In2MedEd
Strategies for Achieving Remission of Major Depressive Disorder
Thursday, October 20, 2011
12:00 pm- 1:30 pm

Faculty:
Barbara Jones Warren, PhD, RN, CNS-BC, PMH
Professor, Clinical Nursing
Ohio State University College of Nursing
Columbus, OH

Madhukar H. Trivedi, MD
Betty Jo Hay Distinguished Chair in Mental Health
Professor of Psychiatry
University of Texas Southwestern Medical Center
Dallas, TX

Denise Vanacore, PhD, CRNP, ANP-BC, PMHNP
Associate Professor of Nursing
Coordinator, Nurse Practitioner Program
Gwynedd Mercy College
Gwynedd Valley, PA
Adult and Psychiatric Nurse Practitioner
Lansdale, PA
Dr. Warren:

Good afternoon again. I'm Barbara Jones Warren. I'm very glad to see all of you here. I understand we have over 1,200 registrants at this conference, and it's really a great exciting time. I do want to welcome you to today's luncheon symposium that's going to focus on strategies for achieving remission of major depressive disorder.
Strategies for Achieving Remission of Major Depressive Disorder

This educational activity has been provided by Continuing Education Provider Unit, Boston University School of Medicine and co-provided by In2MedEd

This activity is supported by an unrestricted educational grant from Otsuka America Pharmaceutical, Inc.
You'll notice that one of the things that is also in the packet of information is the faculty disclosures.

Those are in the [informational packet]. You have a copy of those.
Diagnosis of Major Depressive Disorder

Symptoms: Major depressive disorder occurs if most of the following symptoms are present: a depressed mood most of the day, irritability, loss of interest or pleasure, diminished energy or fatigue, changes in appetite, sleep disturbances, difficulty concentrating, and thoughts of death or suicide.

Factors: Genetic, psychological, and environmental factors can contribute to the development of depression.

Handout included in the appendix of the activity resource download
HANDOUT – Pharmacologic Treatment of Major Depressive Disorder

Pharmacologic Treatment of Major Depressive Disorder

Major depressive disorder (MDD) is the most common form of depression. It is characterized by a persistent feeling of sadness or loss of interest in activities previously enjoyed. MDD affects approximately 17% of adults in the United States, according to the National Institute of Mental Health. The disorder can last for days, weeks, months, or years and can be lifelong in some cases.

ACUTE PHASE TREATMENT

Antidepressants are the mainstay of treatment for MDD. They work by altering the balance of chemicals in the brain that affect mood. The most commonly used antidepressants are:

- Selective serotonin reuptake inhibitors (SSRIs)
- Serotonin-norepinephrine reuptake inhibitors (SNRIs)
- Monoamine oxidase inhibitors (MAOIs)
- Tricyclic antidepressants (TCAs)
- Atypical antidepressants

Other treatments that may be used in combination with antidepressants include:

- Psychotherapy
- Physical therapy
- Nutritional therapy
- Brain stimulation therapy
- TAU therapy

MONITORING AND MANAGEMENT

Antidepressants can take several weeks to begin working. It is important to continue taking the medication even if symptoms improve. It is also important to continue taking the medication for several months after symptoms have improved, as relapses can occur if treatment is stopped too soon.

ADVERSE EFFECTS OF ANTIDEPRESSANTS

Antidepressants can have several side effects, including:

- Nausea
- Weight gain
- Insomnia
- Sexual dysfunction
- Tachycardia
- Diarrhea

It is important to report any side effects to a healthcare provider. In cases of severe side effects, the dose of the antidepressant may need to be adjusted or a different medication may be prescribed.

REFERENCES

Some other things that are in your packet of information, I believe it is on your left-hand side, there are some handouts that we think will be available, will be helpful for you in your practices, and in your work settings that talk about treatment issues, talk about the DSM [Diagnostic and Statistical Manual of Mental Disorders]. Also, there’s one sheet in there that really is aimed for patients and kind of helps patients to understand some of the things they can anticipate, how to get the best results from your depression treatment. So that is there. You can take those and photocopy those and use them as you need to.*

*See appendix for full size handouts
Let's begin,

Most of us are all very familiar with the *DSM* and that five of these following symptoms are required during the same 2-week time. At least one must either be the depressed mood or the loss of interest or pleasure. You also have the significant changes in appetite and weight, too much/too little; sleep, too much/ too little; psychomotor kind of agitation or retardation, those kinds of things; fatigue or loss of energy.
Feelings of worthlessness or hopelessness, inappropriate kind of guilt feelings; this whole thing with concentration issues and problems; and, of course, the recurrent thoughts of death or recurrent suicidal ideation without any specific plan or suicide attempt or specific plan for committing suicide.
In addition, these symptoms really have to be clinically significant distress. They have to cause that; we all know that. Impairment in the social, the occupational, or other important areas of functioning. They cannot be related to a clear medical diagnosis or condition. Cannot be due to the direct physiological effects of a substance or general medical condition. Cannot be better accounted for by bereavement and cannot meet criteria for a mixed episode.

The prevalence of major depressive disorder, and I think this is of extreme importance to all of us in this room, the 12-month prevalence rate is really 6.7%, and 30.4% of these cases are classified as severe. One in 6 Americans will suffer from MDD at some point in their lifetimes. Women are 70% more likely than men, and non-Hispanic whites 60% more likely than non-Hispanic blacks, to experience depression during their lifetimes.

It’s really the second leading cause of role disability in the US—I think we’re all aware of that—followed by back and neck pain, which most of us have had at some point in our lives probably, arthritis, specific phobias and stroke.
So we have another question for you now: How many patients achieve remission of major depressive disorder with an initial antidepressant?

1. Three quarters
2. One half
3. One third
4. Not sure
There we go, 59% of you said one third, and that is the answer.
Here’s the undertreatment of major depressive disorder prevalence, and this is just an interesting way to present the stats. I think it’s a nice slide to look at. You’ll see that all patients who are treated or untreated, only 52% of people actually receive treatment, and then more startling is really that 38% receive minimally adequate treatment. When patients are treated with the initial antidepressant, only one third achieve remission with that initial antidepressant.
In 1 study, only 49% of individuals with major depressive disorder treated by psychiatrists received an adequate dose of antidepressant medication for greater than 90 days. Only 57% of patients had ≥3 follow-up visits in 90 days. Patients receiving inadequate pharmacotherapy were also less likely to have follow-up visits. Finally, the investigators thereby determined that patients receiving inadequate pharmacotherapy were “largely invisible in everyday practice.”
Psychiatric mental health nurses—that's all of us that are sitting in here for the most part—are more conservative than psychiatrists in the application of management strategies for patients with difficult-to-treat major depressive disorder. We're more likely to prolong therapy with an initial antidepressant in an attempt to achieve response before switching the patient to another agent.

Really significant are the increased rates of hospitalization and outpatient office visits. Annual cost of therapy are 2 to 6 times higher for patients with incomplete responses versus those who respond to treatment.

So the impact of undertreated major depressive disorder is really functional impairment, multiple comorbidities, increased risk of suicide, and a diminished work performance. These are all things that we’re dealing with probably on an everyday basis in practices.
Factors contributing then to the lack of remission of MDD with acute treatment are really undertreatment, which is one of the biggest things, with ineffectiveness of treatment and inadequate doses or the duration of treatment, safety and tolerability issues, comorbidities, and poor adherence.

A lack of remission of major depressive disorder with acute treatment, the consequences for that are, of course, a significantly higher risk of relapse, psychosocial disability, 3-times-faster time to relapse into major depressive episodes, and more chronic future course.
So, the reemergence of major depressive symptoms in patients achieving remission, really the reemergence of symptoms occurs in about 40% of patients. Recurrence is chronic, requiring long-term treatment as evidenced in about 50% of patients within 5 years. So factors that contribute to our patients having this return of the symptoms include loss of efficacy of antidepressants over time, poor adherence to those antidepressants, life-altering events, and concomitant medical disorders that happen.

