PHYSICIANS DISCUSS THE USE OF ALGORITHMS WHEN DECIDING WHAT TREATMENTS ARE APPROPRIATE FOR PATIENTS WITH NONPSYCHOTIC DEPRESSION.

Depression continues to be challenging to manage, in part because of the myriad of treatment options available to the clinician and the patient. Treatment algorithms can help the clinician decide which treatment strategies to use, but an inherent flaw in algorithms is that they take too long to develop and therefore fall out of date quickly as new treatments are approved and new strategies are studied.

On October 12, 2005, Madhukar H. Trivedi, M.D., a Director of the CME Institute of Physicians Postgraduate Press, Inc. and a nationally recognized expert in the development of treatment algorithms, assembled a group of experts to discuss the use of algorithms in the treatment of nonpsychotic major depressive disorder. Their discussion appears here.

This special Commentary is another in a series of independent projects undertaken by the CME Institute of Physicians Postgraduate Press, Inc. as a service to its members and the broader academic and clinical community. Visit www.psychiatrist.com to listen to audio selections from this discussion.

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Use of Treatment Algorithms for Depression

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THE EFFECTIVENESS OF AND NEED FOR ALGORITHMS IN DEPRESSION

Dr. Trivedi: The effectiveness of treatment algorithms rests on 3 principles. The 3 broad categories requiring special attention are (1) the determination of the need for sequential treatment algorithms; (2) what should be the placement of various treatment interventions in treatment algorithms with sequenced treatments, e.g., at what point should combination treatments and somatic treatments be included; and finally, (3) what the process or procedure is to implement algorithms in the clinical setting, e.g., the use of recently developed measurement-based care.[1]

Dr. Osser: It is clear to me that there are significant differences between the likely outcome of people receiving treatment as usual (TAU) as opposed to algorithm-driven treatment. In the Texas Medication Algorithm Project (TMAP),[2] that difference was seen primarily in the first 3 months. An important factor in that difference was that the care coordinator identified patients who were not doing well and needed to move to the next step in the algorithm. For the next 9 months of the TMAP study, there was no widening of the difference between the algorithm group and the TAU group, suggesting that, from that point on, both groups did reasonably well (Figure 1).

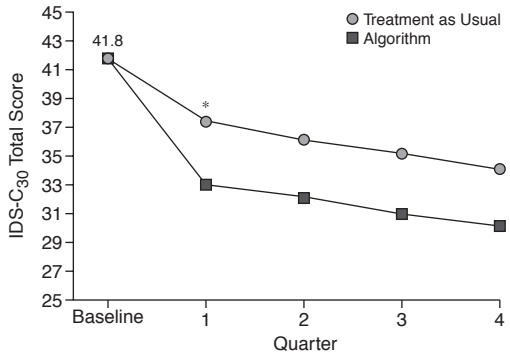
Dr. Trivedi: There is also evidence in primary care from Katon and colleagues,[3] which showed that guideline-driven care produces better outcome than TAU. Unützer and coworkers[4] found similar results. All of these studies have used care coordinators in the algorithm-driven treatment groups. The question becomes whether the better outcomes are related to the use of the care coordinator.

Dr. Shelton: Dr. Trivedi, according to your TMAP article from 2004,[2] I agree that the first quarter is where the majority of change happens, but if you look at the end of a year of treatment, there still is a substantial difference between the TAU and the algorithm treatment patients. TAU patients did not catch up by the end of a year (see Figure 1), but the differences that are achieved are achieved primarily up front and then maintained throughout the year.

Dr. Marangell: The data are fairly consistent in showing that algorithms result in not just better response rates, but improved patient satisfaction as well. Katon et al.[3] found that response rates were 74% with the algorithm versus 44% with TAU and that patients who received algorithm-driven treatment were more likely than patients who received TAU to rate their quality of care as good or excellent (93% vs. 75%).

