Should This Patient Receive an Antidepressant?
Grand Rounds Discussion From Beth Israel Deaconess Medical Center
Risa B. Burns, MD, MPH; Gerald W. Smetana, MD; and Roscoe Brady, MD, PhD

Depression is a major public health problem and a common cause of disability. To help physicians choose among available treatment options, the American College of Physicians recently issued a guideline titled “Nonpharmacologic Versus Pharmacologic Treatment of Adult Patients with Major Depressive Disorder.” The evidence review done for the guideline found no statistically significant difference in the efficacy of second-generation antidepressants (SGAs) versus most other treatments for this disorder. However, rates of adverse events and discontinuation were generally higher in patients treated with SGAs. This Beyond the Guidelines reviews the guideline and includes a discussion between 2 experts on how they would apply it to a 64-year-old man with depression who is reluctant to begin medication. They review the data on which the guideline is based, discuss the limitations of applying the data to real-world settings, review how they would incorporate patient preferences when making treatment decisions, and outline options for patients in whom first-line therapy has failed.

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For author affiliations, see end of text.

Mr. Y is a 64-year-old man who recently saw his primary care physician (PCP) for depression that has been slowly worsening over 2 years. He believes it was precipitated by “trying out” retirement and exacerbated by the 2016 presidential election. He first experienced depression as a young adult, but improved once he found a rewarding career. He has an extensive family history of depression, with several family members receiving antidepressant medications. His medical history is significant for vestibular schwannoma. He is married and lives with his wife. Recently, he increased his exercise regimen to 4 times per week, which he says has helped his depressive symptoms. He does not smoke and has minimal alcohol intake.

On examination, Mr. Y displayed a sad affect but demonstrated good insight. His Patient Health Questionnaire (PHQ-9) score was 9, and his PCP concluded that Mr. Y had mild to moderate depression. He voiced wariness about taking medication and preferred to see a therapist. He and his PCP identified a therapist, but at the follow-up visit with his PCP 2 weeks after starting therapy, he had not noted any improvement. He remained wary of medications and wanted to keep working with the therapist. Mr. Y believed that if he could find something meaningful to do, his depression would improve.

Mr. Y’s Story
I noticed over the past 2 years that I have been directionless, giving up activities, and not taking up new ones. I had been planning for a different lifestyle in retirement but I was unable to do that and then about a
month ago, I found the election to be a triggering event and I experienced extreme anxiety around it and many other issues.

I started seeing a therapist a couple weeks ago. My PCP suggested taking medications but I told her I would prefer to pursue other avenues first. I have the stereotypical reluctance—that I might become addicted, that there might be side effects, that I would be dependent on it, that it would change my personality, etc.

I have a lot of family history of depression. My sense is that I was depressed from my teenage years until my late 20s. I had some therapy in my late 20s and early 30s. Then I got married, started a new career, and took up a very intensive hobby. So for a period of 10 or 15 years I had everything running on all cylinders. Then I started to become dissatisfied and started thinking about alternatives to my job and my leisure activities. Now I am just spending a lot of time sitting at home reading books rather than learning new things or engaging with people. Exercise has been extremely helpful. It does not banish my negative thoughts but it definitely relieves the physical symptoms.

I do not feel that life is not worth living or that I would be better off dead. I actually worry about death and I do not feel death is an answer to anything that is bothering me.

I am going to deal with the therapist and try to figure out whether she can help me, whether we need to go the medication route, or whether things will get better by themselves. So I am thinking that I am not going to be making a decision on medication at least for several months.

See the Patient Video (available at Annals.org) to view the patient telling his story.

**Context, Evidence, and Guidelines**

Depression is a major public health problem and a common cause of disability—the lifetime prevalence of major depressive disorder (MDD) in the United States is estimated to be 16% (1). The American Psychiatric Association defines MDD as the presence of 5 or more symptoms for at least 2 weeks and represent a change from prior functioning (2) (Table 1). Treatments for MDD include nonpharmacologic treatments, such as psychotherapy, cognitive behavioral therapy (CBT), and complementary and alternative medicine (CAM), as well as pharmacotherapy with second-generation antidepressants (SGAs). Response to treatment can be quantified with the PHQ-9, which is commonly used in clinical practice, or the Hamilton Depression Rating Scale (HAM-D), which is more commonly used in clinical trials (Table 2) (3, 4). Regardless of treatment type, response rates tend to be modest. In the case of SGAs, about 40% of patients do not respond to treatment and 70% do not achieve remission (5).