So, here’s how we really can look at this. Compared to our psychiatrist colleagues, we’ve been shown to spend a little bit more time with patients during visits for medication management and have a greater focus on health education, and it really points to the opportunities that we have in order to be able to work with our colleagues and to work with our patients to be able to help them get better.
Knowledge and skills in implementation really of these APA [American Psychiatric Association] guidelines and patient education is important. Strategies aimed at reinforcing close adherence to therapeutic plan.
And can we please welcome Dr. Trivedi.

Dr: Madhukar H. Trivedi, MD:

Thank you very much. I'm very excited to be here. I think that I’ll rapidly go through the slides, but I wanted to make one important point. Over the last 10, 15 years with the treatment of depression, it has now become very clear that it is not a short-lived episodic illness in most patients, and therefore, 2 things are very clear. One is, it's a much more difficult disease to treat than we used to think. It used to be, and that is actually the big push since the SSRIs [selective serotonin re-uptake inhibitors] came on board, the move of treatment of depression into primary care was unfortunately associated with the assumption that it’s easy, but it is very clear it's not, as you already saw data showing that there are many people who don’t do well on the antidepressant, at least the first or the second. And the second issue, which I think should be appealing to all of you and that is we have now begun to realize clearly that this is like any other chronic medical disease. It is not going to be enough to just give a medication or just give “depression-focused” psychotherapy. Patient engagement in the treatment, continuous monitoring, and getting full-scale awareness of the chronic nature of the illness for both us as treaters and for patients is going to be essential if we’re going to make any change in the kind of data you saw where only a third of the patients or 40% of patients even barely get adequate treatment. I think that is going to have to change
When we talk about depression, most of us actually remember that there are ultimately 3 phases as with any other chronic medical disease. There is an acute phase where the immediate goal obviously is symptom resolution and getting patients back to where they were, but that's not enough if it is a chronic disease, so, therefore, continuation of treatment so that you prevent these symptoms from returning. And, more importantly for a large proportion of patients where they have a long-term illness, you have to think about maintenance treatment where the goal is to prevent another episode or a recurrence from happening. And there are many individual issues with it. Hopefully we'll get a chance to discuss that.
In terms of management for depression treatment, our avenues for treatment are actually expanding. We have obviously 20-25 antidepressant medications available in the United States at least currently, and there are many more being studied. Hopefully, we'll get more medications as we go along. A very quick point about that, people wonder why, if we have already 20 medications, why do we need 1 more? I always tend to remind them that even with something that we have studied for 50-60 years like hypertension, we're still wanting to look for new novel antihypertensives, so similar issues are going to happen with antidepressant medications. But then, we also have other treatments, mainly depression-focused psychotherapies, so that is not the long-term psychodynamic psychotherapy but more depression focused.

Psychotherapy is cognitive behavioral therapy, interpersonal psychotherapy, etc. And ECT (electroconvulsive therapy) has always been available. We are now getting more data on that, but there are other treatments like phototherapy, vagus nerve stimulation. There are now recently rapid transcranial magnetic stimulation (rTMS) treatments as well as very exciting data on exercise. In the interest of full disclosure, some of the larger exercise studies for depression actually we have done in Dallas, so I personally have a lot of faith in it but there are peer-reviewed publications you can look it up.
This was already mentioned earlier, but this is sort of a cartoon version of what happens to patients when they are symptomatic. They come to us and we start some form of treatment. Most often, like it or not, it is medications in the United States. And then we follow them over a longer period of time. Obviously, at least in my practice, not more than 1 or 2 patients fit this bill. They have a much more jerky response so that it’s not as straightforward. But the 2 points to keep in mind, 1 is by the time they get to this critical 6- to 12-week period, half of them have already stopped the medication. Again, I think this is mainly because we have not done a good job of explaining to the patient that this is not going to go away and that your stopping this medication is only going to mean that you have to return for treatment. We have to do it in a collaborative manner, but that message, I think, is not well explained.

And then the other issue is this longer-term management. The longer-term management requires even more education and more participation on the part of the patient. And this, unlike many other diseases, unfortunately still maintains a lot of stigma; so therefore, everybody in the patient’s life including their dog feels empowered to tell them, “Oh, just quit this.” And I think that it is our job then to really engage the patient and not let that happen because 60% to 70% of patients starting an antidepressant in the US have been on an antidepressant within the previous 14 to 16 months, clearly suggesting that these patients had started, stopped, and the episodes came back. That has to stop if we are going to make a change in
We have many treatments, and yet only a third of the patients with major depressive disorder actually achieve remission on the first antidepressant. And I don’t care whoever comes and tells you that this antidepressant is better than that, I think there is now convincing evidence in the literature that no one antidepressant is profoundly better than another medication in a group of patients. Remember, for any individual patient obviously there are differences and in fact, the 1 medication that works for that patient is clearly better than anything else. But as a group, any given antidepressant will lead to remission in only a third of the patients. And then what to do with that is the biggest challenge for our field, and therefore, that practice is very variable.

When do you decide to do this, 4 weeks, 8 weeks, 10 weeks, 12 weeks? When we decide to make that change in the treatment strategy is still unclear. Whether you at that point switch to another antidepressant or you augment with a second antidepressant, or psychotherapy, or exercise, or something else is also really very variable. And then the biggest challenge I think, and therefore, again I’m very excited to be here as opposed to another medical meeting is because the use of standardized instruments to try to monitor this has not become a routine part of practice. Anybody treating diabetes no more treats patient with diabetes without getting hemoglobin A1c’s, but we somehow are capable of
So this is I think if you can leave today with 1 message, then I would say that use measurements and use them every time. The most uncomfortable question I get asked when somebody, when I’m talking about this, as you can see I have had this Kool-Aid about measurements, so I talk about it a lot. But they ask, how often should I do this? And I tell them, every time you are not sure that the patient is better, worse, or not is when you should do it, which means every time you see the patient.

So the options are augmentation, switching, or combinations. And that is not the topic of the discussion, so I’m not going to focus too much on it except to say that the advantage of an augmentation often is that you’re adding another treatment and allowing the first one to have more time. The cost of that is obviously in terms of adverse events, drug-drug interactions, and the cost of the treatment itself as in cost of the pill.
The APA Guidelines were originally, or one of the versions was done in 2000, and then recently in 2010 were updated, and the few things that happened between that time are that the whole idea of suicidal ideation and behavior monitoring has become front and center for all our treatments, and in fact for a lot of medications that work on the nervous system and in fact those that don’t. There’s a lot of interest in monitoring that. The second is obviously all of you, at least a lot of people, are aware of the STAR*D [Sequenced Treatment Alternatives to Relieve Depression] trial. This was, and I’ll describe the results in a second, this was a large-enough trial that it ranks as the largest trial done in the clinical [setting] for the treatment of depression in the United States and in fact outside, also. There have been other major clinical trials obviously during that time, and there has been expansion and understanding of psychotherapy, new medications have come along. And there is, in fact, a lot of interest now in complementary and alternative treatments also.
So this was the STAR*D trial. The basic question in this one, what we were asking was, as I mentioned earlier, the first treatment is clearly important and we have to make important decisions about which one to use, but the biggest challenge for us is what do you do after the first one doesn’t work? And so STAR*D was designed to answer that question after this first treatment being citalopram, as in do you switch to 1 of these many treatments? Do you augment with 1 of these 3? And if that doesn’t work, do you then go to another, switch to a mirtazapine, nortriptyline, or an augmentation with lithium or thyroid? And if that doesn’t work, do you go to the fourth treatment step with an MAOI [monoamine oxidase inhibitor] or a combination of venlafaxine plus mirtazapine? The options in this were, at that time this was done, started in 1999, these options were so to speak the state-of-the-art options available at that time. It actually doesn’t so much matter which particular option we’re talking about because the idea was to design a study that looked at the principles of this, so that after the first 1 doesn’t work, which is an SSRI, if you switch to another SSRI [like] sertraline or a dual-mechanism agent [like] venlafaxine-XR or bupropion, or cognitive therapy, which one is better? Those were the kinds of questions we were asking.
In short, what we found is the first treatments led to remission rates of about 30% on the first treatment, and then after the first one, if patients went to a second step and had an augmentation, then the remission rates were about 30, similar remission rates, a little lower if they were switched to a second single antidepressant. There was a slight difference in who went into augmentation versus switch. Those who were a little better or at least were able to tolerate citalopram ended up in augmentation. So with the head-to-head comparison one has to be careful and not automatically assume that augmentation is better. Augmentation is indeed better for somebody who is tolerating the first one and maybe even is a little better than they were when they started. Otherwise, in general, augmentation overall does seem to have a little better benefit than if you switch over to a second or a third or a fourth antidepressant.