Dr. Fava: If you ask me whether there is a need for treatment algorithms in depression, I would say absolutely, but I question if we truly

Figure 1. Mean Scores on the Inventory of Depressive Symptomatology–Clinician-Rated Scale (IDS-C) During 12 Months of Algorithm-Guided Treatment or Treatment as Usual[a]



[a]Reprinted with permission from Trivedi et al.[2]
*p = .002.

know what algorithms should look like. We often have to base these algorithms on consensus, expert opinion, or anecdotal impressions rather than scientific evidence, because evidence is lacking in many areas of depression treatment. In addition, the algorithms currently in use have never been tested against each other. One of the problems with most algorithms is their emphasis on monotherapy. Such an emphasis does not reflect clinical practice, where polypharmacy is often used from the start to enhance chances of remission. In my mind, these algorithms that emphasize monotherapy lack ecological validity.

ALGORITHM TREATMENT OPTIONS

Monotherapy Versus Combination Therapy

Dr. Trivedi: Given Dr. Fava's comments, one outstanding question in our field is when is it appropriate to start using combinations and become more aggressive with pharmacotherapy and/or psychotherapy. How far into an algorithm should that step be? The TMAP algorithm for depression,[2,5] which was developed in the late 1990s, recommends 3 monotherapy steps before turning to combination treatment (Figure 2). Increasingly, clinicians have begun to disagree. Dr. Fava, it sounds like you were making the argument that fewer monotherapy steps should precede combination therapy in a depression algorithm. Should combination therapy be earlier, as a second step or even a first-line treatment?

Dr. Shelton: I agree with Dr. Fava that the evidence for the benefit of multiple sequential monotherapies is limited.

Dr. Marangell: That is a very important point and is separate from whether or not algorithms are useful. Sequential studies, except for projects like the Sequenced Treatment Alternatives to Relieve Depression study (STAR*D),[6,7] and studies to compare combination treatments are rare, and so we have few data to address these questions.

Dr. Trivedi: Even with STAR*D, the design was to start with a selective serotonin reuptake inhibitor (SSRI) and then go to combination and more complicated treatments (Figure 3).[8] The subsequent publications from STAR*D[1,6,7] again highlight the need to be aggressive early on in terms of treatment choices and the use of adequate dose and duration of treatment exposure.

Dr. Marangell: We need to let clinicians know that the recommendation to stick with several rounds of monotherapy, particularly with a single-mechanism agent like an SSRI, is not consensus at this juncture, but the data for our suggestions for more aggressive pharmacotherapy are also limited.

Dr. Fava: It is very difficult for researchers to find support for and conduct studies that compare next-step options like combination treatment, but at the same time, these are the kind of studies that patients and consumers need so that clinicians can have more guidance when making treatment decisions.

Dr. Osser: Absolutely. We can speculate that the TMAP patients did not separate from the TAU patients any further during the last 9 months of the study because they received sequential monotherapy as opposed to combination therapy, but we have no evidence to support that speculation. There are so many options available, for both monotherapy and combination therapy. Quitkin and colleagues[9] recently suggested that the remission rate could be as high as 95% in completers after 3 sequential monotherapies (Figure 4). That would be tough for combination therapy to beat, so I think it is difficult to have a clear sense that moving earlier to combinations would be appropriate.

Dr. Marangell: A 95% remission rate? That is very high.