Most patients with MDD are seen initially by a PCP, with almost 8 million visits annually (6). To help guide PCPs, the American College of Physicians (ACP) issued a clinical guideline in February 2016 on nonpharmacologic versus pharmacologic treatment in MDD (7). It summarized and graded evidence on the comparative effectiveness and safety of nonpharmacologic interventions and SGAs alone or combined and made recommendations based on an evidence review from the Agency for Healthcare Research and Quality (8, 9). That review evaluated treatment options for depression, including psychotherapy, CBT, CAM, exercise, and SGAs, and examined response (defined as ≥50% improvement in HAM-D scores), remission rates (defined as HAM-D score ≤7), and harms (adverse events [AEs]).

The evidence review examined the effectiveness of SGAs compared with nonpharmacologic interventions as initial treatment, including 43 head-to-head clinical trials whose results are summarized in Figures 1 to 3. Overall, there was no statistically significant difference in efficacy between SGAs and most other treatments for adult outpatients with mild to severe MDD. Rates of AEs and discontinuation were generally higher in patients treated with SGAs, although the strength of the evidence for this finding was generally low (8, 9).

The evidence review further examined the comparative effectiveness of augmenting the initial SGA versus switching for patients who did not achieve remission. However, only 2 trials compared the benefits and harms of such strategies (10, 11), and the review found that neither strategy had greater efficacy or risk for harm (8, 9).

Given the lack of clear benefit of one treatment strategy over another, ACP recommends that clinicians choose either CBT or SGAs for initial treatment of patients with MDD after discussing treatment effects, AEs, cost, accessibility, and patient preferences.

**Clinical Questions**

To structure a debate between our 2 discussants, we mutually agreed on the following questions to consider when applying this guideline to clinical practice and to Mr. Y in particular:

1. What is the comparative effectiveness of the available pharmacologic and nonpharmacologic therapies for MDD, and what are their harms?
2. How do you help patients choose among available therapies in terms of cost, efficacy, harms, and availability of services?

**Table 1. Diagnostic Criteria for Depression**

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feelings of sadness, hopelessness, depressed mood</td>
<td></td>
</tr>
<tr>
<td>Loss of interest or pleasure in activities that used to be enjoyable</td>
<td></td>
</tr>
<tr>
<td>Change in weight or appetite (either increase or decrease)</td>
<td></td>
</tr>
<tr>
<td>Change in activity: Psychomotor agitation (being more active than usual)</td>
<td></td>
</tr>
<tr>
<td>or psychomotor retardation (being less active than usual)</td>
<td></td>
</tr>
<tr>
<td>Insomnia (difficulty sleeping) or sleeping too much</td>
<td></td>
</tr>
<tr>
<td>Feeling tired or not having any energy</td>
<td></td>
</tr>
<tr>
<td>Feelings of guilt or worthlessness</td>
<td></td>
</tr>
<tr>
<td>Difficulties concentrating and paying attention</td>
<td></td>
</tr>
<tr>
<td>Thoughts of death or suicide</td>
<td></td>
</tr>
</tbody>
</table>

*From www.cdc.gov/mentalhealth/basics/mental-illness/depression.htm.
**BEYOND THE GUIDELINES**

**Table 2. Hamilton Rating Scale for Depression***

<table>
<thead>
<tr>
<th>Item</th>
<th>Rating 0–4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressed mood</td>
<td>(0-4)</td>
</tr>
<tr>
<td>Feelings of guilt</td>
<td>(0-4)</td>
</tr>
<tr>
<td>Suicide</td>
<td>(0-4)</td>
</tr>
<tr>
<td>Insomnia: Early</td>
<td>(0-2)</td>
</tr>
<tr>
<td>Insomnia: Middle</td>
<td>(0-2)</td>
</tr>
<tr>
<td>Insomnia: Late</td>
<td>(0-2)</td>
</tr>
<tr>
<td>Work and activities</td>
<td>(0-4)</td>
</tr>
<tr>
<td>Retardation: Psychomotor</td>
<td>(0-4)</td>
</tr>
<tr>
<td>Agitation</td>
<td>(0-4)</td>
</tr>
<tr>
<td>Anxiety: Psychic</td>
<td>(0-4)</td>
</tr>
<tr>
<td>Anxiety: Somatic</td>
<td>(0-4)</td>
</tr>
<tr>
<td>Somatic symptoms: Gastrointestinal</td>
<td>(0-2)</td>
</tr>
<tr>
<td>Somatic symptoms: General</td>
<td>(0-2)</td>
</tr>
<tr>
<td>Genital symptoms</td>
<td>(0-2)</td>
</tr>
<tr>
<td>Hypochondriasis</td>
<td>(0-4)</td>
</tr>
<tr>
<td>Loss of weight rated by history</td>
<td>(0-2)</td>
</tr>
<tr>
<td>Insight</td>
<td>(0-2)</td>
</tr>
</tbody>
</table>

Total score: ___

0-7 = Normal
8-13 = Mild depression
14-18 = Moderate depression
19-22 = Severe depression
> 22 = Very severe depression

* From reference 4.

