Managing Depression After Initial Treatment

A Review of Next Steps in Major Depressive Disorder

CME Available Until:
December 31, 2021

This activity has been approved for 1.50 AAPA Category 1 CME credits

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Provided by:

AAPA

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MedicalLogix

ACTIVITY OVERVIEW

Major depressive disorder (MDD) remains a top cause of disability worldwide and in the United States. In the U.S., roughly one in six people will have at least one episode of MDD over their lives. When combined with chronic medical conditions, as it frequently is, MDD is responsible for a 60-80% mortality increase. PAs and other providers in primary care hold a foundational role in managing depression. Some international estimates place the prevalence of MDD in primary care at roughly 20%. In the U.S., the majority of ambulatory care visits for depression continue to be through primary care providers. The reasons for the reliance on primary care to manage MDD are potentially manifold. These include difficulty in receiving psychiatrist-mediated care, stigma associated with seeing a psychiatrist, or having a relatively mild depression that is more appropriate for primary provider care. PAs hold a key place in managing depression in the U.S.. As such, care of patients with depression can be improved by increased PA training in the ongoing assessment and follow-up management of MDD. This educational program will strengthen PAs' clinical acumen in treating the large numbers of depressed patients in the U.S..

AAPA TAKES RESPONSIBILITY FOR THE CONTENT, QUALITY, AND SCIENTIFIC INTEGRITY OF THIS CME ACTIVITY.

EDUCATIONAL OBJECTIVES

At the conclusion of this activity, the PA should be better able to:

- Implement validated depression measurement scales in the primary care setting.
- Identify patients with suboptimal response and choose among evidence-based strategies for medication switching and augmentation.
- Outline new and emerging medications for MDD with a foundational understanding of their mechanisms of action.

ACCREDITATION STATEMENT

This activity has been reviewed by the AAPA Review Panel and is compliant with AAPA CME Criteria. The activity is designated for 1.5 AAPA Category 1 CME credits. PAs should only claim credit commensurate with the extent of their participation. Approval is valid through December 31, 2021.

Estimated time to complete this activity: 90 minutes.

HOW TO RECEIVE CREDIT

There are no fees for participating and receiving CME credit for this activity. Participants must: 1) read the educational objectives and faculty disclosures; 2) study the educational materials; 3) complete the post assessments in Learning Central.

In order to receive credit, participants must complete the post-test and evaluation. You will be able to access your certificate of completion in Learning Central as soon as you complete the post-test with a minimum score of 70%. Your certificate will be available under "Transcript" for your records.

DISCLOSURE POLICY STATEMENT

All individuals in a position to control the content of this activity have disclosed their relevant financial relationships with commercial interests. Disclosures from the author(s) are listed below.

Lawrence Herman, DMSc, MPA, PA-C, DFAAPA
Moderator
President
Palantir Healthcare, LLC
Boiling Springs, SC

Past President
American Academy of PAs
Alexandria, VA
Speaker's Bureau: Novo Nordisk

Catherine Judd, MS, PA-C, CAQ-Psy, DFAAPA
Clinical Assistant Professor
Southwestern School of Health Professions
Department of Physician Assistant Studies
University of Texas Dallas PA Program
Dallas, TX
Disclosure – No relevant financial relationships to disclose

Oliver Oyama, Ph.D., ABPP, PA-C, CAQ-Psy, DFAAPA
Associate Director, Family Medicine Residency
Professor of Family Medicine
University of South Florida College of Medicine
Turley Family Health Center
Clearwater, FL
Disclosure – No relevant financial relationships to disclose

ACTIVITY PLANNERS

John Gentile, Megan Gentile, Joanne Jeffers, and Joshua Hwang, Medical Logix, LLC have no relevant financial relationships to disclose.

AAPA STAFF ACTIVITY PLANNERS

Cheryl Holmes and Daniel Pace have no relevant financial relationships to disclose.

OFF-LABEL/UNAPPROVED PRODUCT(S) DISCUSSION

This program discusses the off-label use of lithium, thyroid hormone and buspirone.

DISCLAIMER

The opinions and comments expressed by faculty and other experts, whose input is included in this program, are their own. This enduring material is produced for educational purposes only. Please review complete prescribing information of specific drugs mentioned in this program including indications, contraindications, warnings, and adverse effects and dosage before administering to patients.

Lawrence Herman, DMSc, MPA, PA-C, DFAAPA: Hello, and welcome to this *Clinical Dialogue* and *eCase Challenge* program, "Managing Depression After Initial Treatment: A Review of Next Steps in Major Depressive Disorder." I'm Dr. Lawrence Herman, President of Palantir Healthcare, LLC in Boiling Springs, South Carolina, and a Past President of the American Academy of PAs in Alexandria, Virginia.

Joining me in this conversation are two expert clinicians, PA Catherine Judd and Dr. Oliver Oyama. Catherine is a Clinical Assistant Professor at the School of Health Professions, Department of Physician Assistant Studies at the University of Texas-Southwestern Medical Center in Dallas, Texas.

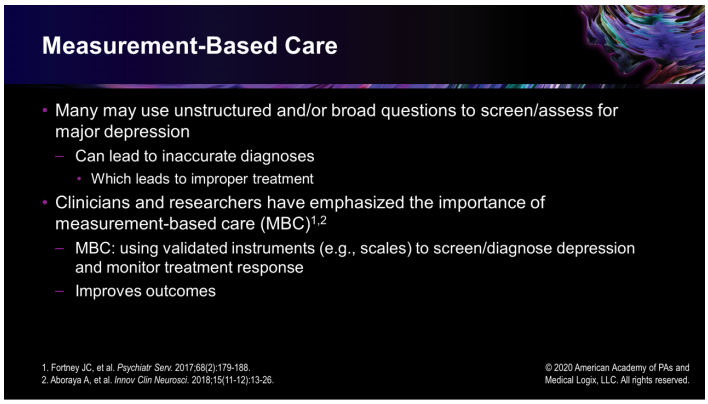
Oliver is a PA and a clinical psychologist, Professor in the Department of Family Medicine at the University of South Florida College of Medicine and Associate Director of the University of South Florida Family Medicine Residency in Clearwater, Florida. My thanks to both of you for your involvement in this important continuing medical education activity. So, let's get started.

Before getting into the heart of things, I'd like to discuss the importance of this educational activity on depression assessment and proper treatment, because we're undertreating these patients. This is extremely common. In fact, only one out of four patients meeting the criteria for diagnosis of major depressive disorder actually receive adequate treatment, and the majority of patients remained symptomatic despite treatment with first-line antidepressant monotherapy.

To treat our patients effectively, first we have to recognize that they may be depressed, and to do that, we need to assess them appropriately. It's impossible for us to do a complete psychiatric assessment in our primary care clinics the same way that you might in your psychiatric clinics. So, Oliver, let's talk about the importance of assessing and screening patients for major depression.

Oliver Oyama, Ph.D., ABPP, PA-C, CAQ-Psy, DFAAPA: Larry, I think it's very tempting, particularly in a fast-paced primary care setting, to use unstructured and broad global questions to evaluate for major depression. But what we find is that that often leads to inaccurate diagnoses, and then with inaccurate diagnoses comes inaccurate treatment approaches.

The focus in the more recent past has been on measurement-based care, and that's using validated instruments to assess for depression and also to monitor treatment, and the research seems to indicate that by doing that, it improves outcomes.

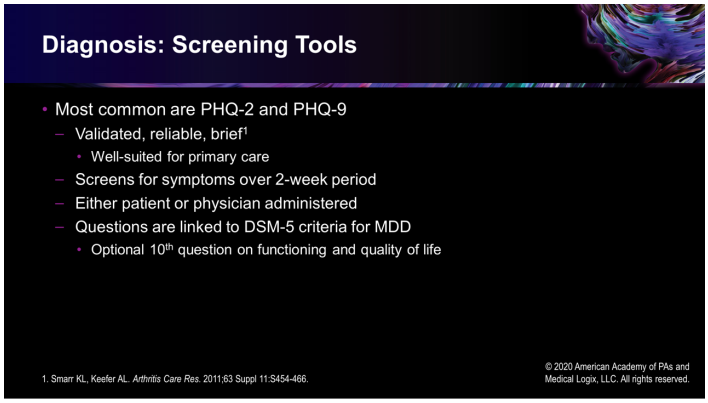


Lawrence Herman: Oliver, do you want to talk about the most common screening tools that we would use that are validated? We can talk about PHQ-2s or PHQ-9s.

Oliver Oyama: Absolutely. There are a number of validated scales out there. We have research-focused scales, clinical-focused scales, scales that a clinician would administer and those that a patient administers themselves. But the focus really, and the preference in primary care, are validated and reliable instruments that are efficient to use in point of care. I think the most common one that our viewers will know about is the PHQ-2 and the PHQ-9. Maybe Catherine might want to talk a little bit about those.

Catherine Judd, MS, PA-C, CAQ-Psy, DFAAPA: Thank you, Oliver and Larry. For screening assessment, the PHQ-2 and the PHQ-9 screening for symptoms over the previous 2 weeks are both patient administered, and thereby don't take up a lot of provider time. The advantage of the PHQ-9 is those nine questions are tied directly to DSM-5 symptoms of MDD.

Now, there are some versions of the PHQ-9 that have a tenth question that asks about functioning and quality of life, which are important measurements during the course of treatment, since treatment goals and the response to treatment in whatever form -- pharmacological, behavioral -- remission and restoration to wellness is our object and our goal.