The big problem was and is, remains, remember that this group of patients when they went to the third step or the fourth step, they have been in treatment. Each step was 12 weeks, so by the time they were here, it was already 24 weeks, 6 months. Some of us can't stay on the same project for 6 months, right? And then by the time patients ended up here, they had been in treatment for 36 weeks approximately. That is why, actually, the impact of STAR*D has been so widespread. This kind of study has not been done. It's actually a fairly difficult study to do. I used to look much younger when we started.
So the big challenge for our field is the following. So, let’s assume that going from step to step produces good outcomes. I think a bigger challenge, which today we won’t settle, but, is that if patients take 2, 3, 4 steps to get better, those patients, even after they get into full remission at the end of third step or fourth step, the vast majority of them actually relapse. So this is clearly showing that this is a difficult disease to treat.
So let me shift focus to 1 more thing and then we'll talk about the measurement and the guideline issue. In the early ‘90s, we actually did another study which was to look at the question of, if you had a treatment algorithm and you went into public sector psychiatry settings and half the physicians used the algorithm plus measurements and the other half used only the algorithm, does that make a difference? And this is the result from that study showing that those patients who were on the algorithm plus measurement, those patients had a significant improvement compared to those who were being treated in the usual-care manner.

And remember, the usual-care treatment was not bad. These were treatments being done in public sector by qualified clinicians. So patients were getting better, but the improvement level in this study arm was clearly significantly better than the usual-care arm. So these two studies, actually in my mind, emphasize the importance of measurements as you go along in the treatment of depression.
So the new guidelines that were just published last year from the APA—you can read it online—but the 4 important things in my view for us in terms of clinical practice that are really emphasized is that, switching or augmentation after an inadequate response to an optimized initial antidepressant trial is very strongly emphasized, mainly because the more rapidly you get patients into remission the better the long-term outcomes, as you saw with STAR*D. The more time it takes to get to remission, the higher the relapse rates. So this would mean that you have to make these decisions quickly in the first 3 to 6 months and not wait too long. The second issue is that in the meantime atypical antipsychotics have been approved for use in the United States, and so that was added as an option for augmentation for people who are not doing well on a monotherapy with an antidepressant.

Some novel treatments were also included in the guidelines. One was the rapid transmagnetic stimulation. Any of you involved with any groups that do rTMS)? So rTMS treatment is gaining ground; although, there are still reimbursement issues that people are struggling with, but I think that it is a nonpharmacological treatment where you put a magnet and you do basically rapid magnetic stimulation that does not lead to seizures like ECT does and has been shown to be effective. And the biggest piece is that it emphasized the use of measurement-based care for unresolved symptoms. That would help us guide our treatment strategies if the patient is not doing well.
So the new guidelines basically also in the process have emphasized the psychiatric management, the disease management, including patients in decision-making, and really also focused a lot of attention on strategies to address inadequate response because there’s now a lot of data showing that patients, when they start on an antidepressant, they drop out. That’s 1 problem and we have to do something.

The other big problem is they start on an antidepressant and the same antidepressant continues for a long period of time without apparent benefit. So the strategy of making changes in the treatment sort of plan doesn’t happen. So patients get on an SSRI and stay on it for 12 months and they are still symptomatic. That needs to change, and that’s the big focus of the new guidelines.
So the guidelines, obviously, like all other evidence-based approaches, used levels of evidence to decipher what should be the recommendation. So level 1 is obviously that there are very well-designed multiple randomized controlled trials you recommend with significant confidence; and then if there are some clinical trials with good evidence but some other trials not showing the same benefit, there is moderate certainty; and then there may be places where we have some evidence from open-label trials where we can't be so certain, is the least certain recommendation from guidelines.
There is a question now, and I get to play music or stand by.

Do you use standardized ratings of severity and adverse events during treatment of depression?

And the options you have for the clicker are:

1. Sometimes
2. Only at baseline
3. Only when current treatment does not work
4. At every clinical visit
5. Never
So 4. So, I have already done my task. I can leave. Or maybe I can work with those who said they never do it. So this is a good recommendation.

Again, in the interest of disclosure, I was a member of the panel writing the guidelines for the American Psychiatric Association.
New: Use of Rating Scales

- Tailoring treatment plan to match the needs of the particular patient requires a careful and systematic assessment of the type, frequency, and magnitude of psychiatric symptoms as well as ongoing determination of the therapeutic benefits and side effects of treatment [I]

- Such assessments can be facilitated by integrating clinician- and/or patient-administered rating scale measurements into initial and ongoing evaluation [II]

- New Rating Scales: Quick Inventory of Depressive Symptomatology (QIDS-C16) and Psychiatric Diagnostic Screening Questionnaire (PDSQ)


The rating scales, really, the one main issue is that it would, it does, help tailor treatment plan to match with the needs of the particular patient, and it requires systematic and careful assessment that includes type of symptoms, frequency of symptoms, and the magnitude of psychiatric symptoms as an ongoing determination of the benefits. And the reason I find this so helpful is that if you think about it, when a patient comes in, the normal clinical interview or interaction follows something like this: the clinician asks the patient, "How are you? How have you been doing?" And what I find most puzzling in my mind when I do it is that the patient often gives me a very long, convoluted, expansive history of what happened in the elevator when they came because they ran into somebody. We forget about all the important things that were target symptoms that the patient struggles with all the time between the times we see them; whereas, with an itemized rating scale that the patient often fills out before you see them makes them actually think through this much better. And I think that if any of you have not used it, if you use it in 10 patients over 3 months, I can tell you that you will actually never see a patient without doing that.

These will obviously, can sort of facilitate integrating clinician and patient-administered ratings. There are many rating scales. I have been very seriously engaged with development and psychometric development of the Quick Inventory of Depressive Symptoms that you see here, but I am of the opinion that actually it doesn’t matter which rating scale, with some nuances some are better than others. But
actually matter. So if you’re using a PHQ-9 [Patient Health Questionnaire], if you’re using a Beck Depression Inventory, there are many such available, but think about using it so that it helps you ultimately focus on this issue of type, frequency, and magnitude of symptoms so that you can monitor them over a longer period of time because otherwise what happens is.... I started my career doing chart reviews for a cost-effectiveness study, and you see things like, “Patient better, decrease dose,” “Patient worsening, continue dose,” and you have no idea what the rationale was. Whereas, and I don’t know about you, but if I go back in time 3 months, 6 months back in my patient charts, I can’t really exactly remember all of my reasoning for the decision; whereas, if there are numbers, then it makes it easier.

So the other thing, obviously, is the issue of suicide monitoring, and we have to do a careful and ongoing evaluation. There are many components of it, and ultimately some of it depends on the individual patient’s presentation, but we have to think about thoughts, plans, intent, means, and behaviors. We have to think about other psych symptoms and general medical conditions that may increase the risk. Assessment of past and recent suicidal behavior clearly is important because it is 1 of the biggest predictors of future behavior. Delineation of stressors helps out because that is 1 way of reducing suicidal risk, and then reviewing family history. They are all important as you assess suicidality.
I already mentioned about exercise, so I’m going to skip it. If you are interested, we’ll do it at the question-and-answer session. One key issue with exercise, if you do use it as an adjunct, as a treatment for depression, you want to give the patient real recommendations about the quantity as in the dose of the exercise. Think of exercise as any other pharmaco therapy you’re using. If it’s too low, it’s not going to work. When I started doing these studies about 12 years back—we’ve done now a series of these—I remember sitting in my office, and my office looks out over a walkway over which has a bus, sort of a tram kind of thing in our medical school, and one of the employees of the university I was seeing and says, “Oh, you’re doing an exercise study. It’s so wonderful.” And I said, “Yes.” And he says, “I exercise every day.” I said, “I see you walking every day. That’s not the exercise I’m studying.” So you have to have some rigor in the exercise for it to work, and that's something you have to try to keep in mind.