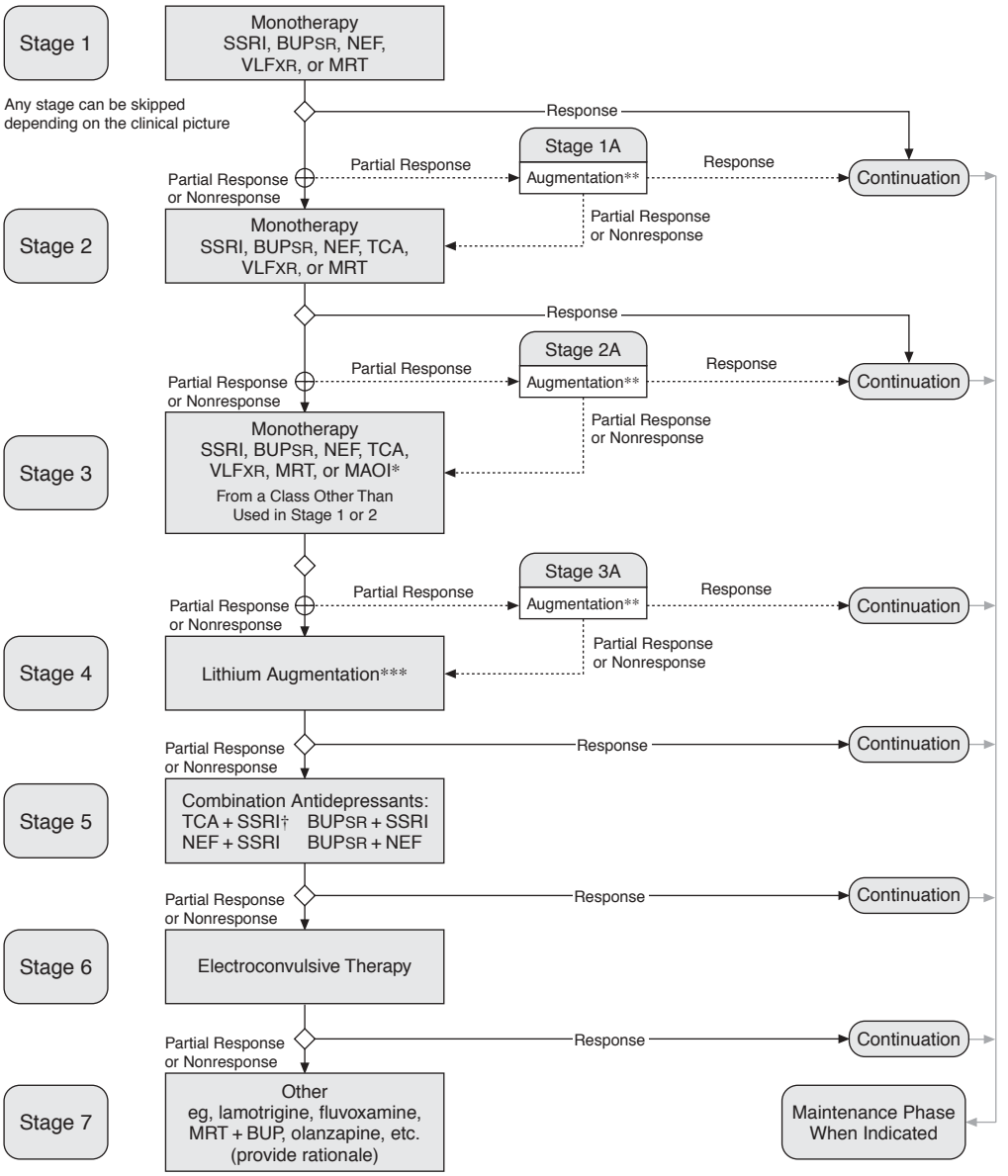
Dr. Osser: It was not a controlled study; they examined data from 3 studies and extrapolated data from that pooled data set.

Dr. Fava: It is a very high rate and may be explained by considering that if there is a 50% chance of remission after every trial of monotherapy, 3 sequential monotherapy trials would have a high cumulative rate of remission. We have done a similar study[10] that was truly sequential, and we found that the remission rates were about 20%. If you look at real-world populations, the chances of remission are very low after 3 sequential monotherapies.

Dr. Trivedi: The question of combination treatment versus sequential monotherapy would be difficult to investigate with a randomized trial, but the lack of evidence does not imply that combinations are not effective.