**DISCUSSION**

**A Primary Care Physician’s Viewpoint**

**(Dr. Gerald W. Smetana)**

**Question 1: What is the comparative effectiveness of the available pharmacologic and nonpharmacologic therapies for MDD, and what are their harms?**

The 2016 ACP guideline found convincing evidence that many nonpharmacologic treatments for depression were as effective as SGAs and often had fewer side effects (Figures 1 to 3) (7, 9). For example, the guideline identified 5 trials of SGAs versus CBT with low or medium risk of bias. The ACP defines CBT as therapy that is “based on the idea that faulty thinking patterns generate maladaptive behaviors and negative emotions. Cognitive and behavioral interventions focus on changing an individual’s thoughts (cognitive patterns) in order to change behavior and emotional states” (9). Response rates were similar for SGAs and CBT. In a meta-analysis of 3 trials, more patients receiving SGAs stopped treatment because of adverse effects than those receiving CBT (8% vs. 3%), although this trend was not statistically significant (relative risk [RR], 2.51 [95% CI, 0.40 to 15.46]) (12-14). Data from studies that compared SGAs with interpersonal therapies, third-wave behavioral therapy, and psychodynamic therapies were of low quality.

Low-quality studies have shown that acupuncture may be as effective as SGAs as first-line treatment for depression. In a systematic review of 8 trials, the response rate was similar for acupuncture versus SGAs (RR, 1.06 [CI, 0.97 to 1.17]) (15); however, acupuncture is very well-tolerated when compared with SGAs and is nearly free of side effects.

Surprisingly, St. John’s wort was found to be as effective as SGAs. In the review accompanying the ACP guideline (9), response rates (52% vs. 54%) and remission rates (30% vs. 36%) were similar for SGAs and St. John’s wort based on analyses of 9 trials (n = 1513 participants), and it is generally well-tolerated. However, one concern is the lack of standardization of dosing and potency in commercially available products. Treatment discontinuation rates due to AEs were significantly lower than those for SGAs and St. John’s wort (7% vs. 4%). In a separate systematic review of 35 studies, data on AEs were available in 15 trials; specific side effects were less common for St. John’s wort than SGAs (16).

Adverse events are common among SGA users (Table 3) (17). Up to 40% of patients treated with SGAs experience at least 1 AE (15). Sexual side effects, including reduced libido, and erectile dysfunction in men, are common among patients who choose selective serotonin reuptake inhibitors (SSRIs)—rates may be as high as 50% to 70%. Nausea, headache, sweating, weight gain (except for bupropion), and insomnia are also common. In addition, drug interactions can increase the risk for the uncommon but serious serotonin syndrome, a condition characterized by agitation, confusion, autonomic hyperactivity, muscular rigidity or twitching, and rarely high fever and seizures. Selective serotonin reuptake inhibitors can also precipitate manic episodes in patients with bipolar disorder misdiagnosed as MDD.

Thus, Mr. Y’s reluctance to begin SGA therapy is understandable and supported by literature. If his response to counseling is not adequate, he has several other viable choices besides an SGA, including CBT, acupuncture, and St. John’s wort. Of these, the ACP guideline recommends CBT.

**Question 2: How do you help patients choose among available therapies in terms of cost, efficacy, harms, and availability of services?**

We can help patients choose among the available options through shared decision making. Some patients are primarily concerned about specific side effects. For a patient in whom sexual side effects would be unacceptable, CBT or CAM treatments would be preferable to SGAs (other than potentially bupropion). For a patient who is worried about weight gain but opts for SGAs, fluoxetine and bupropion would be the preferred choices. Alternatively, a patient could forgo SGAs altogether, and choose CBT, acupuncture, or St. John’s wort, none of which are associated with weight gain.

However, when rapid treatment response is required—for example, a patient with disabling depression who is unable to work or go to school or has passive suicidal ideation—SGAs are likely to work more quickly than CBT. Patients considering SGA therapy need to understand that response rates are generally no more than 50%, and remission rates average 30%. It usually takes 6 to 8 weeks to experience the full benefit of a particular SGA. Thus, it may often require as long as 4 to 6 months of drug trials to find one that provides...
a response and has a side effect profile satisfactory to the patient.

