. 2002; 16(4):273-283.

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