Oliver Oyama: Larry, another scale that I use quite often is the Geriatric Depression Scale. This is an instrument with 15 items that's standardized for use with geriatric populations. I've also used the Edinburgh Postnatal Depression Scale, a ten-item scale specifically for women in the postnatal period. The United States Preventive Service Task Force, as you know, recommends that we screen everybody age 12 and above for depression, but specifically makes a note of pregnant and postnatal women for a screening focus.

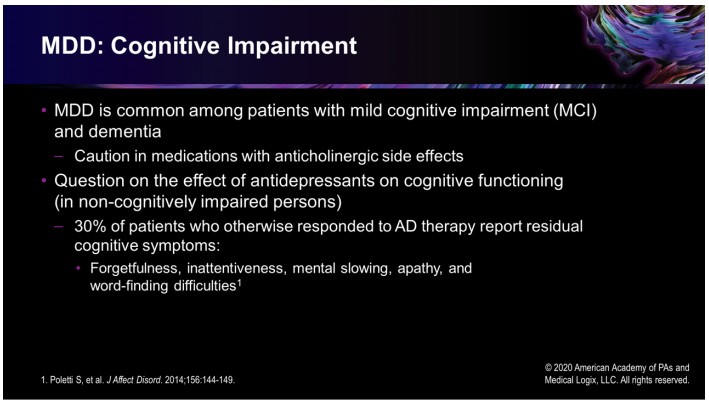
Lawrence Herman: There are some additional tools. There are a whole host of them. But one of the other ones that I'm familiar with is the Mood Disorder Questionnaire. Can you speak to that, please?

Catherine Judd: I'm glad you asked about that, Larry. The Mood Disorder Questionnaire, MDQ, is critically important not to miss bipolar depression. An episode of MDD is integral to a diagnosis of bipolar disorder, and it's estimated that approximately 67% of our bipolar patients initially present to their health care providers as depressed. And consequently, not only is the diagnosis of bipolar missed, but inappropriate treatment is frequently prescribed.

Lawrence Herman: Now, there are other patient populations -- and I think about the patient with dementia.

Obviously, dementia and depression are not mutually exclusive. So, Catherine, in your practice, what do you do once you've determined that a patient has early mild or moderate dementia in terms of treating their MDD?

Catherine Judd: Well, you know, I think that's an interesting question that you're asking, and I think there's actually two questions we need to address. One is treating depression in the patient who's cognitively impaired. And one of the things is that with the antidepressants that we have available, we need to be very careful in terms of anticholinergic side effects, for one. The other thing that we also know is that antidepressants may or may not have an effect on cognitive functioning.

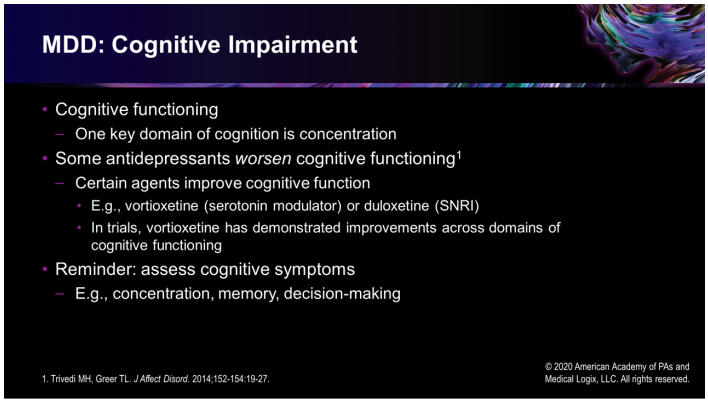


And so I think it's important to look at the four key domains of cognitive functioning. Now, when we're using the PHQ-9, we have one question that may lead us to wonder or speculate or want to query a patient about their own sense of cognitive function, and that's the question about concentration.

The reality is, Larry, that some of the medications that we're using to treat depression actually worsen cognitive function, and there is evidence, on the other hand, that there are other medications that may improve it, such as vortioxetine or duloxetine.

There have been clinical trials that have been done assessing cognition whereby vortioxetine has shown improvement in these four key domains of cognitive functioning.

Bottom line is, it's important when we're treating these patients to assess their cognitive symptoms initially and through the course of treatment.



Lawrence Herman: When a patient presents in any setting -- but including a primary care setting -- with MDD, we need to rule out a number of things, and they're relatively simple to do, but essential. Oliver, where should we start?

Oliver Oyama: I think we should start with a focus on what we do in other non-psychiatric areas in our clinical world. If a patient comes in with a headache, we're going to evaluate what are all the medical explanations for headache? What are potential psychiatric explanations for headache, and what are substance-related explanations?

So that's exactly what I do with MDD. A patient that presents with depression or anhedonia, I think about medical explanations, hypothyroid being top of the list. But you can have renal problems, hematological problems and so forth that have as a symptom depression. Other psychiatric disorders, such as bipolar disorder that we mentioned earlier, but anxiety disorders can present with depressive symptoms, as can schizophrenia and personality disorders.

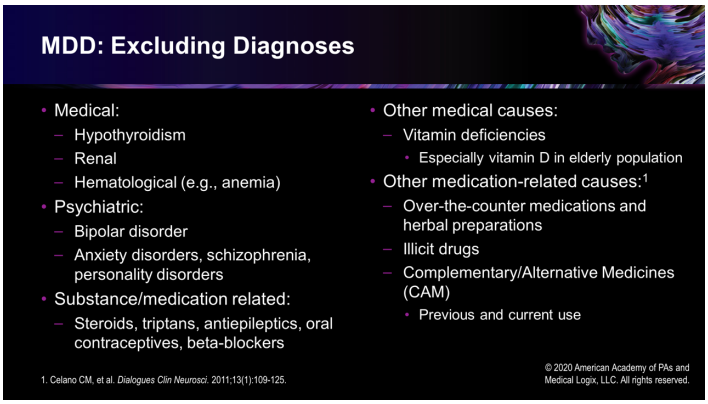
And then finally, I would have us remember that substances -- recreational substances, illicit substances, but also iatrogenic substances, steroids that we prescribe for other problems, triptans, antiepileptics, oral contraceptives all have as not uncommon side effects depression.

Lawrence Herman: And I think that there are even some common, as an example, cardiovascular drugs that I think of. Beta blockers, I've had patients as an example. So we really need to look at the list of drugs that patients were on and consider that polypharmacy may be contributing to this.

There are other contributors, Catherine. What would you include in that list?

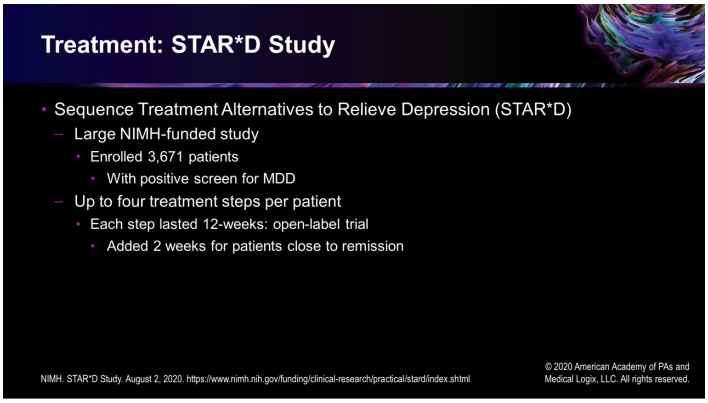
Catherine Judd: I also look for vitamin deficiencies, in the elderly, particularly vitamin D.

And I think we also need to look at over-the-counter medications, illicit drugs, as well as alternative therapies. We need to take a very, very careful history in terms of not only current substance use and medication use, but previous substance and medication use.



In terms of treating MDD, when we're looking for evidence-based resources, I think one of the important things is to look at evidence-based algorithms. And in this regard, I think it's important for us to talk about STAR*D, which is the Sequence Treatment Alternatives to Relieve Depression, which was a large NIMH-funded study that enrolled nearly 4,000 patients who had screened positive while seeking routine and medical and psychiatric care.

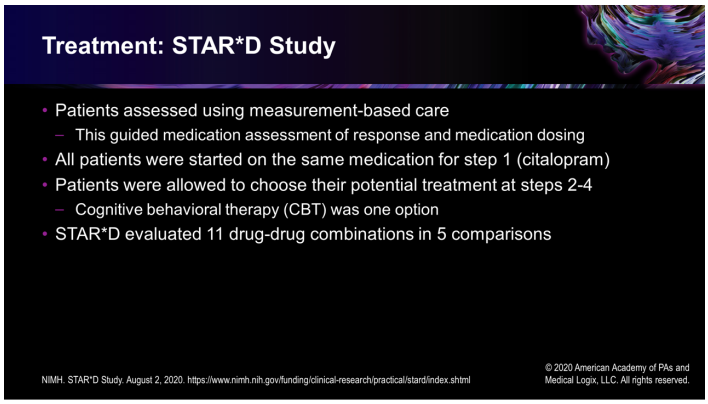
STAR*D provided up to four treatment steps per patient, and it was designed to provide a pathway in selecting the next step treatment for the patients who fail to reach remission from their initial antidepressant monotherapy. And each step consisted of a 12-week open-label trial and an additional 2 weeks for those patients who were thought to be close to remission.