New: Promote Exercise (and Other Healthy Behaviors)

- RCTs demonstrate at least a modest improvement in mood symptoms for patients who engage in aerobic exercise or resistance training
- Regular exercise may also reduce the prevalence of depressive symptoms in the general population, with specific benefit found in older adults and individuals with co-occurring medical problems

RCT, randomized controlled trial.
The depression-focused psychotherapy, as I mentioned, cognitive-behavior therapy and interpersonal psychotherapy, behavioral activation—the kind that Neil Jacobson from Seattle developed—are all very useful and have very good, strong evidence for efficacy.

There was some discussion in the guideline development process about psychodynamic psychotherapy, but even that, the final version of the guidelines includes the psychodynamic psychotherapy as a treatment option, but you want to still make it depression-focused in order for it to be of most use.
So this is where I just talked about the discussion about psychodynamic psychotherapy. Obviously, the question of when to use psychotherapy alone, when to use it as a combination with medications, when to use it as a second-step single agent, are the kinds of things that hopefully we'll get into in discussions.
The new antidepressant agents that were discussed that are now included in the new guidelines are escitalopram, that was approved after the last guidelines were developed in 2000; duloxetine, the combination of fluoxetine and olanzapine is also approved, as you all know; reboxetine is a norepinephrine reuptake inhibitor, and those people who work in the northern part of the US may have occasion where they deal with it because it is approved in Canada, but it is also clearly used in Europe a lot. And then desvenlafaxine was approved over the last several years. In fact, there is another new 1 called vilazodone that's been approved recently that's not in the guidelines because it was approved after the guidelines were released.
The maintenance treatment part I just mentioned earlier. The recommendations are stronger because of the renewed awareness now that a large proportion of patients have a long-term illness which requires maintenance-phase treatment because if you stop even after 1 year, symptoms could return; and so therefore, these patients may end up needing maintenance phase treatment indefinitely.

I think I don’t start the discussion about need for indefinite treatment with patients until I got to a later point because of 2 things. One is, I don’t know if that is indeed true for this patient because the course of the outcome during the acute and continuation phase helps me determine that, and the second is, otherwise patients also get discouraged and may quit treatment earlier.
So, the key issue remains the ongoing periodic and making sure you do thorough reevaluation of whatever treatment strategy is started, to start an antidepressant medication. At 4 to 8 weeks you have to reassess whether that treatment is working or not and with medication, for example, you may want to try to optimize that treatment, switch to another one, or augment with a second antidepressant. Same thing with psychotherapy, you may want to add or change to a medication at the end of 4 to 8 weeks if there is no improvement, or if there is absolutely very little improvement by 12 weeks, it seems a good time to start thinking about a next step.
So finally, I think the clinical factors to consider when choosing an antidepressant medication include quality and quantity of clinical trial data, and that is something that I think people realize obviously who have followed the guideline literature, but we did a very thorough review of all existing data. Patient symptom profiles is a very important, intriguing question. I don’t think we have enough data on how best to match patients with treatments based on their specific symptom profiles. There are some guidances, for example, for atypical depression—that is, patients who present with reverse vegetative symptoms and have lethargy and atypical symptoms that an MAOI may be better than a tricyclic, or an SSRI may be better than a tricyclic for that group. Anticipated side effects and patient adherence I think are the key issues to educate patients on. Obviously, some of these antidepressants will be associated with side effects. Our task is, I think, that we don’t do a good enough job of educating them. Especially things like sexual dysfunction and weight gain are the kinds of issues that we have to start talking to patients early on and patient preference obviously is clearly the most important. In that algorithm study I showed you, one of the biggest predictors of treatment outcome—that is, at the beginning of treatment if you wanted to find out who was going to do well on those algorithms, the best predictor of that was patients’ perception of benefit. Those patients who thought this treatment approach is going to help me were the ones that did the best.
Dr. Vanacore:

Well first, I would like to thank both Dr. Trivedi and Dr. Warren because they’ve really laid the groundwork for the next piece that I’m going to talk about, which is what do we do when we’ve done all these wonderful strategies and we still don’t have the patient to remission; we still haven’t gotten to that goal?
So, as we look, this is a slide that talks about what is treatment-resistant depression versus what is pseudoresistance? So as we look at treatment resistance, we know that it clearly means that we’ve used all those strategies in the APA guidelines and we’ve encouraged the patient to continue with their psychotherapy and keep taking that medication that they don’t want to take, but they’re still not getting remission of symptoms.
As we look at what is pseudoresistance, we have to really ask ourselves, can we answer yes to these first 4 questions in this slide? So did the patient adhere to treatment? Was the treatment dose optimized for that patient? Was the duration of therapy sufficient? Was it long enough? And was the diagnosis correct and was there a comorbidity that maybe is saying that’s why we didn’t get to success with treatment?
So as we look at which patients can we predict nonresponse in, who can we say we know that this is not going to work well? First we have to look at some of our clinical factors, and they are simple things like chronicity, extremes in age (either the very old at first onset of depressive symptoms or a very young individual at first onset of depressive symptoms), and family history. And we know that family history plays a big part in looking at depression.

The other pieces we want to take a look at are psychiatric comorbidities. Is there a comorbid anxiety disorder that’s there? And maybe what you’ve done is you’ve really gotten to remission with your depression; however, there’s now this underlying anxiety disorder that we haven’t touched and we haven’t started to treat that part.

The other part is comorbid medical illnesses. Every patient that I see always gets a TSH [thyroid stimulating hormone]. The office knows that if patients are coming back for that first set of blood work and a TSH isn’t on there and they don’t do it, boy, they’re going to raise the roof because that is 1 of the biggest things that I see, is making sure that we’ve hit those endocrine disorders including diabetes, thyroid problems, and many others: cardiovascular problems, vitamin deficiencies, I’m really big on screening for vitamin D deficiency and magnesium deficiencies.
Lastly, we really want to look at our depression subtypes because if a patient comes in and maybe they have really melancholy features of their depression and we’ve tried to use a drug that maybe wasn’t the best choice for that particular subtype, we again may get treatment resistance.

So let’s take a look at some of the guidelines. I know that Dr. Trivedi did a great job of going over the APA guidelines, and another piece of this is he mentioned that, well, would you treat a diabetic without checking a hemoglobin A1c? Would you treat a hypertensive without deciding what stage of hypertension they are? We really need to look at staging our patients who have depression. Are they a stage I? Are they a stage II? Have they failed 2 agents? Have they only failed 1 agent? Have we augmented and had failure? Thase and Rush and Souery as well as a few others have several staging guidelines. And so we should be looking at our patients and going, this patient is actually a stage II or a stage III depression patient, and maybe that means that they need to stay on that antidepressant a little bit longer or they need to stay in psychotherapy a little bit longer. So just like we don’t want to leave out that PHQ-9 or those screening tools that we talked about for screening for this, we also want to make sure that we’re staging it when we’re diagnosing it.
The next thing I want to talk about a little bit, and this slide is kind of a summation of what strategies do we want to look at? So the next couple slides will cover some of these topics right here.
First, we want to look at have we successfully evaluated the adequacy of treatment? Is the dosage adequate? Was the duration of therapy adequate? And sometimes in folks who may be treatment-resistant or have a really strong family history, instead of waiting that 6- to 8-week period, sometimes it’s a little helpful to wait to that 12-week period. Sometimes we kind of rush into let’s do something different or let’s switch the dose or let’s switch the agent, and sometimes (I call it) the tincture of time may actually help. And so another 2 weeks on that dose may just be the trick.