If we look at the TMAP results,[2] the rationale that you will continue to have additional benefit over the following

Figure 2. Texas Medication Algorithm Project (TMAP): Strategies for the Treatment of Nonpsychotic Major Depressive Disorder[a]



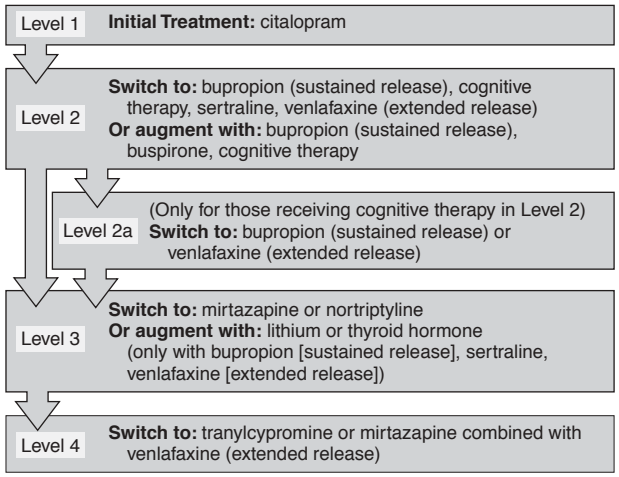
[a]This algorithm is in the public domain and may be found on the Texas Department of State Health Services Web site at http://www.dshs.state.tx.us/mhprograms/timamdd1algo.pdf. For more information, see Trivedi et al.[1] and Crismon et al.[4]
Abbreviations: BUPSR = bupropion sustained release, MAOI = monoamine oxidase inhibitor, MRT = mirtazapine, NEF = nefazodone, SSRI = selective serotonin reuptake inhibitor (includes fluoxetine, sertraline, paroxetine, and citalopram), TCA = tricyclic antidepressant, VLFXR = venlafaxine extended release.
Symbols:* = Consider TCA or VLF if not tried, ** = Augment with lithium, thyroid hormone, or buspirone, *** = Skip if lithium augmentation has already failed, † = Most studied combination.

9 months with algorithm-driven treatment is valid. One might assume that the TAU group would catch up during the year of treatment if the only differences during the first 3 months were the amount of patient contact and support. However, there was no catch-up in TMAP—even at the end of 1 year, patients who had algorithm-driven treatment had a more robust response than the TAU group (see Figure 1). The major benefit from using algorithm-driven treatment was accrued in the first 3 months, and that benefit was never lost compared with treatment as usual.

Dr. Shelton: You would expect that if the treatment during the first 3 months was more effective, you would have a continuing differential rate of change instead of the leveling off that we see in Figure 1.

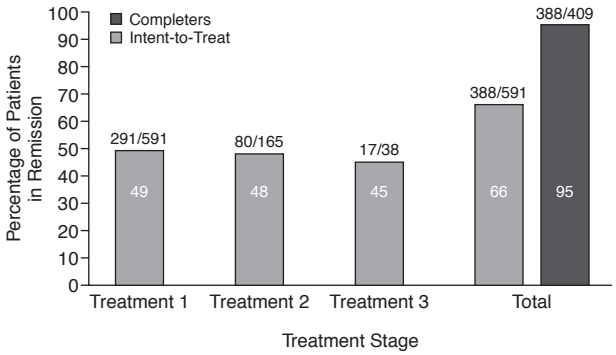
Dr. Trivedi: That is exactly where this question of modifying the algorithm so that it is more aggressive

Figure 3. Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Algorithm[a]



[a]Reprinted with permission from Rush et al.[8]

Figure 4. Proportion of Intent-to-Treat Patients and Completers in Remission[a,b]



[a]Reprinted with permission from Quitkin et al.[9] Sample 1 (N = 171) and Sample 2 (N = 420); combined (N = 591).
[b]For the percentages shown, the numerator is the number in remission for both samples, and the denominator is the number for both samples who received a new treatment during that period. For example, 165 patients (44 + 121) received a second drug and 80 patients (58 + 22) remitted. Therefore, 48% (80/165) remitted with Treatment 2.

comes in—would that difference continue to grow if we use atypical antipsychotics or other combinations earlier in the algorithm? The TMAP results cannot answer that question.