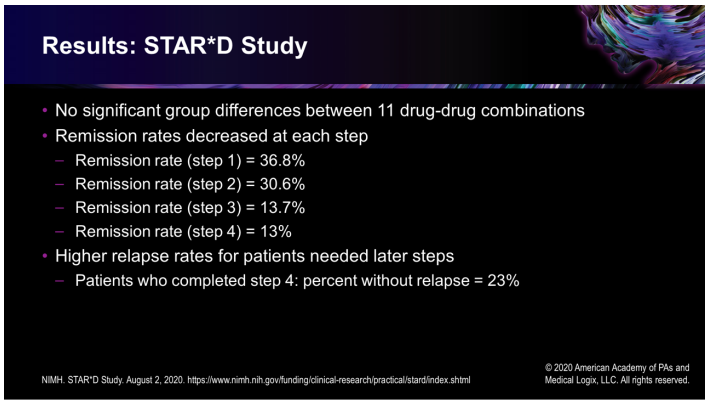
Antidepressants were administered using a system of, once again, measurement-based care that involved assessing symptoms and side effects at each visit to guide the aggressive medication dosing to ensure the likelihood of achieving remission, and that that was maximized, and those who did not reach remission were truly resistant to the medication.

Now, STAR*D allowed patients to select their treatment options for randomization at steps two and four. And the goal was to empower patients. It was to strengthen the therapeutic alliance and optimize adherence and improve outcome.

And interestingly enough, STAR*D evaluated the relative effectiveness of 11 pharmacologically distinct drug-drug combinations in five head-to-head comparison treatments. Also, in addition, interestingly enough, cognitive therapy was also available as a switch or drug augmentation option in step two.

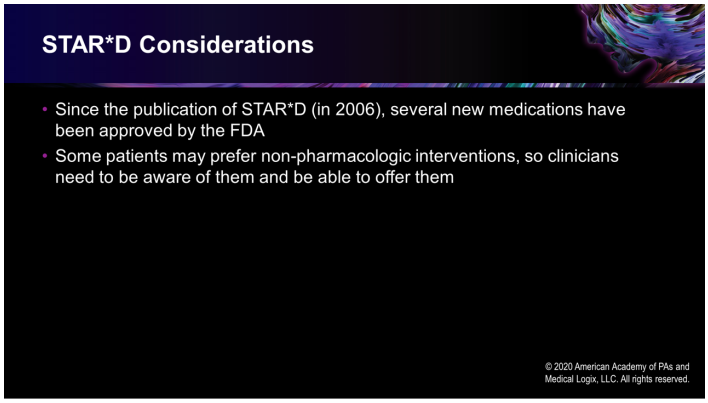


Without getting lost in the weeds of the data analysis and subsequent reviews of STAR*D, the message in STAR*D for us is, number one, there are no significant group differences between any of those 11 drug-drug combination treatments. Those patients that completed step four in this algorithm, only 23% of those were considered remitted without relapse.



Lawrence Herman: I think it's important for folks who are not intimately familiar with STAR*D to know that there are some newly approved or more recently approved FDA medications that are not in that algorithm that are now utilized at various steps.

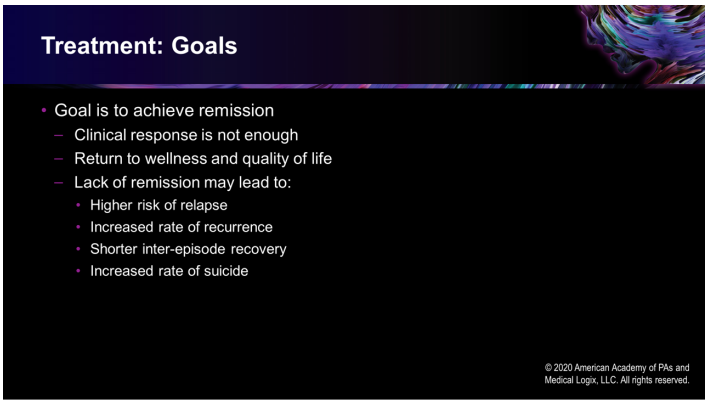
Catherine Judd: The other thing to remember, there are some patients who may not want to take medication. And so therefore, we also need to be able to offer them and be aware of nonpharmacologic interventions.



Lawrence Herman: Such is the case with every other intervention in medicine, when possible, I think it's important for us to acknowledge that the ultimate treatment goal here is not a degree of response, but remission.

Catherine Judd: You're absolutely correct, Larry. Ultimate goal of treatment is beyond response. It's beyond response, and our goal is remission and a return to wellness and quality of life.

Not achieving remission has real consequences on the disease course, with higher risk of relapse, increased rate of recurrence, shorter periods of inter-episode recovery, and not to mention increased risk of suicide.



Lawrence Herman: From a practical approach, Oliver, how do we make that choice? How do we decide between different treatment options?

Oliver Oyama: You're exactly right, Larry. I think that in practice, we have to use sound clinical judgment supported by evidence, but we have to consider real-world context. What is available for this particular patient? What is assessable? What is affordable for the patient? What is acceptable to them?

I oftentimes am concerned about what the patient's history is with their psychiatric symptoms. Is there a history in that patient or in their family with psychiatric symptoms? That will help guide my decisions about what to choose for treatment.

Lawrence Herman: And Oliver, there are a few other things that we need to explore, albeit briefly. Both men and women, a history of sexual abuse. We certainly need to look at a past history and a current history of suicidal ideations, correct?

Oliver Oyama: Absolutely. Very important.

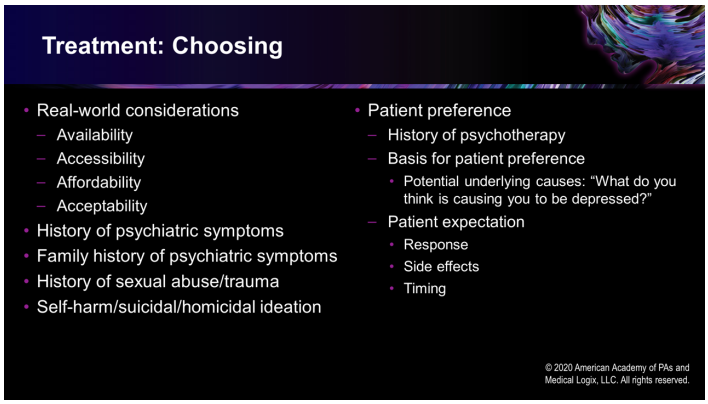
Lawrence Herman: Catherine, in a primary care setting, sometimes we have to choose between referral for counseling, medications or combining them both. What's the best way to make that choice?

Catherine Judd: I think in making decisions about medication versus therapy, patient preference is most important. And also, a patient's history, if they've engaged in psychotherapy in the past.

I want to also know the basis of their preference, if they have one. And so I may also ask a patient, for example, "What do you think is causing you to be depressed?" and depending on the response, may tip the balance towards therapy versus medication.

I might also go back to what we just talked about in terms of a history of trauma, particularly sexual abuse and a history of violence, confirming once again the diagnosis and, as we said previously, the risk of suicide.

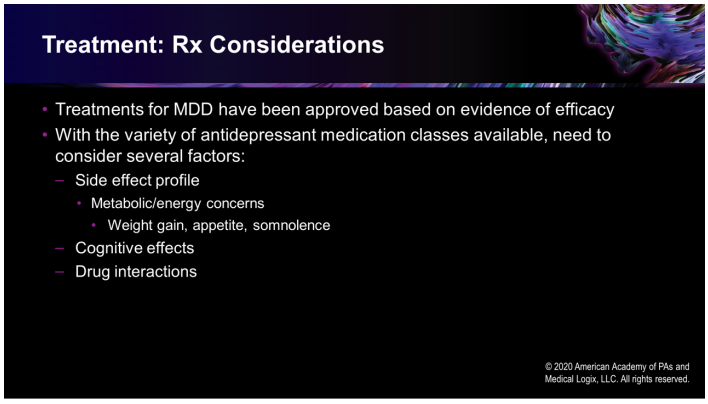
When it comes to selecting a particular medication, discussing with the patient what their expectations of treatment may be, what they might expect of treatment, the length of time to response of their symptoms, the length of time of treatment.



Lawrence Herman: Let's take a moment and speak about the nuts and bolts of utilizing various drugs, and what a primary care provider needs to consider as they treat patients with pharmacotherapy and they don't see what is an adequate response, or they don't see a response at all.

Catherine Judd: Okay, so let's drill down into your question, because you brought up several issues. Number one, the first thing we know about all of these medications is that they work. Okay? They all work. They've gone through placebo double-blind trials and been approved by the FDA because they work.

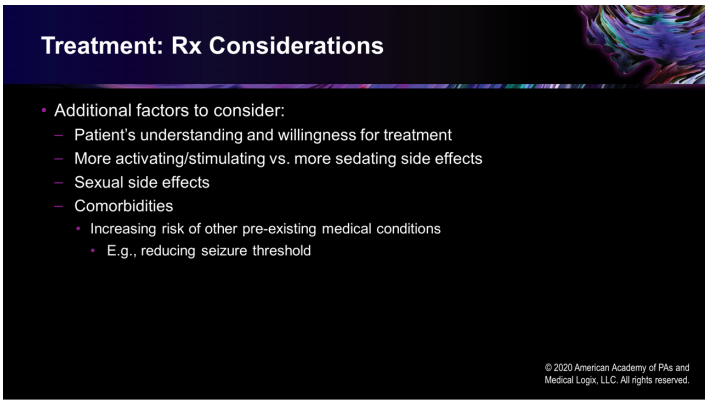
However, every patient is different. And so, when we're looking at which of the various medications we have available, we have six different classes of medication that are available with different mechanisms of action. You need to look at things like metabolic concerns. We need to look at side effect profiles. We need to look at side effects such as weight gain, appetite, somnolence, the effect on cognition, drug-drug interactions with other meds they may be taking.



So after we've had the opportunity to describe the treatment choices and expectations, we then need to step back and assess the patient's willingness and understanding and acceptance of what they are wanting in terms of their treatment.