One of the things you have to do with dosing, though, is make sure that you’re increasing that dose until you get remission. Most people get symptom reduction and go, “Okay, I’m done,” and we really want to make sure that we’re following through and getting all the way to remission.
All right, well, what do we do when we want to change an antidepressant? Which highway are we going down here? There are a couple of different options. Obviously, we’ve already heard that citalopram is the first place we’re going to start with the STAR*D trial and the APA guidelines, but after we’ve done that, which highway do we want to choose to go down to pick another agent? I’m always a big proponent of going to another SSRI and the reason that I feel that that’s important is because each of the SSRIs, even though they are encompassed in 1 particular group of drugs, has a little bit different pharmacokinetic and brain chemical effect. So trying another SSRI may actually just do the trick for that individual, so I’m always a proponent of trying an in-class switch first. And believe it or not, in-class switches have actually shown in the studies that they could be 50% effective, so if I can do that and make it an easy switch, that’s generally where I like to start. Out-of-class switches are a little bit more difficult. People like to start with your SNRIs [serotonin–norepinephrine reuptake inhibitors], which are your venlafaxine [Effexor] and duloxetine [Cymbalta]. You can also start with bupropion [Wellbutrin] or mirtazapine [Remeron]. A switch to an MAOI causes a lot of difficulty because you’ve really got to wean them off that 1 drug and then you’ve got to start a second drug and start that MAOI.
Our next slide talks a little bit about what are we going to do to augment? And on here we’ve got the initial antidepressant plus either a non-MAOI antidepressant, or adjunctively doing something different like a second-generation antipsychotic, adding lithium, adding thyroid hormone, or adding an anticonvulsant, or even some of the psychostimulants can be used. Modafinil works well, as well.
Some of your nonpharmacologic strategies that we can talk about include adding psychotherapy. We’ve already talked a little bit about electroconvulsive therapy [ECT], and we know from the CORE study that electroconvulsive study (sic) is very, very useful. We’ve talked a little bit about transcranial magnetic stimulation. Dr. Trivedi went over what some of the options are for that and that’s been around for a while. It’s been around since 1987, but we’re really not sure where it fits yet. We don’t kind of have it slotted into a place like we have ECT slotted into those guidelines. Vagal nerve stimulation is another one, and again, that’s been around for a really long time but we haven’t slotted it into a place. And where in our staging model are we going to look at using vagal nerve stimulation as a possible outcome?
So this is my last slide. And I’m a big model person, so I like this idea that we really want to combine our strategies. We want to use that drug strategy. We want to use psychotherapy. We want to use other strategies to make the patient get to remission because our ultimate goal is remission. From a primary care perspective, we don’t expect our hypertensive patients to be less hypertensive. We want to get them to being normotensive. In our depression patients, we really want to look at not getting them less depressed but getting them to remission.
So at this time, what I’m going to do is we’re going to talk a little bit about a couple of case studies, so we have some interactive case studies that we’re going to start. So what I’d like you to do first of all is gather back those clickers that you have so graciously kept through this whole thing. Find the 1 that has the tape. Who’s got the tape? All right. That’s going to be the lead person at your table, and that person is going to be doing the clicking. All right? Push all those others aside.
And we’re going to start out with our first case, which is Anna.

Anna is a true story. She is a 42-year-old woman from my office who had a 5-month history of depressed mood, hopelessness, weight gain, excessive sleeping, and crying at least 5 days per week. So how this started was in the office that I practice in there are several adult nurse practitioners that are in primary care. There’s myself—I’m an adult and psych NP—and we have a clinical nurse specialist who is a psychiatric clinical specialist. So Anna first went in and thought, “I’m just going to go make an appointment,” and she went in to see the clinical nurse specialist, so that’s where she started. The clinical nurse specialist did a PHQ-9, which is our favorite tool in my office. We use it on every patient at every visit. And she had a score of 16.
So what happened was the clinical nurse specialist called the primary NP, the adult NP, in and said, “Please do something.” And so the primary NP started the patient on paroxetine 20 mg, saw the patient back and did a dosage increase. Well, the PHQ score at a month really didn’t make a whole lot of change, all right, so not much happened. The dose was increased to 40 mg. Patient came back after 2 months on the higher dose and still really not making any strides. We still have PHQ score of 14 and she was still seeing the psychotherapist, and so they called me into the room and introduced me to Anna. So I went in and I went to see Anna.
And at that moment we had talked about the fact that she had little improvement in her initial symptoms. She was now complaining of medication side effects. So she was really unhappy with where we were, and she really was showing me that she was trying to keep this chart. She was really trying to monitor her symptoms, but she wasn’t getting a lot of success.
So now we’re going to take a moment and we’re going to do clickers. You’re going to have a few minutes to make a decision on this.

What would you do next for Anna?

1. Continue the paroxetine at 40 mg/d for another month and then reassess
2. Reduce paroxetine dose to 20 mg/d
3. Reduce paroxetine dose to 20 mg/d and add lithium
4. Switch the patient from paroxetine to another SSRI

SSRI, selective serotonin reuptake inhibitor.
And the audience said switch patient from paroxetine to another SSRI.
And what we really did was, we switched the medication from paroxetine to citalopram. We went directly to 40 mg and we saw a moderate decrease in her depressive symptoms after 8 weeks on the citalopram. We saw a good improvement finally on her PHQ-9, and all of those side effects that were occurring while she was on the paroxetine had dissipated. So we were pretty happy with where we were. She was continuing with behavioral therapy. However, remember she still had a few symptoms still going on.
So, pick up those clickers again.

How would you manage Anna’s major depressive disorder symptoms at this point?

1. Continue citalopram 40 mg/d and reassess after 4 to 6 more weeks
2. Switch from citalopram to an SNRI
3. Switch from citalopram to a nonselective MAOI
4. Continue citalopram 40 mg/d and add bupropion
Okay, and the audience said... very good, 93% of you said number 4, we’re going to add bupropion.
And what did we do? We did add bupropion. We added 150 mg to the citalopram. We waited 3 weeks. We increased it to twice a day, and at that moment, 4 weeks later on her next visit she had a dramatic improvement in her PHQ-9. She was functioning back at work. Her relationship at home was good, and she had a significant decrease in her symptoms. So we were really very pleased with where we were.
So we continued her on the citalopram 40, the bupropion 150, and she sustained her improvement.

Case Study: Anna—Continuation-Phase Treatment

- Patient continuing on citalopram 40 mg/d plus bupropion 150 mg bid
- Improvement in MDD symptoms sustained
So let’s think about some of the things that we learned from what we just went through. First of all, adherence in patients is really important, and that’s a really big piece. She was really honest that she was adhering to it. She admitted to the side effects and was really clear that she didn’t want them anymore. Making sure that you’ve optimized your current antidepressant therapy before you decide to switch or add anything is really important. And go back to the drawing board and revise the treatment plan if there’s minimal or no improvement for an adequate period of duration.
Okay, we’ve got a second case to do. Here comes Ben. Ben is a 38-year-old man who has suffered untreated periods of depression since the late teenage years. His symptoms worsened over the last 9 months, but the patient cannot cite a really specific cause as to when this occurred or what occurred with it. He’s not able to perform at work, and he struggles to get up in the morning and get ready to go to the office. He spends much of his time being a couch potato and not wanting to get out of bed. His PHQ-9 was a score of 17.
Case Study: Ben—Acute-Phase Treatment

- Started on fluoxetine (an SSRI) 20 mg/d
- Minimal response at 4 weeks
- Dose increased to 40 mg/d
- PHQ-9 score of 10 after 4 weeks at higher dose
- Complains of drowsiness and sexual side effects

PHQ, Patient Health Questionnaire; SSRI, selective serotonin reuptake inhibitor.