Residual Symptoms and Augmentation Strategies

Dr. Trivedi: If I had to focus on what should be different in a future algorithm, I would start with the questions of whether or not to start combinations earlier, as we just discussed, and then whether or not to identify and engage in targeted treatment of specific residual symptoms—like insomnia, anhedonia, fatigue, and physical symptoms—and if so, with which augmentation strategies? Physicians are often left without clear guidance on how to treat residual symptoms. Does it help to switch antidepressants? Does it help to augment with a different type of agent? Does it help to initially prescribe a treatment that is focused on a common residual symptom? Dr. Fava, you and your group have done a fair amount of work on this topic—would you measure and target specific treatments for specific residual symptoms?

Dr. Fava: The main challenge in my mind is that when it comes to residual symptoms, we rarely really examine residual symptoms in a systematic way. For that reason, there has been a less-than-expected emphasis on the treatment of residual symptoms in algorithms, and we have often settled for incomplete response in clinical practice.

The work of Paykel and coworkers[11] as well as Thase and colleagues,[12] among others, has clearly shown that incomplete response is associated with a poorer treatment outcome and a greater chance of relapse and recurrence. Their results indicate a need for targeting residual symptoms. The 2 DSM-IV symptoms that are most commonly present as residual symptoms in depression are fatigue and sleep disturbances, which certainly suggests the importance of targeting these common residual symptoms.

On the other hand, there are many other symptoms that are not part of the DSM-IV nomenclature and yet greatly affect the well-being of patients and their quality of life. Those symptoms could also be targeted if we were to measure them systematically. An example is the presence of residual cognitive symptoms—memory, attention problems, concentration problems, problems finding words and so forth—which in my experience are common among patients who have responded to antidepressants but still have residual symptoms.

Dr. Shelton: My colleagues and I have identified at least 2 dominant domains of symptoms in depressed patients, the fatigue/anergia symptoms and the anxiety/worry/rumination types of symptoms, and our data with bupropion[13] suggests that bupropion is robustly effective for anergia and not differentially effective from placebo for the anxiety-related symptoms. The problem that exists in pure randomized trials is that if we can identify 2 groups of people—anergic and anxious—after the initial phase of treatment and randomly assign them to one treatment or the other, we would probably get a washout of antidepressant effect, simply because some people in each group are going to respond to one treatment and some people to the other treatment.

Dr. Osser: So if you treat a patient with the "wrong" type of medication for his or her symptoms, it may be

unnecessary to add another agent for those symptoms. Instead, you could merely switch the patient to the alternative medication.

Dr. Shelton: In fact, sometimes we do that, and that is part of the quandary here—do you add on, do you switch, do you dramatically change the mechanism of action? Dr. Fava, your earlier point that the monotherapy approach is not always the most effective adds to the difficulty. In the absence of any method or mechanism for targeting symptoms, just changing to a different medication arbitrarily will probably fail to help the majority of patients.

Dr. Osser: We do have data supporting switching from one antidepressant to another, even within the same class; quite a few people do get better.[14,15] Where is the evidence that you have a better chance of improving people if you add a medication as opposed to switching medication? There have been numerous reviews of that literature, and they conclude that the odds are about the same with those 2 interventions.

Dr. Fava: The sequential data from our group suggest that the chances of remitting with sequential monotherapy are meager.[10] They certainly confirm the impression that many clinicians have that the switch data in the literature involved patients whose level of treatment resistance was not prospectively ascertained, and for that reason it is unclear whether these people were truly resistant or not.