Oliver Oyama: By and large, since all these medications are equally efficacious, we're targeting -- matching the medication with a particular patient, looking at a side effect or a tolerability profile. So do you need a patient to be more stimulated, or do you need a patient who has a number of medications on board to have a medication that has less drug-drug side effects?

Do you have a patient who would not be happy if a medication caused sexual side effects? Or, if they have a history of seizure, could the medication that you're using increase the risk for seizure? So a lot of drilling down and making a decision about a medication in the area of MDD has to do with looking at side effect profile and tolerability.



Lawrence Herman: Some of the medication classes, primary care providers may not necessarily have the same level of familiarity that the two of you have, and they may not be comfortable. And those two classes would be things like antipsychotics as well as drugs that may have the ability to stabilize mood. Take a moment and speak to that, please.

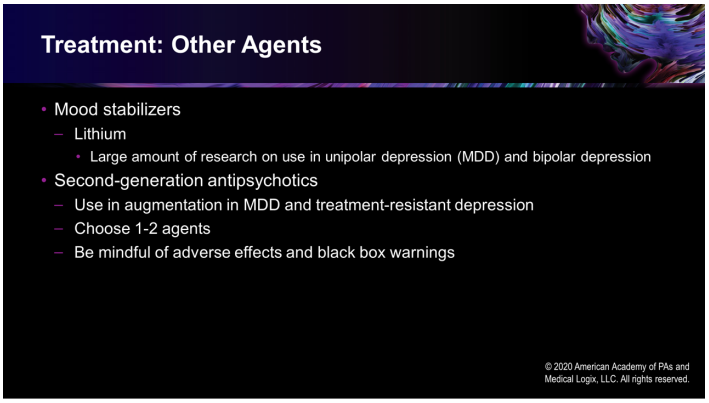
Oliver Oyama: The use of lithium, interestingly, the gold standard medication for mood stabilization, there's been research dating back to the 1960s for its use in the treatment of unipolar depression, not just bipolar depression, with some very good evidence.

I think that many primary care providers are concerned about using lithium, fearing what they've learned about lithium toxicity. But honestly, at the dosing that we tend to use in primary care and careful selection of patients, I don't find that that's a major issue in primary care. In the psychiatry world, where we use much higher doses of lithium, that's where I'd be much more concerned.

And then the second-generation antipsychotics, have been huge in the treatment of depression. We've had a number of medications over the last 7 to 10 years to be used for either the augmentation of the antidepressant treatment or for the treatment of treatment-resistant major depressive disorder. So, second-generation antipsychotics are here to stay. They're very effective.

And my recommendation to a primary care provider is, pick one or two that you'd like to get comfortable with and get some experience with, and you'll find that your patients will respond nicely.

Catherine Judd: These medications do have efficacy. They're effective, but providers need to pay attention to the black box warnings, and particularly there's more and more attention being given recently to the risk of tardive dyskinesia.

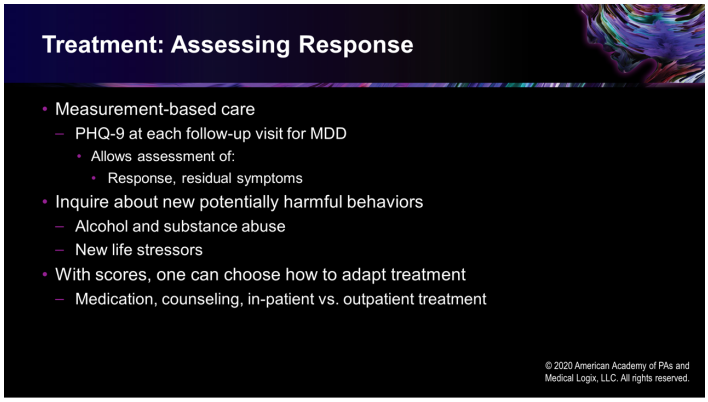


Lawrence Herman: In primary care, of course, everybody's concerned about their schedule and the time that they have available for patients and taking care of multiple medical comorbidities. So time constraints are real. There's no doubt about that. What should we focus upon during a follow-up or a series of follow-up visits to assure remission?

Oliver Oyama: I certainly would start with doing a PHQ-9 with every patient diagnosed with MDD at every follow-up visit. That will give you a sense of how well your treatment is working, if there are any residual symptoms that you still need to identify, and then, if so, how do you want to address them? By making medication changes? Encouraging follow-up in outpatient counseling?

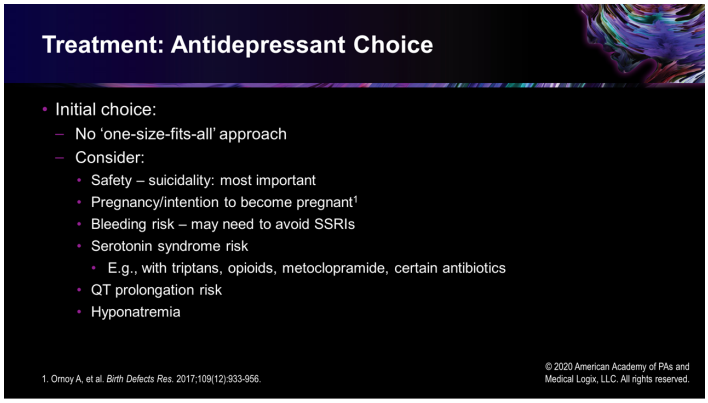
I also want to make sure that nothing new is going on with the patient in terms of a change in deleterious behaviors. Have they started drinking? Have they noticed anything else going on in their life that might make treatment remission that much more challenging?

I think that you can do these follow-up visits in no more than 15 minutes and be very efficient in dealing with that follow-up visit.



Lawrence Herman: In other diseases -- as an example, diabetes -- we have some pretty clear-cut algorithms, although they're getting more confusing now in diabetes than ever before, as an example. But clinicians have a tendency to have a category of drug that they start with and then a drug within that category that is their go-to drug. How do we make that initial choice? What is our deciding factor in choosing an antidepressant?

Oliver Oyama: Larry, I wish there was one answer to that question, but there isn't. But let me tell you how I think through making that decision about that first medication. And the first thing I'm going to think about for any medicine is safety. Does this patient have suicidal tendencies? Is this person pregnant? Do they have a bleeding risk such that I should stay away from an SSRI?

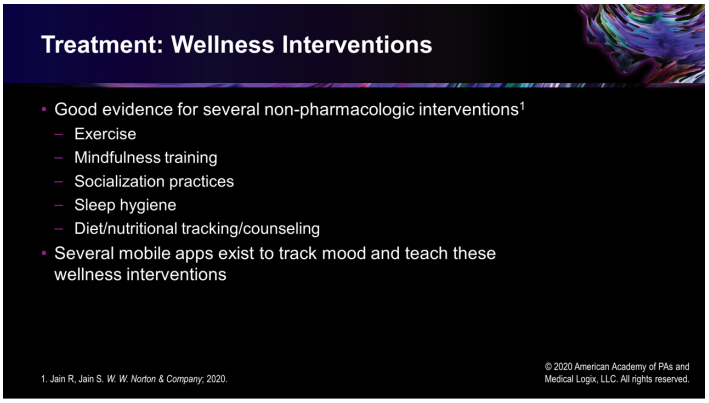


Are there risks for serotonin syndrome because they have concurrent triptans on board or opioids or metoclopramide or certain antibiotics? Is there an issue with QT prolongation? Is there hyponatremia? So, safety has to be your first threshold consideration when making a decision about medication. And then follow up soon after that with side effect profile and tolerability.

Lawrence Herman: Catherine, there are a host of other things that we need to consider when treating patients with MDD, including wellness interventions. Would you take a moment to speak a little bit about some of those, please?

Catherine Judd: In terms of wellness interventions for treating patients with major depressive disorder, interventions, nonpharmacologic interventions, we have very good evidence particularly in terms of exercise, for example. We've been able to demonstrate in terms of using other behavioral interventions, such as mindfulness, socialization, sleep hygiene, diet, nutrition, et cetera.

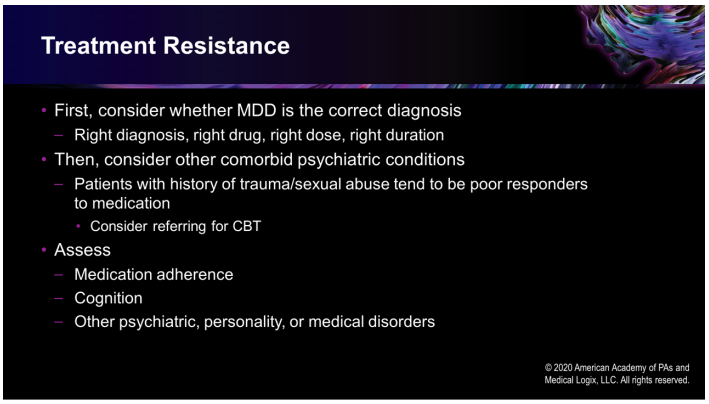
And so, I think consequently, these kinds of interventions must also be incorporated into the pharmacotherapy. And these interventions don't demand a lot of provider time. There are many, many apps out there that patients can be referred to, and it's a case, I think, of providers becoming familiar with maybe one or two or three that they're familiar with, and be able to suggest these to patients and suggest to them that they use these.



Lawrence Herman: Catherine, can we take a moment and define treatment resistance, and then talk to us about how you address this in your patient population?