Potential barriers to CBT and acupuncture are the lack of readily available trained providers and cost. The cost range for CBT in the United States is approximately $60 to $200 per hour (18). Medicare and Medicaid cover a portion of the cost, as do most commercial insurance plans. Commercial plans may limit the number of covered sessions per year. The cost of acupuncture in the United States ranges from $50 to $100 per session (19) and is not covered by Medicare or Medicaid (20). Coverage by commercial insurance varies. Some patients may worry about the stigma associated with seeing a CBT counselor and the effect of being labeled as “depressed.” This can be minimized to some extent by offering CBT services within primary care settings.

Many patients have strong positive views about use of “natural” treatments as opposed to prescription pharmacotherapy, and such preference for “natural” treatments is supported by the evidence. Mr. Y is concerned about side effects, including worrying that he will become “addicted” and need treatment indefinitely. We should respect his preference, and explore nonpharmacologic options for him. Should he opt for SGA at a later point in time, we can reassure him that he will not become addicted and inform him that initial treatment courses are typically 9 to 12 months followed by a reassessment of the indications for ongoing treatment.

**Question 3: What are the treatment options for patients who do not respond adequately to initial therapy?**

When there is no response to an SGA as the first-line treatment, switching or augmenting with medications works more quickly than augmenting with cognitive therapy. This was best demonstrated in the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) trial (21). In that trial, citalopram nonresponders either switched therapies or had another therapy added (augmentation). Augmentation with medication (bupropion or buspirone) worked more quickly than augmentation with CBT, but response rates were similar after 14 weeks. For patients who switched, there was no difference in response rates or time to response between switching to CBT or a SGA (sertraline, venlafaxine, or bupropion). However, more patients discontinued treatment due to AE in the SGA groups than in the CBT groups. The ACP guideline concluded, based on limited evidence, that there is likely no difference among the various switch or augmentation options.

For nonresponders to initial treatment, it is important to consider the possibility that the initial diagnosis was incorrect. Bipolar disorder, posttraumatic stress disorder, or dual diagnosis with alcohol or drug misuse may all be mistaken for major depression.

Mr. Y has a clear preference for counseling as initial treatment and has already begun this approach. He does not have an urgent need for a rapid treatment response. Should he not have adequate symptom reduction, choices for augmentation would be SGA, acupuncture, or St. John’s wort. Given his concern about the side effects of SGAs, I would recommend acupuncture or St. John’s wort. It is likely that augmenting the counseling with one of these strategies rather than switching would be preferable, although this has not been well-studied.

**A Psychiatrist’s Viewpoint (Dr. Roscoe Brady)**

**Question 1: What is the comparative effectiveness of the available pharmacologic and nonpharmacologic therapies for MDD, and what are their harms?**

The ACP guideline summarizes the randomized controlled trial evidence for treating MDD. However, a concern with these trials is the extent to which the results can be generalized to real-world settings. Although the guideline compares efficacy and tolerability of interventions, it does not factor in accessibility. I argue that for the PCP, this factor may determine initial treatment at least as much as tolerability or efficacy.

In trials comparing CBT with SGAs, typically about 85% of persons in the CBT treatment group attend CBT sessions multiple times a week for several months (12, 13, 22). For a CBT-trained psychiatrist in a setting that allows 8 visits per patient per month, an SGA and CBT...
are equally effective. However, for a PCP whose choice is either to prescribe an SGA or to refer the patient outside the practice for CBT, the results are less clear. To address this question, 1 study found that prescribing an antidepressant is twice as likely to enable patients to achieve remission as referral to outside mental health providers (23). The same study found that the cost in health care spending (for example, costs for medication, CBT therapy sessions, outreach, emergency department visits) per day free of depression was lower in the pharmacotherapy group than in the group referred to CBT (24). A study conducted in the offices of general practitioners in the United Kingdom produced a comparable result. That study compared 2 treatment groups: frequent visits to the general practitioner plus “supportive care” (for example, referral to psychotherapy, exercise regimens) without an SSRI prescription, versus “supportive care” in combination with an SSRI. That study similarly concluded that the addition of an SSRI was both more efficacious and more cost-effective (25).

Given the benefits of SGA use, how does the literature guide a PCP in choosing among the available options? Currently, there is little high-quality evidence regarding differences in efficacy between SGAs or for predicting response to specific SGAs (26). The largest clinical trial using SGAs to treat depression in outpatient practices (including primary care offices) suggested that an initial trial of an SSRI achieved remission in about 30% of patients and a substantial reduction in symptoms in an additional 17% (27).