So, where did we start with the acute phase of treatment? We started him on fluoxetine at 20 mg, minimal response after 4 weeks so we increased the dose to 40 mg. PHQ score was improved at 10 after the 4 weeks of the higher dose except for what did we see when we got that higher dose? Some drowsiness and sexual side effects.
All right, so gather up those clickers.

What would you do next?

1. Continue fluoxetine 40 mg/d and reassess after 4 weeks
2. Decrease fluoxetine dosage to 20 mg/d and recommend psychotherapy
3. Switch from fluoxetine to duloxetine (an SNRI)
4. Switch from fluoxetine to mirtazapine (a TeCA)

SNRI, serotonin-norepinephrine reuptake inhibitor; TeCA, tetracyclic antidepressant.

One minute, pick up those clickers and let's go.
And the audience said? Switch from fluoxetine to duloxetine.
And next slide, what did we really do? Well, we switched the fluoxetine to mirtazapine, 15 mg. We had the resolution of those side effects that were so uncomfortable. We had little improvement in the depressive symptoms after 4 weeks, and so we gradually stepped up to 30 mg and then to 45, went up to 45 mg of mirtazapine and referred the patient for some psychotherapy. All right, one last clicker question, here we go.
Case Study: Ben

How would you manage Ben’s MDD symptoms at this point?

1. Continue mirtazapine 45 mg/d and reassess after another 4 weeks
2. Continue mirtazapine 45 mg/d and add venlafaxine 75 mg/d
3. Continue mirtazapine 45 mg/d and add aripiprazole (an atypical antipsychotic) 5 mg/d
4. Discontinue mirtazapine and switch to venlafaxine (an SNRI) 75 mg/d

SNRI, serotonin-norepinephrine reuptake inhibitor.

How would you manage Ben’s MDD symptoms at this point?

1. Continue mirtazapine 45 mg/d and reassess after another 4 weeks
2. Continue mirtazapine 45 mg/d and add venlafaxine 75 mg/d
3. Continue mirtazapine 45 mg/d and add aripiprazole (an atypical antipsychotic) at 5 mg/d
4. Discontinue mirtazapine and switch to venlafaxine (an SNRI) 75 mg/d

One minute to make a decision.
And the audience response said, continue mirtazapine and start aripiprazole. Next slide, please.
We actually did that with a result of improvement in symptoms at 4 weeks.
Case Study: Ben—Continuation-Phase Treatment

- Patient continuing on mirtazapine 45 mg/d plus aripiprazole 5 mg/d
- Patient continuing cognitive-behavioral therapy with psychotherapist
- Improvement in MDD symptoms sustained

So at this point he’s in the continuation phase of treatment, and he continues to do well with reduced symptoms being sustained, and he’s continuing with cognitive therapy.
So let’s look at a few learning points here as well. Again, the importance of assessing the need to increase the dose, switch to another medication or add another medication during acute-phase pharmacotherapy for MDD

- Suboptimal response
- Side effects

- Importance of psychotherapy in conjunction with pharmacotherapy

I’m going to now turn this presentation back to Dr. Warren.

Dr. Warren:
So I thank you so much and I think this has shown to be a great day.

NOTE: Questions provided by the audience during the live session along with the faculty responses have been provided in the Appendix.
### Diagnosis of Major Depressive Disorder

Approximately 1 of every 6 Americans will suffer from major depressive disorder (MDD) at some point in their lives. However, only slightly more than half of all individuals with MDD receive treatment. Achieving the goal of delivering therapy to a greater proportion of MDD patients hinges, to a large degree, on improved recognition of the disorder.

**DSM-IV CRITERIA**

According to the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text rev), a diagnosis of MDD requires that at least 5 of the symptoms listed below be present during the same 2-week period. These symptoms must represent a change from previous functioning. Furthermore, at least 1 of the symptoms must be either depressed mood or loss of interest or pleasure.

- Depressed mood most of the day nearly every day
- Markedly diminished interest or pleasure in all or almost all activities most of the day nearly every day
- Significant changes in appetite or weight when not attempting to change
- Insomnia or hypersomnia nearly every day
- Psychomotor agitation or retardation nearly every day
- Fatigue or loss of energy nearly every day
- Feelings of worthlessness or excessive or inappropriate guilt nearly every day
- Diminished ability to think or concentrate, or indecisiveness, nearly every day
- Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide

In addition, the symptoms:

- Must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
- Cannot be related to a clear medical diagnosis or condition
- Cannot be due to the direct physiological effects of a substance or general medical condition
- Cannot be better accounted for by bereavement
- Cannot meet criteria for a mixed episode

**COMPONENTS OF THE PATIENT ASSESSMENT**

A comprehensive assessment is necessary to determine whether a patient fulfills the diagnostic criteria for MDD. In general, the evaluation should include the following:

- History of the present illness and current symptoms
- Psychiatric history (including identification of previous symptoms of mania, hypomania, or mixed episodes and responses to previous treatments)
- Medical history
- Personal history (including the individual’s psychological development as well as responses to life transitions and major life events)
- Social and occupational history
- Family history (including mood disorders and suicide)
- Past and current use of illicit drugs and other substances that might trigger or exacerbate depressive symptoms
- Mental status examination
- Physical examination and review of systems
- Review of prescription medications and use of over-the-counter medications
- Appropriate tests to rule out possible medical causes for depressive symptoms

*continued →*
RULING OUT MEDICAL CONDITIONS AND MEDICATIONS

When establishing a diagnosis of MDD, a variety of medical conditions and medications must be considered as possible underlying causes of depressive symptoms.

Specific medical disorders that may be associated with a major depressive episode include:
- Neurological conditions (for example, stroke, Parkinson’s diseases, dementia, or multiple sclerosis)
- Thyroid disorders
- Metabolic disorders (for example, hypercalcemia)
- Malignancy
- Infectious diseases

In addition, many medications used to treat general medical conditions may induce depressive symptoms, such as
- Chemotherapy drugs
- Steroids
- Some antibiotics
- Transplant and antirejection drugs

CONCLUSIONS

The well-documented underdiagnosis and undertreatment of MDD speak to an unmet need for greater recognition and improved management of this disorder. First and foremost, progress in this area depends on better identification of MDD if patients are to receive proper therapy and achieve the best possible quality of life.

REFERENCES

Pharmacologic Treatment of Major Depressive Disorder

Major depressive disorder (MDD) carries the risk of wide-ranging, potentially serious consequences. A wealth of research has confirmed that this disorder is associated with marked functional impairment, a diminished quality of life, and an increased risk of suicide.1,2 Unfortunately, studies have also shown that a significant proportion of patients with MDD remain poorly served. Only approximately half of all individuals with MDD are receiving treatment.3 Of those who are treated, only 38% are receiving therapy judged to be “minimally adequate.”4 Furthermore, just one third of patients with MDD achieve remission with an initial antidepressant, despite the fact that a wide range of such medications are available.4,5

ACUTE-PHASE TREATMENT

Acute-phase treatment of MDD should be directed toward inducing remission of the major depressive episode and producing a full return to the patient’s baseline level of functioning.6 The efficacy of antidepressants is generally comparable within and across classes.6 Therefore, the choice of medication is primarily based on the anticipated side-effect profile or tolerability in the individual patient, as well as the pharmacologic properties of the drug.

According to updated guidelines issued by the American Psychiatric Association (APA) in late 2010, the optimal choice of initial pharmacologic therapy for most patients with MDD is:

- A selective serotonin reuptake inhibitor (SSRI);
- A serotonin-norepinephrine reuptake inhibitor (SNRI);
- Bupropion (an atypical antidepressant); or
- Mirtazapine (a tetracyclic antidepressant).

Nonselective monoamine oxidase inhibitors (MAOIs) such as phenelzine, tranylcypromine, or isocarboxazid should be reserved for use in patients who do not respond to other agents.