Catherine Judd: Before we decide that a patient has treatment-resistant depression, we need to make sure we've made the right diagnosis, we have the right drug for the right dose and the right duration. Then, when there's not been at least a 50% response in symptoms, then we can talk about treatment resistance.

So we need to be careful before we call a patient treatment-resistant. We need to go back to the history, particularly trauma. Patients who have a history of trauma, sexual abuse, frequently are poor responders to medication, and those are the patients, before I would call them treatment-resistant depression, I would refer them to cognitive behavioral therapy.



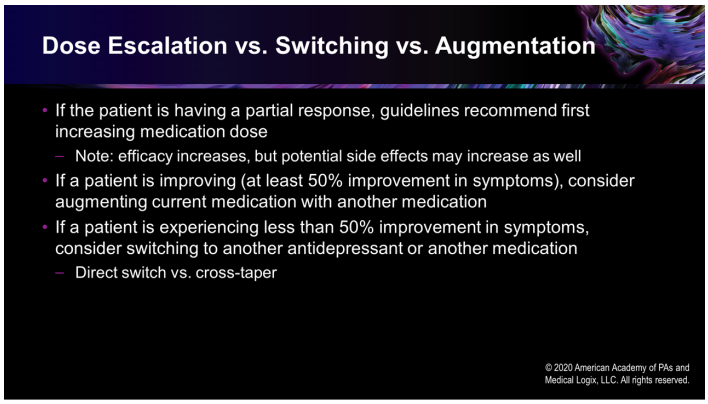
In terms of treatment resistance, we need to assess adherence. We need to assess cognition. There are a number of factors affecting the ability to reach remission. Among them is pretreatment severity, the severity of the depression in the first place, the length of the current episode, the presence of other axis I, II or III disorders, the length of the illness and treatment nonadherence. So I think we need to cautiously use the label of treatment-resistant depression and make sure we've done our homework before we put that label on a patient.

Lawrence Herman: Is the strategy when we consider escalating or changing medications -- should we focus first on a different medication within the same class, or should we actually begin to augment with a second medication from a different class, Oliver?

Oliver Oyama: Well, actually, Larry, some of the guidelines suggest that we should very first try to increase the dose of the medication if it is working at all. And I would increase that dose a little bit. But understand that when you increase the dose of these antidepressant, the efficacy increases, but potentially at the cost of an increase in the side effect from that particular medication. That shouldn't dissuade a prescriber from doing that, and there's good research to suggest that there can be some good effect just from increasing the dose.

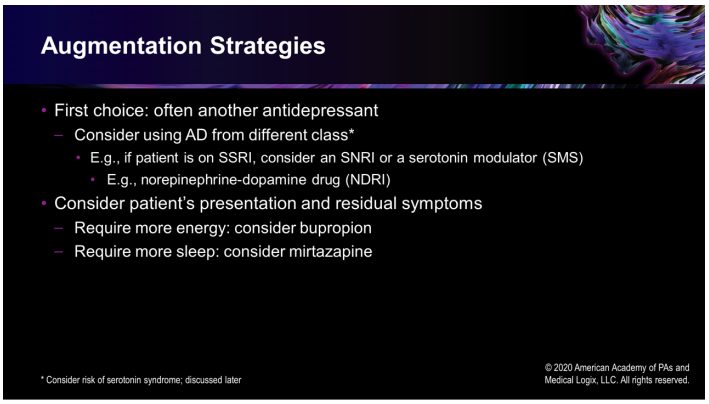
When I think about augmentation versus switching, Larry, the way that I think through is if a patient is improving -- has at least 50% improvement in their symptoms, I may augment that medication with another medication. We can talk about specifically what my augmentation strategy might be.

If a patient is experiencing less than 50% improvement in their symptoms on a particular medication, then I'm going to think about switching to another antidepressant or another medication, and I'll either do a direct switch or a cross-taper, depending on which medication that I'm using.



Lawrence Herman: From a primary care perspective, for folks who may not be familiar with this, can you speak a little bit about some of those strategies for augmenting?

Oliver Oyama: Absolutely, Larry. My first choice often is to choose another antidepressant, and I'll usually choose another antidepressant in a different class. If I have a patient initially on an SSRI, I may go to an SNRI or a serotonin modulator or even a dopamine norepinephrine drug like bupropion.

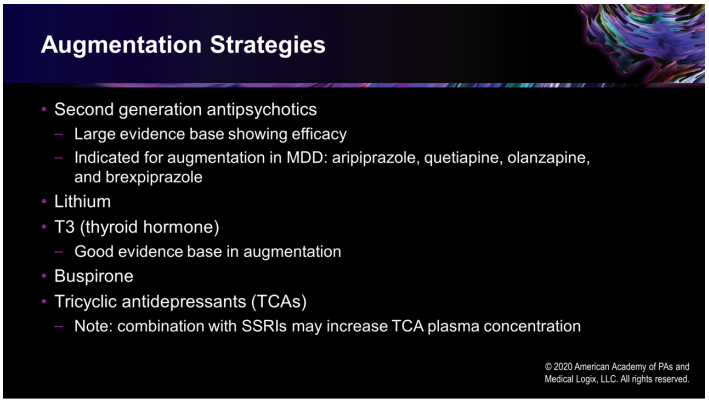


It really depends on what the patient is presenting with, what any residual symptoms might be. Do they need more energy? Maybe bupropion might be a good augmentation. Do they need more sleep? Maybe mirtazapine might be a better augmentation.

Another approach that I'll use, because of such great evidence for efficacy, are the second-generation antipsychotics. And specifically the ones indicated -- aripiprazole, quetiapine, olanzapine and brexpiprazole -- are those medications that I would use to augment another antidepressant.

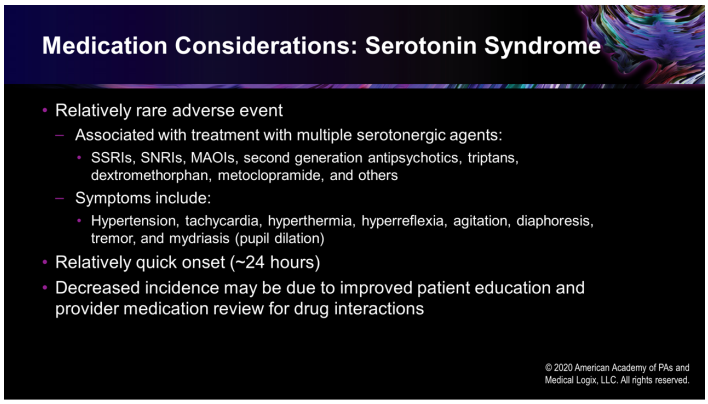
We mentioned lithium, and I won't talk specifically any more about that. There's good evidence for the use of T3s, dating back to the 1960s also. T3 hormone for augmentation, not often used in primary care, but in psychiatry something that there's good evidence for.

Buspirone has found a place as an augmentation strategy, and don't forget also those older antidepressants, the tricyclic antidepressants in select patients where it's safe to use can be very useful. The combination of an SSRI with a TCA actually increases the plasma concentration of the TCA due to the inhibition of cytochrome P450.



Lawrence Herman: Catherine, I have personally seen serotonin syndrome twice, both in the emergency department, not in a primary care setting. In spite of the fact that we mentioned it, and we do need to be aware of it, I think it's important that the audience recognize that that's a relatively rare adverse event that you see with SSRIs. Is that correct?

Catherine Judd: I would agree that it's not common, but I would attribute that fact that we don't see it very often to the fact that probably providers and prescribers are doing a fairly good job at patient education and reviewing medications where there may be a drug-drug interaction or where there may be a risk for serotonin syndrome.

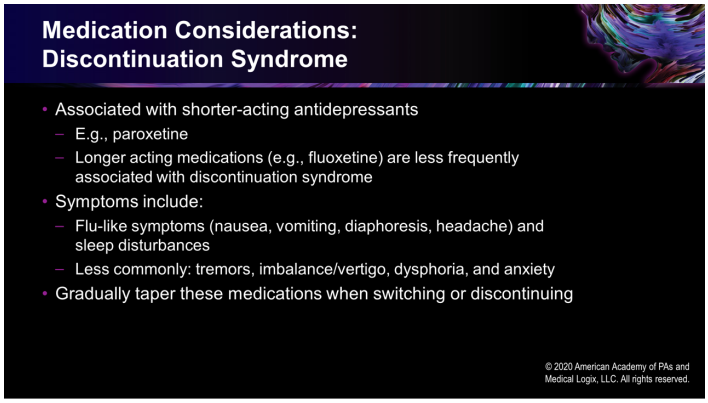


Lawrence Herman: I think one of the things that occurs more frequently occurs when people either are nonadherent to medications or the prescriber makes an abrupt change in medications, in particular if the patient abruptly discontinues their medication. Can you speak to that briefly, please?

Catherine Judd: I think that point's well taken. And I think in the literature, it's been recognized that there is a discontinuation syndrome to these medications, and there is a withdrawal.

And what we're seeing is in the shorter-acting antidepressants, particularly among the SSRIs, such as paroxetine, for example, there is a definite discontinuation syndrome with that medication. It's a short-acting, short-half-life drug. And, in fact, what we frequently call it when we see it is the flu without the fever, because those are the symptoms that patients are experiencing.

The longer-acting medications, such as fluoxetine, that has a very long half-life, including an active metabolite, you don't see that. But I think we do need to recognize that. And when we're looking at strategies to switch or add medication, we need to build in a schedule for tapering these medications and not do it abruptly.