**Question 2: How do you help patients choose among available therapies in terms of cost, efficacy, harms, and availability of services?**

In helping a patient choose between available therapies, the patient and clinician should have a shared understanding of treatment options. A physician can provide new knowledge, supplement existing patient knowledge, and if needed correct misinformation regarding possible approaches. For example, Mr. Y's concerns about becoming addicted to antidepressants are unwarranted. Once the physician and patient have a common knowledge base, they can discuss the actual prevalence of AEs with SGA treatment and explore which AEs are least acceptable and can tailor their SGA choice to minimize AEs (Table 3).

In my experience, accessibility is a major determinant of initial treatment. Can patients find a therapist who accepts their insurance and can incorporate visits into the patient’s weekly routine? Other determinants are whether patients can afford the specific medication and adhere to a daily therapy and/or exercise regimen. Another consideration is the severity of current and prior depressive episodes. Has this episode of depression affected their level of functioning? Has it cost them a job or a significant relationship? I would argue that a “yes” to either of those questions requires referral to a psychiatrist or advanced practice psychiatric nurse who can prescribe SGAs and provide follow-up. If there are no such concerns and the patient has a strong preference for nonmedication treatment, which is also accessible and sustainable, then the clinician and patient can probably agree on a trial of nonpharmacologic therapy.

There should be a plan for evaluating the effectiveness of that therapy. If the patient isn’t adhering to twice-weekly CBT therapy at a 4-week follow-up visit, should it still be pursued? I suggest that nonpharmacologic interventions be evaluated as we do SGAs. If patients have not been able to incorporate a nonpharmacologic treatment into their life or have not responded to that treatment by 10 to 12 weeks, I would suggest adding an SGA.
Question 3: What are the treatment options for patients who do not respond adequately to initial therapy?

Response to antidepressant treatment should ideally be assessed using a standardized tool, such as the HAM-D. In the STAR*D trial, this symptom scale (rather than global impressions of mood) was credited with allowing primary care settings to achieve outcomes comparable to psychiatric clinics (27). Using the same definitions of response (50% reduction in symptom scales) and remission (HAM-D <7) as STAR*D would allow clinicians to better make decisions about when to switch SGAs versus supplementing with an additional SGA.

If the initial treatment is an SGA and the SGA is well-tolerated and results in some clinical improvement but the patient does not achieve remission after a trial of adequate duration (that is, 10 to 12 weeks) (27), the most effective next step may be augmentation of the initial SGA with another SGA, such as bupropion (28, 29). For patients who do not respond to the initial SGA or find its side effects problematic, it may be preferable to switch the initial SGA to a different SGA (30). In the STAR*D trial, patients who did not achieve remission with an initial trial of an SSRI (citalopram) were as likely to respond to a different SSRI (sertraline) as they were to a different class of SGA (for example, venlafaxine or bupropion) (11). There is evidence that CBT is an effective second step in patients who do not respond to an initial SGA, but for the PCP, concerns about the efficacy of prescribing versus successfully referring to a cognitive behavioral therapist, as described earlier, remain (21).

For patients who do not respond to 2 adequate antidepressant trials, the next step should be referral to a psychiatrist or advanced practice psychiatric nurse, as subsequent medication trials have a substantially lower chance of success, necessitating more intensive follow-up (31). Multiple failed trials also raise concerns that the clinical presentation may be complicated by other psychiatric illnesses, such as a substance use disorder, bipolar disorder, or posttraumatic stress disorder. These conditions may be more easily discerned with frequent visits to a psychiatrist or advanced practice psychiatric nurse.