Several factors can contribute to a lack of remission in response to acute treatment7-9:

- Inefficacy of treatment
- Inadequate dose or duration
- Safety and tolerability issues
- Comorbidities
- Poor adherence

In general, a patient should receive adequate treatment for 4 to 8 weeks before being judged as not responsive or only partially responsive to a specific antidepressant.4 If response is incomplete at that point, the clinician may opt to switch to another non-MAOI antidepressant from the same pharmacologic class or a different class. Another possibility is to change to an MAOI after allowing a sufficient interval off the previous medication in order to avoid dangerous pharmacologic interactions.

No particular demographic or clinical characteristics have been shown to predict which individuals will respond to specific antidepressants.10 However, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial found that more than 50% of patients will achieve remission after 2 treatment steps (the initial antidepressant followed by switching to or adding another).11 The prospects for remission decrease markedly with each successive step. In the STAR*D trial, the cumulative remission rate after 4 acute treatment steps was 67%. This means that approximately one third of MDD patients are not likely to achieve remission at this point and will require other strategies. According to the new APA guidelines, current options for patients with incomplete responses to antidepressant monotherapy include adding a second non-MAOI antidepressant or a nonantidepressant medication, such as lithium, thyroid hormone, or a second-generation antipsychotic (ie, aripiprazole or quetiapine).12

continued ——>
CONTINUATION- AND MAINTENANCE-PHASE TREATMENT

Continuation-phase pharmacotherapy is strongly recommended following successful antidepressant therapy during the acute phase. To reduce the risk of relapse, patients who have achieved remission with antidepressant treatment during the acute phase should continue such therapy for 4 to 9 months during the continuation phase, generally at the same dose(s) as in the acute phase. If a relapse occurs during the continuation phase, a return to acute-phase treatment is necessary. At that point, a common strategy is to increase the antidepressant dose.

Once the continuation phase has been completed, patients who have experienced 3 or more previous episodes or who have chronic MDD should proceed to the maintenance phase of treatment to reduce the risk of a recurrent depressive episode. Maintenance therapy should also be considered for patients who have additional risk factors for recurrence (such as residual symptoms, ongoing psychosocial stressors, early age at onset, or family history of mood disorders). During the maintenance phase, the antidepressant medication(s) that elicited remission during the acute phase and that sustained remission during the continuation phase should be continued at full therapeutic dose.

CONCLUSIONS

Greater awareness and implementation of evidence-based guidelines are needed to enhance the prospects for achieving and maintaining remission in patients with MDD. Tailoring acute-phase treatment, adjusting medications and regimens when necessary, and making a commitment to thorough follow-up are also crucial ingredients in making remission a reality for greater numbers of individuals affected by this debilitating disorder.

REFERENCES

How to Get the Best Results from Your Depression Treatment

If you’ve been diagnosed with depression and your clinician has prescribed medication, it’s important to know what you can do to get the most benefit. Here are some tips.

Before you start taking an antidepressant medication:

- Make sure your clinician knows about any medical conditions you have and any other medications (including over-the-counter products) you’re taking.
- Be sure to ask your clinician what to expect from your treatment—like how much it might help your symptoms and how long it might take to work.
- Talk to your clinician about possible side effects of your medication. It’s good to know about potential side effects ahead of time, so you can let your clinician know right away if you have problems.

After you start taking an antidepressant medication:

- Make a commitment to take your medication exactly as prescribed. Some medications for depression take a few weeks to start relieving symptoms. You might get discouraged or be tempted to stop the treatment, but it’s important not to give up hope during this time. Having patience can be really hard when depression is taking a toll on you. Try to keep in mind that you need to stick with your treatment if you’re going to feel better.
- Call your clinician right away if you notice anything out of the ordinary in your physical or mental health. Different people react in different ways to medications for depression. You might experience side effects that your clinician can easily manage by changing your dose or switching you to another medication.
- Keep your appointments for follow-up office visits with your clinician. Your clinician will need to check on your progress to determine whether your treatment needs to be adjusted. This might mean changing the dose of your medication, switching to another treatment, or adding another medication.
- Remember that your clinician is your partner in this process. Be honest and open about how you’re doing. Your clinician will work with you to make sure you get the best possible relief of your depression with the fewest side effects.
MDD CASE STUDY #1

“ANNA”

INITIAL PRESENTATION:
- 42-year-old woman
- 5-month history of depressed mood, hopelessness, weight gain, excessive sleeping, and crying at least 5 days per week
- Withdrawing from activities except when required to attend
- Not completing duties at work
- Experiencing difficulties at home
- Score of 16 on Patient Health Questionnaire-9 (PHQ-9)

INITIAL ACUTE-PHASE TREATMENT:
- Started on paroxetine (a selective serotonin reuptake inhibitor) 20 mg/d by primary care nurse practitioner 3 months ago
- PHQ-9 score of 15 after 1 month
- Dose increased to 40 mg/d due to inadequate response
- PHQ-9 score of 14 after 2 months at higher dose
- Seeing psychotherapist for past 3 months, but deemed not to be improving
- Referred to psychiatric-mental health nurse practitioner

CURRENT PRESENTATION:
- Little improvement in initial symptoms of major depressive disorder
- Complains of medication side effects, including headache, somnolence, and constipation
- Despite side effects, has been adhering to medication regimen

QUESTIONS TO BE ANSWERED:
- How important is it to assess adherence in patients with an incomplete response to acute-phase pharmacotherapy for major depressive disorder (MDD)?
- Should the dosage of an initial antidepressant be optimized before considering other options?
- What principles should be used to weigh response vs side effects in MDD patients receiving antidepressants?
- What should be done if a patient with MDD shows minimal or no improvement after 4 to 8 weeks at an optimal dosage of an antidepressant?
MDD CASE STUDY #2

“BEN”

INITIAL PRESENTATION:
- 38-year-old man
- History of untreated depressive episodes since late teenage years
- Worsening of symptoms over past 9 months; patient unable to cite a specific cause
- Still able to perform at work, but difficulties getting up in the morning and getting ready to go to the office
- Spends most off-hours in bed watching TV
- Loss of interest in normal activities, including family life with his wife and 2 children
- Score of 17 on Patient Health Questionnaire-9 (PHQ-9)

INITIAL ACUTE-PHASE TREATMENT:
- Started on fluoxetine (a selective serotonin reuptake inhibitor) 20 mg/d
- Minimal response at 4 weeks
- Dosage increased to 40 mg/d
- PHQ-9 score of 10 after 4 weeks at higher dose
- Complains of drowsiness and sexual side effects

QUESTIONS TO BE ANSWERED:
- What factors should signal a need to switch to another medication during acute-phase antidepressant therapy for major depressive disorder (MDD)?
- What factors should signal a need to add another medication during acute-phase antidepressant therapy for MDD?
- What are the principles of continuation-phase treatment for MDD?
In2MedEd
Strategies for Achieving Remission of Major Depressive Disorder
Thursday, October 20, 2011
12:00 pm - 1:30 pm

Q&A – Responses for Participants

Faculty:

Barbara Jones Warren, PhD, RN, CNS-BC, PMH
Professor, Clinical Nursing
Ohio State University College of Nursing
Columbus, OH

Madhukar H. Trivedi, MD
Betty Jo Hay Distinguished Chair in Mental Health
Professor of Psychiatry
University of Texas Southwestern Medical Center
Dallas, TX