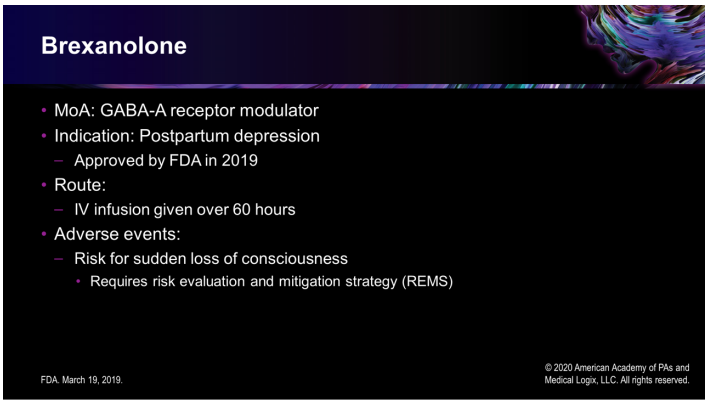


Lawrence Herman: Oliver, there are some relatively new, and there are some emerging agents currently being prescribed, both specifically within the primary care setting, and there are others that likely would only be prescribed within a psychiatric setting. Can you take a moment and speak about those, please?

Oliver Oyama: Absolutely. It's been such an interesting phenomenon. We haven't had an antidepressant in such a long time -- actually, 2013 was the last time we had a general use antidepressant come on the market. But last year we've had two new antidepressants that have come on the market, brexanolone, which is a GABA-A receptor modulator that's indicated for the treatment of postpartum depression.

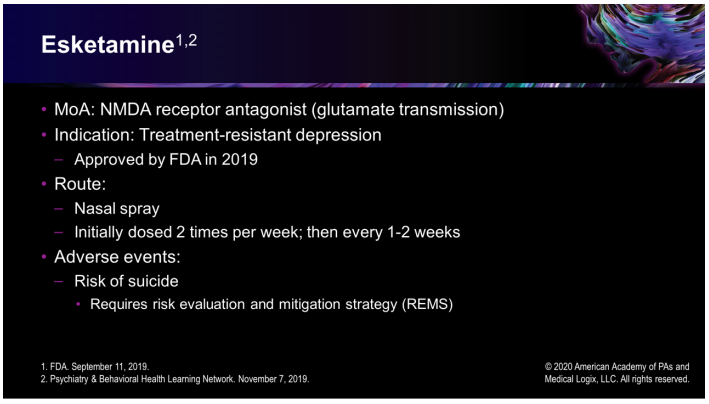
It's an IV infusion over 60 hours. It's a medication that is part of a REMS program, so the clinic has to be part of the risk evaluation

and mitigation strategy because of the risk for sudden loss of consciousness.



And then the second drug, which is an interesting new drug because it's focusing on a different mechanism of action, the NMDA receptor antagonist esketamine, which targets glutamate transmission. This medication came on the market last year. It's indicated specifically for treatment-resistant major depression.

It's an interesting nasal spray that's to be used in combination with an antidepressant. You start off with twice-a-week treatment, and then you graduate to every 1- to 2-week treatments. This medication also is part of a REMS program because of a black box warning secondary to suicide.

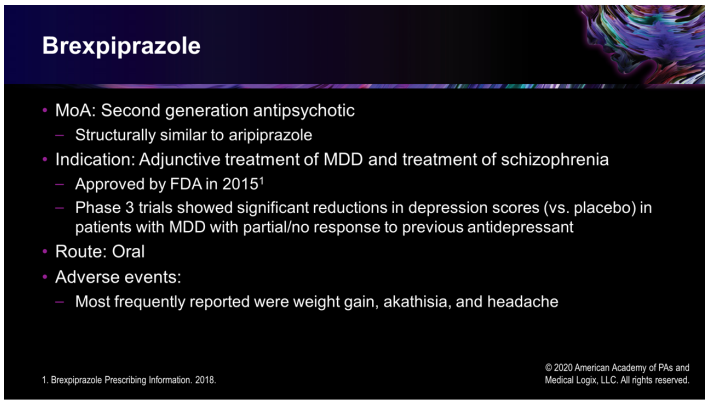


Lawrence Herman: Catherine, about 5 years ago, my memory says, there was another FDA-approved drug that was utilized for both major depressive disorder and schizophrenia that I have seen used in the primary care setting. Can you speak to that?

Catherine Judd: There was a drug that was approved back in 2015, brexpiprazole. It was initially approved by the FDA for the treatment of MDD in adults as well as schizophrenia.

Yes, and this is what's considered a second-generation antipsychotic, and with a similar chemical structure to aripiprazole.

In phase 3 trials, this drug, interestingly enough, showed significant reductions in depression scale scores when it's compared to placebo in patients with MDD who had a partial or no response to a previous antidepressant. In these trials, the most frequently reported adverse effects were weight gain and akathisia and headache.



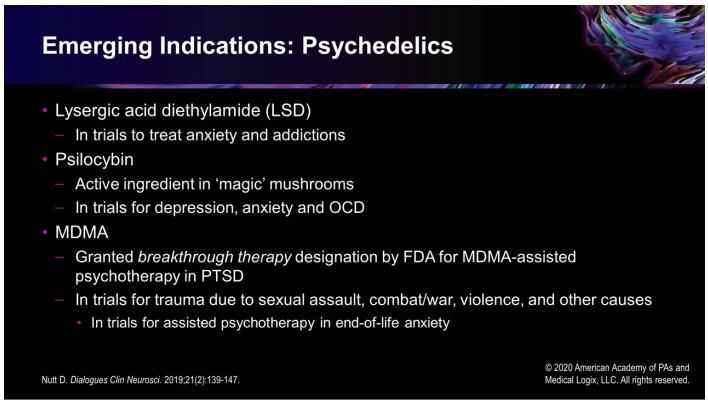
Lawrence Herman: Catherine, I have seen a number of very interesting psychotropic agents in the news recently. I've probably seen more about ketamine than anything else for the treatment of MDD, but there are a number that have emerging psychiatric indications. Can you just briefly mention them so our audience would at least be familiar with their names?

Catherine Judd: One of them is LSD, interestingly enough. This is a schedule I hallucinogenic drug, and researchers are hypothesizing that this could help reduce the burden of psychiatric disease, including anxiety and addiction, and there are clinical trials that are going on with that.

Another one is psilocybin. In the streets, this is known as magic mushrooms. It's the hallucinogenic compound in magic mushrooms, schedule I drug, psilocybin. It has recently gained traction as a promising treatment for several psychiatric conditions, including depression, anxiety and OCD.

And then finally, MDMA, and what's known in the streets as ecstasy or molly, widely known as a mood-altering party drug that increases pleasure, boosts energy, intensifies feelings of empathy. Interesting enough, the FDA granted MDMA a schedule I what they call drug breakthrough therapy designation for assisted psychotherapy for posttraumatic stress disorder. And this happened back in 2017.

And since then, phase 3 trials have been underway and are expected to be completed by 2022 studying whether or not MDMA-assisted psychotherapy can help particularly with patients who have suffered emotional damage from sexual assault, war, violent crime and other traumas. So some really interesting things out there with some pharmacotherapeutics. It's going to be interesting to see what happens and how they develop in their use.



Lawrence Herman: I would be remiss if I didn't take a moment and acknowledge that right now is an unprecedented time in the world today with COVID-19. And as a result, we are seeing that the mental health of our patients and our colleagues is being impacted.

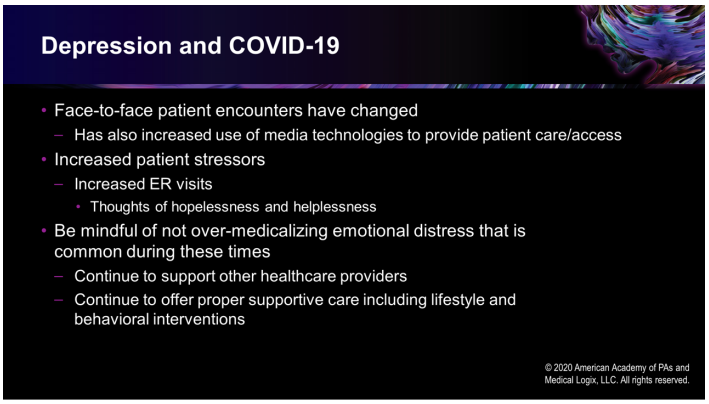
How has that affected your practices? Catherine, what have you seen specifically?

Catherine Judd: I think one of the things that we're seeing as a result of COVID-19 may be considered a double-edged sword. Number one, it has changed our practice in terms of face-to-face encounters with patients. But on the other hand, it has challenged us to use media, electronic media in terms of extending our reach to provide patient care and access.

One of the things that is also happening, as well, is that with the increased stress and stressors, we're seeing, at least in Dallas, an increase in the number of ER visits. We're seeing an increase in the patients presenting with thoughts that life's no longer worth living, the hopelessness and helplessness, and how can they go on?

I think one of the things, though, we need to be very careful, particularly in those individuals who do not have a premorbid psychiatric illness, that we're careful not to over-medicalize the emotional distress that everyone is experiencing now with COVID-19.