Table 3. Mean Incidence of Specific Adverse Events Across Comparative Trials*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Diarrhea</th>
<th>Dizziness</th>
<th>Headache</th>
<th>Insomnia</th>
<th>Nausea</th>
<th>Mean Incidence (95% CI), %†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupropion</td>
<td>8.7 (12.1)</td>
<td>12.5 (21.6)</td>
<td>27.2 (18.3)</td>
<td>16.0 (13.3)</td>
<td>14.8 (8.9)</td>
<td>8.6 (20.5)</td>
</tr>
<tr>
<td>Citalopram</td>
<td>6.5 (11.8)</td>
<td>5 (24.1)</td>
<td>6.4 (17.1)</td>
<td>11.9 (28.4)</td>
<td>10.9 (35.6)</td>
<td></td>
</tr>
<tr>
<td>Duloxetine</td>
<td>5 (20.1)</td>
<td>29.9</td>
<td>13.7 (10.0)</td>
<td>18.6 (15.1)</td>
<td>14.8 (23.5)</td>
<td></td>
</tr>
<tr>
<td>Escitalopram</td>
<td>8.9 (16.1)</td>
<td>NR</td>
<td>8.7 (16.2)</td>
<td>14.8 (25.5)</td>
<td>18.6 (15.1)</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>11.9 (21.6)</td>
<td>7.2 (4.3)</td>
<td>16.6 (10.2)</td>
<td>13.7 (10.7)</td>
<td>14.8 (22.1)</td>
<td></td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>NR</td>
<td>NR</td>
<td>14.5 (41.5)</td>
<td>NR</td>
<td>22.2 (46.8)</td>
<td></td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>8.9 (22.4)</td>
<td>12.0 (2.9)</td>
<td>12.1 (6.3)</td>
<td>8.0 (49.2)</td>
<td>4.3 (8.9)</td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>9.2 (12.9)</td>
<td>10.6 (17.3)</td>
<td>21.2 (11.1)</td>
<td>14.3 (8.6)</td>
<td>18.3 (11.1)</td>
<td></td>
</tr>
<tr>
<td>Sertraline</td>
<td>15.4 (23.6)</td>
<td>7.5 (4.6)</td>
<td>20.2 (12.8)</td>
<td>15.0 (14.3)</td>
<td>19.5 (24.6)</td>
<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>5.5 (10.1)</td>
<td>15.7 (24.4)</td>
<td>12.8 (17.6)</td>
<td>11.2 (19.3)</td>
<td>31.0 (24.3)</td>
<td></td>
</tr>
</tbody>
</table>

† Calculated from data from randomized controlled trials. The method and extent of assessment of adverse events varied among studies, and the pooled incidence should be interpreted with caution.
Returning to Mr. Y, he has benefited from therapy in the past and is successfully referred to a therapist by his PCP. Is this intervention now as likely to succeed as an SGA? The applicability of the cited studies is unclear. The participants in several of the studies cited are a mean age of almost 3 decades younger than Mr. Y. The 1 study to address the efficacy of psychotherapy versus SGA treatment in older adults with a mean age of 71 treated in a primary care setting, suggests that SGA treatment is more efficacious and faster than psychotherapy in this population (32). I would thus recommend education to correct Mr. Y’s incorrect belief that SGAs are addictive. Taking into consideration his lack of clinical acuity (for example, no suicidality), if Mr. Y continued to prefer therapy I would recommend this treatment. If he did not achieve remission after 10 to 12 weeks, I would recommend adding an SGA at that time.

SUMMARY

Our discussants agree that the evidence review found no difference in response rates between SGAs and the other interventions studied. Dr. Smetana suggests that nonpharmacologic interventions, such as psychotherapy (and CBT in particular), as well as CAM therapies, such as acupuncture and St. John’s wort, be considered alternative first-line therapies when discussing treatment options, especially because of a trend toward lower discontinuation rates due to AEs. Dr. Brady concurs that the studies informing the ACP guideline found no difference in response rates between SGAs and other interventions but raises concerns that clinical trials do not reflect the “real world” and that it may be much more difficult for patients in clinical practice to access and afford nonpharmacologic therapies. He provided additional data suggesting that patients treated with SGAs in a real-world setting were twice as likely to achieve remission as those receiving other therapies. Furthermore, he is concerned about variation in quality for treatments other than SGAs, including CBT, acupuncture and over-the-counter formulations of St. John’s wort. In the end, our discussants agreed that it was most important to choose a therapy that fits the patient, because their commitment and follow-through are the most important factors in determining long-term treatment response.

Our discussants had similar viewpoints on helping patients choose a treatment method. They both felt that it was key that physicians convey their knowledge, address the patient’s fears and concerns, and correct any misinformation. Once patient and physician have a common knowledge base, they can work together to choose a treatment best suited to the patient’s lifestyle. Dr. Brady believed it was important, and Dr. Smetana agreed, that physicians evaluate nonpharmacologic treatments in a manner similar to pharmacologic therapies—that is, patients should be seen 8 to 12 weeks after initiating treatment, and if they are not able to follow through or do not respond to the initial treatment, an alternative should be considered.

With regard to treatment if the first choice is ineffective, our discussants agreed that results were similar whether current therapy is augmented or switched to something else. Therefore, our discussants believed that the most important factor in this situation was to find a treatment method that the patient would continue for the long term, because adherence was the best predictor of long-term success. For patients in whom 2 trials of an SGA has failed, Dr. Brady recommended, and Dr. Smetana agreed, that the patient should be referred to a psychiatrist for additional diagnostic considerations.