An example is that some of the studies use a historical approach in which the average duration of failed antidepressant trials is approximately 1 year. I find it very hard to believe that a patient would continue in a failed antidepressant trial for 1 year without any augmentation. These may be patients who lost their response and cannot be equated with those to whom Dr. Shelton was alluding, and that suggests, in my mind, that many of the switch studies really involve the switch of relapsers on SSRI treatment to another SSRI, which is a completely different scenario.

A study[16] that my group published recently included combination therapy right off the start with eszopiclone plus fluoxetine versus fluoxetine plus placebo. Monotherapy was associated with significantly fewer remissions and responses than the combination of fluoxetine plus eszopiclone. The Nelson et al. study[17] of monotherapy with desipramine or fluoxetine versus the combination also showed significantly higher remission rates with the combination. I would disagree with the view that monotherapy switches are the best we can offer to our patients.

Dr. Trivedi: Indeed, that is absolutely correct. Another question is, can you benefit from using a dual-mechanism agent at the outset as opposed to a combination of an SSRI and a non-SSRI? I think that is an intriguing question.

Dr. Osser: Dr. Fava, you conducted 2 studies[18,19] in which you augmented fluoxetine with desipramine or lithium or increased the dose of fluoxetine. In both of those studies, the results were relatively unimpressive for the augmentation with lithium.

Dr. Fava: I believe that lithium is not effective as an adjunctive agent in unipolar depression. One reason that it may have worked in earlier studies is because many of the patients may have actually had bipolar depression, not unipolar depression. If you look at the study by Nierenberg and coworkers[20] of lithium augmentation of nortriptyline, you will see little separation from placebo, and all the most recent studies in unipolar depression have not shown a separation between lithium augmentation and placebo.

The question is, what are effective augmentation strategies? If you use them, do you get a "bigger bang for your buck," so to speak? I think we are starting to see evidence of that.

Dr. Osser: We have a long history of believing in certain augmentations, and then over time, the data have failed to support those strategies—lithium is a good example. For years, it was considered our premier augmentation. TCA augmentation of an SSRI was held in very high esteem starting with Nelson's studies,[17,21] but it has now lost favor. We need more time to be convinced that the current crop of favorites for augmentation is more effective than others, or whether some sampling issue or investigator bias is the reason why they seem to be effective in the preliminary data.

Dr. Trivedi: Dr. Shelton, you have a fair amount of experience with the possibility of using atypical antipsychotics for depression. What is the evidence for that strategy?

Dr. Shelton: There are smatterings of data with the atypical antipsychotics in combination with antidepressants.[22] Although the evidence strongly suggests that atypicals are effective, it is by no means definitive, yet the use of atypicals as combination therapy with antidepressants in unipolar patients is apparently common, at least as I have understood recent utilization data.[23] It may be because this particular combination is a new approach or because clinicians are seeing a robust response, but concerns about side effects and long-term adverse outcome may complicate matters. Of course, the costs of these agents can also be prohibitive. Right now, the use of atypicals in depression is probably out of proportion to the level of data that exists in the literature.

Dr. Trivedi: I think that a lot of clinicians are wondering where and how to use atypical antipsychotic agents for the treatment of depression and at what dosages. The recently published results from STAR*D[1,6,7] also highlight the need to consider alternative options for treatment-resistant depression.

Dr. Shelton: As I understand the utilization data, the vast majority of the growth in atypical use over the last several years has been in mood disorders, including nonpsychotic unipolar depression. I am often asked about the

appropriate use of these medications—should they be second-line, should they be third-line, and so on. We lack the answers to those questions.

We may also encounter barriers in trying to gather reliable data on this issue. Studies of augmentation in depression often use a core group of unresponsive patients that are quite unlikely to respond to any medication, and studies with this design may give the appearance that the treatment under investigation is not very effective. In fact, all that is true is that the medication was used as a last resort in patients who may not respond to anything—some studies with the monoamine oxidase inhibitors, for example, have this limitation.