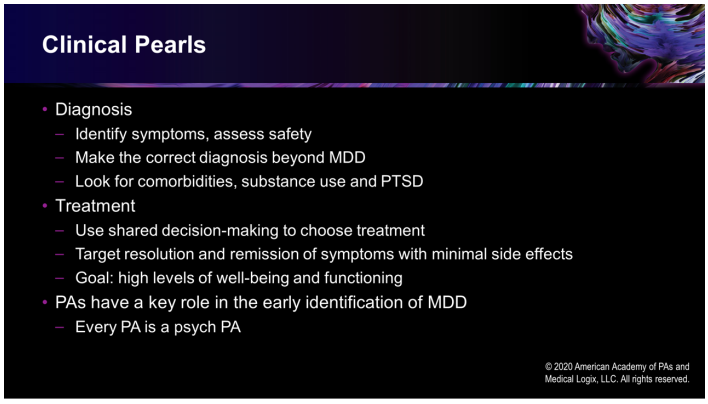
So I think we have to be careful that we're supportive of our patients, we're supportive of one another as health care providers, and that we're providing not only appropriate care, but supportive care, as well as suggesting lifestyle and behavioral interventions that can be very effective in terms of managing the stress that we're all feeling at this time.



Lawrence Herman: At this point, I'd like to ask each of you as to your specific closing thoughts and a clinical pearl on assessing and treating patients with major depressive disorder. Catherine?

Catherine Judd: Thank you, Larry. And thank you for the opportunity to participate in this discussion. I think first and foremost, we need to be identifying symptoms, assess safety. We need to be making a correct diagnosis beyond MDD and looking for the comorbidities of substance use and PTSD. We need to prescribe treatment and utilize shared decision-making. Our goal needs to be the resolution and remission of symptoms with minimal side effects.

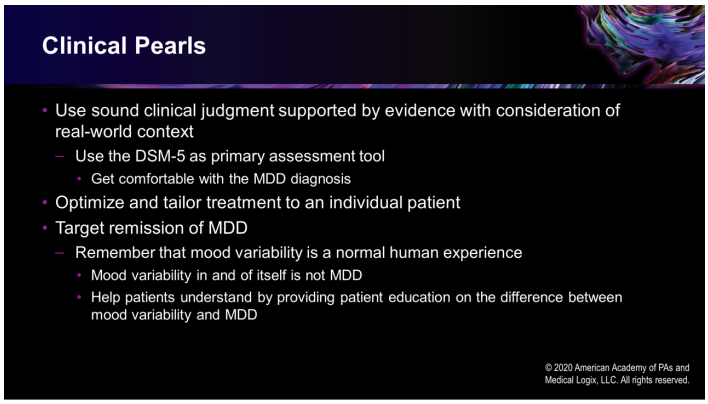
We need to be treating -- the goal of our treatment is the highest level of well-being and functioning for our patients. And as PAs, we have a role in the management of MDD in primary care with early identification. As treatment brokers for multidisciplinary team management, we're managers of chronic care and comorbidities and patient education. And my mantra as a PA in psychiatry for all PAs is that whatever your area of practice is, whatever discipline, that every PA is a psych PA.



Lawrence Herman: Oliver, what would you like to leave our audience with, please?

Oliver Oyama: Just the thought that, again, use sound clinical judgment supported by evidence with consideration of real-world context. Don't get too far away from the DSM-5. That in fact is our diagnostic nomenclature, and you want to get comfortable with the MDD diagnosis. Optimize and tailor treatment to an individual patient so that what you use for one patient might not be the same thing you use for another patient.

And then ultimately, target remission of MDD, with the understanding, however, that mood variability is a normal human experience. And as Catherine was suggesting earlier about over-medicalizing, mood variability in and of itself is not MDD. We have specific clinical criteria for it. So, save the diagnosis of MDD for people who truly meet clinical criteria and help patients understand by providing good patient education that mood variability in and of itself is not MDD.



Lawrence Herman: I would like to thank both of our expert faculty, Dr. Oliver Oyama and PA Catherine Judd, for their great insights and discussion. And I'd like to thank you, our audience, for participating in this *Clinical Dialogue*.

References:

Aboraya A, Nasrallah HA, Elswick DE, et al. Measurement-based Care in Psychiatry-Past, Present, and Future. *Innov Clin Neurosci.* 2018;15(11-12):13-26.

Celano CM, Freudenreich O, Fernandez-Robles C, et al. Depressogenic effects of medications: a review. *Dialogues Clin Neurosci.* 2011;13(1):109-125.

Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. *Br J Psychiatry*. 1987;150:782-786.

Esketamine Nasal Spray Posts Positive Results in Two Phase 3 Trials | Psychiatry & Behavioral Health Learning Network. Accessed November 7, 2019. https://www.psychcongress.com/article/esketamine-nasal-spray-posts-positive-results-two-phase-3-trials

FDA. FDA approves first treatment for post-partum depression. FDA. Published March 19, 2019. Accessed August 2, 2020. https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-post-partum-depression

FDA. FDA approves new nasal spray medication for treatment-resistant depression; available only at a certified doctor's office or clinic. FDA. Published September 11, 2019. Accessed November 7, 2019. http://www.fda.gov/news-events/press-announcements/fda-approves-new-nasal-spray-medication-treatment-resistant-depression-available-only-certified

Fortney JC, Unützer J, Wrenn G, et al. A Tipping Point for Measurement-Based Care. *Psychiatr Serv.* 2017;68(2):179-188.

Geriatric depression scale. Accessed September 27, 2020. https://geriatrictoolkit.missouri.edu/cog/GDS_SHORT_FORM.PDF

Jain R, Jain S. The Science and Practice of Wellness: Interventions for Happiness, Enthusiasm, Resilience, and Optimism (HERO). *W. W. Norton & Company*; 2020.

NIMH. Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study. Accessed August 2, 2020. https://www.nimh.nih.gov/funding/clinical-research/practical/stard/index.shtml

Nutt D. Psychedelic drugs-a new era in psychiatry?. *Dialogues Clin Neurosci.* 2019;21(2):139-147.

Ornoy A, Weinstein-Fudim L, Ergaz Z. Antidepressants, Antipsychotics, and Mood Stabilizers in Pregnancy: What Do We Know and How Should We Treat Pregnant Women with Depression. *Birth Defects Res.* 2017;109(12):933-956.

Poletti S, Sferrazza Papa G, Locatelli C, et al. Neuropsychological deficits in bipolar depression persist after successful antidepressant treatment. *J Affect Disord.* 2014;156:144-149.

Smarr KL, Keefer AL. Measures of depression and depressive symptoms: Beck Depression Inventory-II (BDI-II), Center for Epidemiologic Studies Depression Scale (CES-D), Geriatric Depression Scale (GDS), Hospital Anxiety and Depression Scale (HADS), and Patient Health Questionnaire-9 (PHQ-9). *Arthritis Care Res (Hoboken).* 2011;63 Suppl 11:S454-466.

Thornicroft G, Chatterji S, Evans-Lacko S, et al. Undertreatment of people with major depressive disorder in 21 countries. *Br J Psychiatry.* 2017;210(2):119-124.

Trivedi MH, Greer TL. Cognitive dysfunction in unipolar depression: implications for treatment. *J Affect Disord.* 2014;152-154:19-27.

Trivedi MH, Rush AJ, Wisniewski SR, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry*. 2006;163(1):28-40.

Williams N. The Mood Disorder Questionnaire. *Occup Med (Lond).* 2017;67(2):165-166.

eCASE CHALLENGE

Maria is a married 30-year-old woman who is a graduate student in biology. She returns to the clinic for follow-up for major depressive disorder (MDD). She first presented approximately 2 months ago, complaining of depressed mood, crying spells, trouble sleeping, difficulty concentrating, decreased energy, and fatigue for the past year. At her first visit, she was administered the PHQ-9 and she had a score of 12.

She was initially treated with a selective serotonin reuptake inhibitor (SSRI) but felt nauseous while taking them. She was started on a trial of mirtazapine, a noradrenergic and specific serotonergic antidepressant (NaSSA), which was titrated up to the maximum dose of 45 mg QHS. She reported her mood, appetite, and sleep might be slightly improved, but continues to have difficulty concentrating, finishing assignments related to her studies, and is afraid she may dismissed from the program because of her poor performance.

Her mental status examination reveals that the patient is pale and appears of normal body weight, dressed in casual slacks and sweater. Grooming is fair and without makeup. She speaks slowly, often not responding to questions for approximately 10 seconds before answering. She describes depressed mood and lack of energy and says she feels no pleasure in life. Her husband is good to her, but she feels abandoned by many of her friends. She has no social contacts other than occasional visits by her parents. She feels worthless and blames herself for her problems. She is often anxious and worries about the future. She worries about how she will repay her financial debts. Her speech is clear and coherent. Her thought processes are organized, logical, and goal oriented. She endorses no active suicidal or homicidal ideation but does have fleeting thoughts that things might be better if she were not alive. She denies hallucinations, paranoid delusions, and other psychotic features.

Biometrics:

- Height: 5 feet 1 inches
- Weight: 132 lbs. (previous 124 lbs.)
- Current BMI: 24.9 kg/m2

Vital Signs:

- Heart rate: 59 bpm
- BP: 111/72 mmHg
- Respirations: 18/minute

Past Medical History:

- Major depressive disorder (diagnosed 2 months ago)

Family History:

- Aunt with major depression
- Patient wonders if her sister suffers from depression

Social History:

- Non-smoker
- Alcohol use: prior - social/on occasion (2 glasses of wine on weekends), currently – denies alcohol use
- Occupation: PhD student in biology
- Spouse: married, no children (not currently planning for pregnancy, using barrier contraception)

Current Medications:

- Mirtazapine 45 mg at bedtime

Known Allergies:

- None

Recent Laboratory Findings:

- TSH: 1.2 mIU/mL [within normal limits]
- HbA1C: 5.4%
- Liver function tests: normal
- Electrolytes: normal
- BUN/Creatinine: 16/0.8

You would like to get a better objective sense of her depression. She was previously given a screening Patient Health Questionnaire, PHQ-2, before you interviewed her, and it was positive. You will follow-up today to see how her PHQ-9 score has changed compared with her last visit. This leads to the first clinical question.