With regard to Mr. Y, our discussants felt that he could continue seeing his current therapist and that there was no need for an urgent change in treatment at this time. They believe that his commitment to therapy and motivation to improve predicted the likelihood of a good response. However, if Mr. Y did not improve by 8 to 12 weeks, Dr. Smetana would suggest adding acupuncture or St. John’s wort while Dr. Brady would encourage the patient to consider adding an SGA.

A transcript of the audience question-and-answer period is available in the Appendix (available at Annals.org). To view the entire conference video, including the question-and-answer session, go to Annals.org.

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References


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**APPENDIX: COMMENTS AND QUESTIONS**

Dr. Deborah Cotton: We’d like to let the audience ask some questions. Normally, the first question comes from Dr. Zeidel, Chief of Medicine, who’s not here today. But I see a lot of people bursting to ask some questions.

Dr. Robert Boland: Thanks so much. First, thanks for doing this. This was really awesome. I appreciate the effort that went into it. In addition to access, I also wrestle with—and I wonder what your thoughts are, either of you—the issue of blinding in the studies. We know that depression has a high placebo response and these responses are affected by expectation, unless the study has done an incredibly clever control to blind for the expectation one gets from psychotherapy, which most studies have not (you can’t really blind psychotherapy, they know they’re getting it most of the time). I wonder if, out of the box, most comparative studies are biased toward a greater psychotherapy response. What are your thoughts? Am I being too critical?

Dr. Smetana: In many of these trials, you are correct: The placebo response is quite high—anywhere from around 30% to 50%, depending on the trial. And you’re correct that we can’t, obviously, have a placebo control group against psychotherapy as the intervention. I think that this is a potential factor to consider when interpreting these trials and how we would apply them to practice.

Dr. Bruce Landon: I worry about heterogeneous treatment effects—particularly in cases like this—but in this case, I also worry about heterogeneity of the treatment. For example, I have a pretty good understanding of what it means to give someone 20 mg of fluoxetine, but when I send someone to CBT, it’s a total black box to me; I have no idea exactly what’s going on in the room or whether the therapist is adhering to correct CBT technique. Do we have any data on the heterogeneity of the effectiveness of CBT?

Dr. Brady: Yes—it is a problem. As an analogy: I think of antidepressants as McDonalds, or the McDonalds of depression treatment. In other words, I have the assumption—accurate or inaccurate—that the generic fluoxetine that CVS dispenses is the same here versus somewhere else, just like you can walk into a McDonalds anywhere in any state in this country and it tastes the same. There may be some differences between certain generic formulas—but you get the point—in contrast to CBT, as one good example, or these other interventions like acupuncture or St. John’s wort. So I make this point for Mr. Y that I wouldn’t recommend acupuncture or St. John’s wort if he doesn’t respond to psychotherapy. In other words, it’s not that I believe the treatments don’t work, but that I have no idea if the St. John’s wort that you get down the street is the same that was used in the trials. I know what extract was used in these trials, and they control it for a specific concentration of hypericin, but I don’t know exactly what Mr. Y’s going to get. This also applies to acupuncture and probably to a variety of therapeutics. Maybe the advantage with SSRIs is that over time you become familiar with what to expect and what not to expect.

This leads to a broader point: When I talk about picking an antidepressant, I don’t stress using the clinical characteristics of the depressive episode when choosing a medication—for example, should we use different medications to treat late-life depression than a first depressive episode at age 25? I don’t believe so, but the literature is unclear. My suggestion to a physician would be to prescribe what you have experience prescribing because you know what to expect, you can tell the patient what to expect, and you will know how to respond to side effects (in other words, you know which side effects necessitate a switch or which ones will go away so the patient can remain on the drug). I can’t say those things for St. John’s wort. I can’t say those things for acupuncture. I agree with you that there is a lot of heterogeneity out there. At least antidepressants have a predictable pattern of intervention and response.

Dr. Jason Matos: You guys had a discussion about the different trials. Don’t we need—especially with someone like Mr. Y—who you said “gets things done”—trials on efficacy and effectiveness that we can label as such so we can see what works for people we know or strongly suspect are going to follow through? What about St. John’s wort? Is this something that we should prescribe as effective and has that been differentiated clearly in the literature?

Dr. Smetana: I would like to reiterate an earlier point: In practice, patients who have already expressed a preference after shared decision making have self-selected to be more likely to respond than patients who had been randomly assigned to one of the treatment choices without their input. If you look at the placebo-controlled trials, there is a clear beneficial effect from SGAs compared with placebo. If you look at the St. John’s wort data, there was a relative risk for response of about 1.5 compared with placebo and a relative risk of 1 compared with SGAs. So among the trials that compared St. John’s wort with placebo, there was a clear preference for St. John’s wort and it wasn’t just the placebo effect. I think that if our patients self-select after shared decision making and we offer a treatment that fits their particular goals and addresses their concerns, we might see higher response rates than what we’ve seen from the trials.
Dr. William Greenberg: I have 2 questions. First: What does the literature tell us about which patients are more likely to respond to antidepressant therapies? These populations are large—to whom would you be more likely to prescribe antidepressants? Second: What does the literature tell us about combining psychotherapy and antidepressant therapy? It’s not necessarily an either-or decision.