Physical and Somatic Treatments

Dr. Trivedi: Let us turn to the role of somatic treatments, such as electroconvulsive therapy (ECT), vagal nerve stimulation (VNS), and repetitive transcranial magnetic stimulation (rTMS).

Dr. Marangell: rTMS is currently investigational in the United States. More than 60 published trials exist, but most were inadequate in terms of dose, duration, and sample size. Well-designed, adequate-duration trials are currently ongoing. The best-case scenario, if those studies are positive, would be for the rTMS data to go to the U.S. Food and Drug Administration (FDA) for approval in 2006 and for rTMS to become a viable clinical treatment soon after. I see rTMS as an acute treatment. The problem with rTMS is that patients have to go to the clinic every day to have the treatment administered there. For a lot of people, though, the idea of magnetic treatment as opposed to medication or an implanted device is appealing. There is still some work to be done to determine whether it would be a feasible long-term treatment. rTMS is similar to ECT in that ECT remains a highly effective acute treatment, but I would argue that it leaves quite a bit to be desired as a long-term treatment.

VNS is now approved by the FDA for use in adults with chronic and recurrent depression. I see VNS as fitting in very differently than rTMS or ECT. The FDA indication for VNS is 4 failed but adequate antidepressant trials during the patient's lifetime. Since VNS uses an implanted device and the data suggest that the response is seen over a longer period of time, I do not see it as competing with other treatments for an acute-treatment position on a depression treatment algorithm. It would perhaps be more appropriate to include a place in an algorithm for VNS for long-term disease modification.

In the VNS study,[24] which included a cohort of highly treatment-resistant patients, 46% of patients responded and 29% were in remission after 1 year of VNS treatment. However, if I had a patient who had been ill for less than 1 year with a first episode of depression and who did not respond to monotherapy, I doubt that I would use an implantable device in that person. However, if I had a patient who clearly had chronic and recurrent disease such that they were likely to need lifetime interventions to treat and prevent episodes, I would consider VNS.

The question, then, is where VNS would fit into an algorithm. It certainly is not a first-line option, but I would argue that it should not be at the bottom of the list, either.

Dr. Trivedi: Although we have the FDA indication which states that the patient should have failed 4 antidepressant trials before becoming a candidate for VNS, in terms of this discussion, it is important to ask if it is likely that VNS deserves consideration as an earlier option for the kind of patient you just described—the patient with a recurrent, chronic, severe course for whom depression is likely a long-term illness?

Dr. Marangell: I think so. It is also important to keep in mind that VNS is usually used in combination with pharmacotherapy, not as a monotherapy. If you consider the chronic and recurrent patient who has already failed 4 antidepressant trials, you may ask whether you should try to get a response with medication while preparing the patient for VNS. Absolutely. Some people also see the question as whether you should choose ECT or VNS, but to me, those are not mutually exclusive. I see ECT as appropriate for the emergent, acute situation, and you could even implant the VNS device in patients immediately after ECT, with the idea that VNS may not work acutely, but it might help keep someone well and modify the disease course over the long run.

Dr. Shelton: To counter the problem with early relapse following ECT, one could consider the possibility of first implanting the VNS device, doing ECT, and then starting VNS treatment immediately following the ECT course. There is a delay inherent in using VNS—you have to schedule surgery for the implantation and then give the patient time to heal before you can begin the therapy. For patients who have had ECT just prior to this process, this delay may give them enough time to relapse, which would bring you back to square one. If the VNS device is in place from the beginning and then turned on immediately after the course of ECT, it might facilitate the long-term maintenance of response. All of this is speculative, of course, because we simply do not know how feasible this course of action would be, but I think it is worth consideration.

CLINICAL RECOMMENDATIONS AND FACTORS AFFECTING ALGORITHM IMPLEMENTATION

Dr. Trivedi: Until we have the kind of evidence needed to answer some of the questions we have raised today, what clinical recommendations can we make?