Denise Vanacore, PhD, CRNP, ANP-BC, PMHNP
Associate Professor of Nursing
Coordinator, Nurse Practitioner Program
Gwynedd Mercy College
Gwynedd Valley, PA
Adult and Psychiatric Nurse Practitioner
Lansdale, PA
<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>How often should I be completing rating scales when I am treating MDD on an inpatient medical floor and am seeing the patient daily?</td>
<td><strong>Dr. Warren’s Response:</strong> I would say you need to complete a rating scale every time you see the patient in order to ascertain how he or she is doing. Choose 1 of the shorter scales, and it is just a matter of updating each time you see the patient. I often just add columns so I do not have to make a completely new sheet for each visitation.</td>
</tr>
<tr>
<td>Sadly, getting an accurate history of antidepressant use from our clients is a struggle. Are simple, concrete, sequential, and successful processes/tools available? Please comment.</td>
<td><strong>Dr. Warren’s Response:</strong> I have created my own intake sheet that covers the biopsychosocial components of clients. It has areas for checkmarks as well as for comments. The tools have been mentioned by Dr. Vanacore in her previous response (see above). I would recommend combining those with an intake/documentation sheet that meets your own needs for your environmental setting. The Zung Depression Inventory and Zung Anxiety Scale are easy to use and free.</td>
</tr>
<tr>
<td>Is there any information on the use of scales when patients are intermittently adherent to treatment?</td>
<td><strong>Dr. Vanacore’s Response:</strong> Whether patients are adherent to therapy or intermittently adherent, I would utilize the same screening questionnaires. Having a therapeutic relationship with the patient and collaboration in the treatment plan are great strategies to improve adherence. Using laboratory tests to identify the medication level is another strategy that helps patients with adherence. (See Reference 1.)</td>
</tr>
</tbody>
</table>
“Remission” clearly implies “no cure”; lifetime condition. Given the work showing recovery rates for major depression of >90% to 99%, is it time to refer to “remission” as early-uncomplicated recovery? Please comment.

**Dr. Warren’s Response:** The process of a client’s recovery is just that—a process. I prefer the term recovery process because it has different components based on the level of a client’s symptomatology, understanding of the symptoms, social support, and knowledge regarding his or her mental illness. I really do not use the term remission as it is not the current terminology that most clients are using.

“Lack of remission” is also a function of misdiagnosis or missed medical diagnosis at a rate of 25% of people who enter the public health system and have medical conditions, which, when diagnosed and treated, result in complete elimination of the conditions. What medical conditions must we differentially diagnose/ rule out before treatment for MDD can be applied?

**Dr. Warren’s Response:** I would always make certain that a complete physical examination (including blood work) is done for clients, as this then sets the stage for what occurs next. I do not look at what we rule out, but what is the actual physical state for the client. If the physical findings are unremarkable, then diagnostic impressions can proceed, including psychotherapeutic modalities and pharmacologic therapies. Of course, even in the presence of physical problems, these latter approaches may be quite valid. Persons often have MDD in conjunction with physical illnesses.

There was a recent study by the National Institute of Mental Health (NIMH), I believe, that showed evidence to support augmentation of selective serotonin reuptake inhibitors (SSRIs) with S-adenosylmethionine (SAM-e). Can you please comment on this? What are your thoughts?

**Dr. Warren’s Response:** There has not been enough evidence to support this approach to treatment. However, the research that has been done does not indicate that the use of SAM-e or any other complementary or alternative medicine (CAM) approach is effective in the treatment of clinical depression. I would suggest that those interested in this topic examine the CAM website through NIMH for further information on the CAM studies. (See http://nccam.nih.gov.)

What are the chances of serotonin syndrome when one augments treatment with a second antidepressant? Would you recommend complementary therapies such as St. John’s Wort or SAM-e?

**Dr. Vanacore’s Response:** According to Boyer and Shannon (2005), serotonin syndrome occurs more frequently when the 5-HT2A receptor is targeted. Serotonin syndrome may occur with the use of a single SSRI or in response to a combination of medications. The most severe cases occur with SSRIs in combination with monoamine oxidase inhibitors. In addition, serotonin syndrome can be caused by other classes of drugs, including antiemetics, antimigraine medications, St. John’s Wort, and SAM-e, as well as foods such as red wine and cheese due to their serotonergic properties. This makes bupropion a great choice as add-on therapy since it has demonstrated less...
potential for serotonin syndrome. The key is discussing the possible side effects with the patient and having them alert you to clinical changes. (See References 2 and 3.)

What is your opinion about the current state of DNA testing for the selection of medication for the treatment of MDD? Are we really there yet? How often do you use it?

**Dr. Warren’s Response:** I would recommend checking the website for the Genome Project, which has a wealth of information about this topic. (See [http://www.genome.gov](http://www.genome.gov).) Only a few indications have come out of that site regarding medications for specific disorders. One of these is isosorbide dinitrate/hydralazine for the treatment of hypertension in persons from African descent. We really are not there yet with respect to DNA testing to tailor treatment regimens in MDD. Rather, we are just starting to scratch the surface. It could be a giant step forward if medications could be personalized to individual genetic makeup.

I have an outpatient practice. Can you speak to how we can help patients stay on their medications longer than 3 to 4 days, rather than discontinuing due to side effects?

**Dr. Trivedi’s Response:** I think that nonadherence is, indeed, the biggest problem in the treatment of MDD. When patients start an antidepressant, they may begin having side effects, so certain principles are important. Clearly, going slower with regard to increasing the dose is 1 thing that helps. Second, and even more important, is informing the patient about the possibility of side effects in advance. The third thing I tell patients is, no matter what side effects they may experience, there are numerous other options for antidepressant medications that can be tried. I tell them to call me if they have side effects so we can address those problems together, rather than the patient making a decision on his or her own whether to continue the medication.

Another problem is that a very small percentage of patients are very sensitive to medications. I routinely obtain histories from all my patients because, if that is the case, doses should be titrated even slower than usual. It’s important to be aware that most of the MDD medications are available in liquid form. This allows more flexibility in dosing if problems are anticipated.

What are the best strategies to lessen and treat the sexual side effects of antidepressants?

**Dr. Vanacore’s Response:** First, an assessment of the sexual side effect and the gender of the patient is important. Ruling out medical causes of the sexual dysfunction is also important. The most common sexual side effects reported with antidepressant treatment are erectile dysfunction, diminished libido, and delayed/attenuated or absent orgasm (dysorgasmia or anorgasmia). Using the Changes in Sexual Functioning Questionnaire (CSFQ) can help to determine the type of sexual side effect. In some individuals, reducing the dose of the antidepressant and adding another antidepressant from a different class, or switching to a different class of antidepressant, may help alleviate the side effects. However, both of these strategies risk sacrificing the therapeutic benefit of treatment. The last strategy is to use medication antidotes such as yohimbe, amantadine, cyproheptadine, etc. (See References 4 and 5.)
Will you please speak to the recent advertisements soliciting clients to file lawsuits because they took sertraline while pregnant, and linking this to birth defects in their children?

**Dr. Vanacore's Response:** Information regarding the safety of SSRIs during pregnancy is sparse. There are no studies I could find that significantly focused on sertraline. There is accumulating evidence that the use of SSRIs during pregnancy produces birth defects, specifically cardiac anomalies. Alwan et al (2007) obtained data on 9,622 case infants with major birth defects and 4,092 control infants born between 1997 and 2002. The conclusion of this exploratory study was that the maternal use of SSRIs during early pregnancy was not associated with a significant increase in congenital heart defects or most other categories of birth defects. (See references 6 and 7.)

If walking is not recommended for depression, what exercise is recommended?

**Dr. Warren’s Response:** As long as a physical indicates no problems, any exercise is permitted if the supervising medical healthcare provider says so. Gentle stretching and meditation may get things going, then walking could be added later according to the client’s physical and emotional status.

What are the recommended “doses” and duration of exercise for patients with MDD?

**Dr. Trivedi’s Response:** Most of the literature is on aerobic exercise. I don’t know if anaerobic exercise or resistance training works or not, but aerobic exercise does, so that is what I recommend. Studies by our group and other investigators have generally shown 2 things. First, the patient should expend roughly 12 kcal per kg of body weight per week. In other words, a patient who weighs 80 kg should have approximately 1,000 kcal of energy expenditure every week. This translates into about 30 to 45 minutes of aerobic exercise 3 to 4 times a week. If they did it at a lower intensity, they would end up having to exercise 1 hour per day 5 times a week, and that takes a lot of time. Therefore, I generally recommend 30 to 45 minutes at medium intensity to achieve an expenditure of 1,000 to 1,200 kcal.

## REFERENCES