Dr. Brady: I’ll field the first question. There was a great review written by Roy Perlis and a couple of other authors published a few years ago that basically asked, “Is personalized antidepressant treatment possible?” (33). I believe, unfortunately, that any of the things that I think of as predicting responses to antidepressants are not things that we do in clinical practice. For example, there are a decent number of imaging studies out there that can predict response to antidepressant medications, which are simply not practical in any kind of real-world setting. Many of these experiments probably won’t be replicated because they require institution-specific expertise. What might come closest to predicting actual response would be, say, a test of executive functioning—in other words, someone getting a significant amount of neuropsychological testing beforehand. People who have high scores in terms of executive performance/executive functioning are much more likely to respond to antidepressants or cognitive behavioral therapy than people who have low executive functioning. To get back to Dr. Matos’s point about people who “gets things done”: A person like Mr. Y, who basically walks out of the primary care office and is in therapy by the 2-week follow-up, has a good prognosis. Because whatever he is engaging in, he made it happen. And that suggests good executive functioning to me.

Are there other aspects of Mr. Y’s presentation indicating that one medication may be more effective than another? This is someone who is not having his first depressive episode in his 60s, he was depressed in his late 20s for years. Does that onset of illness predict antidepressant treatment efficacy? According to the STAR*D trial, it doesn’t.

Here’s something even more confusing: When I see a new patient, I ask, “Have you taken an antidepressant in the past?” If they say “yes,” I ask, “Did you respond?” If they say “yes,” okay, we should start with that medication, correct? But how many times has that process been addressed experimentally? To my knowledge, there’s been only one careful study that has addressed it, and believe it or not, people who—by their report—previously responded to an antidepressant were less likely to respond if they were re-treated with that antidepressant than if they received a different antidepressant.

Unfortunately, there is little that I ask in an interview, or most people ask in an interview, that addresses choosing a particular antidepressant medication that has been validated in actual trials and is something you could readily apply in the clinic.

Dr. Smetana: I would like to make 2 comments as well. First, if you look at the overall response rates, it’s remarkable how consistent the literature is. Almost uniformly, the response rates to antidepressants are around 50% and the remission rate is about 30%. This is true of SSRIs, selective norepinephrine reuptake inhibitors, and the novel antidepressants—it is a very consistent finding. With regard to your question about counseling, I think probably the STAR*D trial looked at that best. Patients who did not respond to citalopram could either switch to counseling or another medicine, or they could have counseling or a second medicine added. In both of the augmentation and switching categories, the counseling group did just as well as the ones who switched or augmented their medication.

Dr. Jacqueline Wolf: Many people who take SSRIs have side effects, especially gastrointestinal ones. Beyond that, there are a lot of things about diet out there that aren’t well studied but our patients are following. Patients are on gluten-free diets or are on FODMAP diets and they’re losing weight. We know that gluten affects the gut bacteria, that neurotransmitters are in the gut and that 95% of serotonin receptors are in the gut. So I have a few questions on this subject. What about trials of just diet and meditation? What was that interpersonal study that you had up there that actually looked better than everything else? [34] Did that trial study diet or meditation? I think we need to look there. Also, did men and women respond differently?

Dr. Brady: There is no doubt in my mind, just from my clinic experience, that diet is key. And I can make it even simpler: hydration. No joke—patients should be told to follow that old advice to drink 7 glasses of water a day. We don’t ask often enough about our patient’s dietary habits. We don’t think about it often enough, we don’t use it as an intervention often enough, and I believe it is not studied often enough. I wish I could claim to have prepared more in terms of thinking about dietary interventions for depression for this talk, but I believe that the take-home is yes. Diet is insufficiently studied. There is a real-world reason to think that we can make a difference in combination with, or maybe in isolation from, antidepressants.

Dr. Smetana: I agree. If you look at the systematic review that was the basis for the ACP guideline we’re talking about today, diet was not one of the included interventions in the nonpharmacologic group. But they did include 2 interventions that I didn’t talk about today: exercise and omega fatty acids, but these were not specifically related to the types of diets you’re describing.

Dr. Cotton: Thank you for joining us today.
Web-Only References