Dr. Shelton: The tension between the approaches we have discussed reveals a flaw in our field now, and it explains why so much variation exists in the clinical setting. We have these 2 main strategies for treating depression—

sequential monotherapy versus augmentation and combination therapies—and unfortunately, insufficient data exist for us to make a definitive conclusion regarding which strategy is more effective. We have supporting data for each.

Dr. Marangell: We always have to consider the pros and cons of each approach dependent on the clinical situation and patient preference. For a patient who started with severe symptoms and is now partially better, many clinicians may see more of an advantage in augmentation as opposed to switching. In a patient with mild depression who is a little skittish about medication and who does not want to take more than one medication, a monotherapy switch may be more attractive. Beyond the science, the clinical factors must be taken into account.

Dr. Trivedi: It is beginning to be clear that depression is very difficult to treat and that true remission rates—notwithstanding some of the open-label trials—in clinical practice are very low, and so we eventually have to think about more complicated treatments and their place—if not as first, second, or third steps—in a treatment algorithm. Moreover, a well-described measurement-based approach that relies on carefully characterized critical decision points that guide clinicians is absolutely crucial.

Dr. Shelton: When we talk about the treatment of depression, we are including at least 2 things—acute response and maintenance of response. When compared with placebo response, the maintenance effect is probably substantially more robust than the acute treatment effect. In a study that my colleagues and I[25] conducted, we took patients after 16 weeks of treatment and randomly assigned them to continuation treatment or placebo. The difference in relapse rates was noticeable, so there is a great deal of difference in what happens to patients under those circumstances.

Dr. Osser: I would like to propose a treatment sequence for augmentations. We have a wide array of possible augmentations with some positive evidence, including the atypical antipsychotics, and a huge disparity in the cost of these options. Atypical antipsychotics cost about 3 times as much as brand-name antidepressants and far more than inexpensive generic medications. One way to sequence these augmentations, if we go by the parity of evidence regarding efficacy, is to start with the least costly, which would put the atypicals toward the end of the list.

Dr. Fava: Lithium would be a fairly inexpensive augmentation, but I would still not recommend it. I would be in favor of looking at all the evidence to see where there is a signal of efficacy. That would be preferable than using cost, because basing decisions solely on cost can lead you to medications that may not be the most effective.

Dr. Osser: Cost, side effect burden, and efficacy should all be taken into consideration. I agree with you about lithium; however, if things seem apparently equal, for example, augmentation with an SSRI or mirtazapine, which are available as generic drugs, compared with an atypical antipsychotic, then cost might be a deciding factor.

Dr. Shelton: You also have bupropion and buspirone and desipramine available as generics. Many medications that have at least some evidence supporting their effectiveness are generic. Most patients would of course prefer an inexpensive drug in the absence of any preferential effect.

Dr. Marangell: Overall, I think there really is a place for algorithms, and one of the keys from a clinician's standpoint is making sure that the algorithms are dynamic and flexible, both in terms of being able to accommodate new data as they come out, but also in terms of accommodating clinician judgment and patient preference.

Drug names: bupropion (Wellbutrin and others), buspirone (BuSpar and others), citalopram (Celexa and others), desipramine (Norpramin and others), eszopiclone (Lunesta), fluoxetine (Prozac and others), lamotrigine (Lamictal), lithium (Eskalith, Lithobid, and others), mirtazapine (Remeron and others), nortriptyline (Aventyl, Pamelor, and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), tranylcypromine (Parnate and others), venlafaxine (Effexor).

Disclosure of off-label usage: The chair has determined that, to the best of his knowledge, eszopiclone, lithium, olanzapine, and fluvoxamine are not approved by the U.S. Food and Drug Administration for the treatment of depression. If you have questions, contact the medical affairs department of the manufacturer for the most recent prescribing information.

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