Question #1

What does the PHQ-2 ask about?

A. Frequency of "Little interest or pleasure in doing things" and "Feeling down, depressed or hopeless"
B. Frequency of "Poor appetite or overeating" and "Feeling tired or having little energy"
C. Frequency of "Suicidal ideation" and "Homicidal ideation"
D. Frequency of "Trouble concentrating on things" and "Feeling bad about yourself — or that you are a failure or have let yourself or your family down"

Measurement-based care (MBC) improves patient outcomes compared with typical standard of care.[12–15] Recently, a randomized trial showed that MBC improved response and remission rates compared with standard of care.[16] Similarly, times to response and remission were reduced. Yet, many practitioners still do not use MBC in their practice for assessing mental health diagnoses. Cited barriers include the following:[17]

- Limited time to administer
- Lack of clinical relevance (i.e., tools are designed for use in trials rather than practice)
- Results of measurements do not impact practice in a relevant way
- Use of the tools may interfere with building rapport
- Overly complicated scales
- Lack of formal training in the use of scales

The PHQ-9 is frequently used to objectively measure symptoms of depression scores across time. The PHQ-9 may be patient or clinician-administered. It assesses the frequency of depressive symptoms, corresponding to the DSM-5 criteria for major depressive disorder over the previous two weeks (Figure 1 below).[18] It is easy to use and quick to administer.

The maximum total score is 27. Scores from 0-4 indicate minimal or no depression; 5-9 indicate mild depression; 10-14 indicate moderate depression; 15-19 indicate moderately severe depression; and 20-27 indicate severe depression.

Figure 1. Patient Health Questionnaire, 9-question version

Over the last 2 weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

How difficult have these problems made it for you to do your work, take care of things at home, or get along with other people? (Circle one)

Not difficult at all Somewhat difficult Very difficult Extremely difficult

These symptoms correspond to the DSM-5 criteria for a major depressive episode. Of note, however, for a diagnosis of MDD, one of the features must be depressed mood or anhedonia (major criteria).

The PHQ-2, is a shortened screening tool, consisting of the first two questions on the PHQ-9 regarding (1) depressed mood most of the day, nearly every day or (2) the loss of interest or pleasure in normally enjoyed activities. Thus, the correct answer is A.

In some versions of the PHQ-9 a 10th question is included which assesses the patients overall level of functioning.

Other useful screening questionnaires include the *Mood Disorder Questionnaire*[19], which is useful in ruling out bipolar disorder in a current episode of depression the *Geriatric Depression Scale*[20,21], is useful in screening for depression in elderly patients.

Case Continues

Maria completes a PHQ-9 questionnaire in clinic, and her score has deceased from 12 to 9. She has been on her current treatment for approximately 8 weeks. She continues to express hopelessness and doubts about her ability to settle down, concentrate, and stay focused enough to complete her dissertation and PhD.

This brings us to our next clinical question.

Question #2

Which of the following antidepressants have demonstrated efficacy in improving cognitive functioning?

A. Citalopram
B. Lithium
C. Sertraline
D. Vortioxetine

Problems with cognition are frequently reported in patients with MDD; however, it is difficult to determine their exact prevalence and incidence.[22] Cognitive issues associated with MDD may include memory impairment, decision-making difficulty, and loss of cognitive flexibility. These symptoms may be associated with disability and limitations in functional recovery. Thirty percent of patients who otherwise responded to antidepressant therapy reported residual cognitive symptoms such as forgetfulness, inattentiveness, mental slowing, apathy, and word-finding difficulties.[23]

Nonetheless, there is evidence that cognitive symptoms improve with antidepressant therapy,[24,25] and there is some evidence that some classes of anti-depressants may be more effective than others in improving specific cognitive symptoms than others.[25]

Three large, placebo-controlled studies in adults with recurrent MDD, short-term treatment with vortioxetine more often than not resulted in statistically significant and clinically meaningful improvements in performance on two objective measures. These included executive functioning, attention, processing speed,

learning and memory. In general, the beneficial effects of vortioxetine on these measures were largely independent of its effect on improving depressive symptoms.[26]

Herrera-Guzman et al. assessed cognitive functioning before treatment with escitalopram or duloxetine, at 24 weeks of treatment, and again after 24 weeks of unmedicated recovery.[25,27] At the end of 24 weeks of treatment, 86% of patients were in full remission and 14% in partial remission. Patients in both treatment groups demonstrated improvement from baseline in verbal and visual episodic memory, working memory, and processing speed. Patients in the duloxetine group showed more improvement in episodic memory and working memory than those in the escitalopram group. Despite evidence of improvement, residual deficits were still present.

Both vortioxetine and duloxetine are associated with improvements in cognitive functioning when treating depression, the correct answer to this question is D. Although antidepressant medication can mitigate depressed mood and neurovegetative symptoms, some medications are more commonly associated with certain side effects than others. This brings us to our next clinical question.

Question #3

Which of the following medications tends to be more associated with weight gain?

A. Bupropion
B. Citalopram
C. Vortioxetine
D. Mirtazapine

Common first-line pharmacotherapy for an episode of major depression includes

selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, sertraline, paroxetine, citalopram and escitalopram; serotonin-norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine, desvenlafaxine, bupropion, and mirtazapine. Side effects vary among the specific medications. In the case of the SSRIs, common side effects may include sedation or activation,

weight gain, headache, gastrointestinal symptoms, and tremor. Sexual dysfunction may or may not emerge as a treatment side effect until later in the course of treatment, weeks to months. In the case of venlafaxine, elevated blood pressure may emerge as a dose-related side effect.

Although efficacy is essentially equivalent among all classes of antidepressants,

tricyclic antidepressants (TCAs) such as desipramine and nortriptyline are not routinely considered first-line agents because of their side effects. In addition to anticholinergic side effects, such as orthostasis, dry mouth and cardiac arrhythmias, TCAs are potentially lethal in overdose. Monoamine oxidase inhibitors (MAOIs) are used less frequently because of

their significant drug–drug interactions and dietary restrictions requiring patients to follow a tyramine free diet.

Some SSRIs, fluoxetine in particular, appear to be associated with weight loss during short-term therapy, but with weight gain during long-term therapy, possibly coinciding with remission of depressive symptoms.[28]

Mirtazapine, with its potent antihistaminergic properties similar to TCAs, is commonly associated with weight gain.[29,30] Given this association, the correct answer is D. In trials, higher doses of mirtazapine resulted in less weight gain, which may be related to different mechanisms of action at higher doses.[29] The novel antidepressants venlafaxine, nefazodone, and bupropion have been shown to produce weight loss in some patients. These agents may be considered as alternative therapy for patients who experience weight gain with other antidepressants.

In contrast to mirtazapine, which may be associated more frequently with sedation and may help patients with insomnia, bupropion is considered to be more "activating". In addition, bupropion may be an alternative for patients experiencing sexual side effects on SSRIs.

Regarding this specific patient, she is of reproductive age, thus one must consider the teratogenicity of antidepressant or augmenting agents when guiding treatment decisions. This leads to the next clinical question.

Question #4

Which of the following antidepressants is generally considered to be safest during pregnancy?

A. Clomipramine
B. Paroxetine
C. Sertraline
D. Venlafaxine

The risk of teratogenicity varies between antidepressants. For the most part, obstetricians feel most comfortable with sertraline given its safety profile during pregnancy and lactation postpartum. Thus, the correct answer to this question in C.

In one review, paroxetine showed questionable risk of fetal cardiac defects. Though more recent studies do not reflect this.[31] Tricyclic antidepressants are generally felt to have a low risk of teratogenicity. Interestingly, however, one large study found that clomipramine was associated with an elevated rate of severe malformations, including cardiovascular defects. Valproic acid, which is used in bipolar disorder, is associated with a 10% risk of neural tube defects.[31]

Following the delivery, most antidepressants are safe for use, except for fluoxetine. Sertraline is commonly used during lactation. As always, this is a decision between the provider and the patient, with good patient education about risk and benefits.

In a recent large multicenter, population-based study, the National Birth Defects Prevention Study (NBDPS), investigators looked at the association between antidepressants and birth defects.[32] The analysis included 30,630 cases of birth defects and 11,478 infants born without major birth defects. The use of venlafaxine was associated with more birth defects than others when taken in the first months of pregnancy. However, the researchers note that there was limited literature on venlafaxine in this data set. In this study, escitalopram was associated with the lower number of birth defects. The other remaining SSRIs analyzed were associated with a small number of birth defects.

Case Continues

As you have been building your relationship with Maria, you screen for a history of trauma, PTSD, or sexual abuse. She denies any current or past traumatic events that she is aware of. Considering available treatment options, she wants to continue pharmacotherapy, but may be open to psychotherapy later. At this point, given the demands of her graduate program, she continues to be extremely worried that she continues to be depressed and struggling with cognition, motivation, and concentration. She

reports significant weight gain since starting mirtazapine. She states she can accept the trade-off, but only if her mood and level of functioning had improved, which it has not.

This brings us to our final clinical question.

Question #5

Based on Maria's case presentation and her preferences, what is the next best step in managing her residual symptoms and failure to reach full remission of her mood symptoms?

A. Augment with monoamine oxidase inhibitor
B. Continue treatment with mirtazapine for 6 weeks
C. Discontinue mirtazapine and refer for psychotherapy
D. Gradually taper mirtazapine and start vortioxetine

Using shared decision making, decisions should be made based on objectively measured response and clinical symptoms.

If a patient experiences a partial response, guidelines recommend first increasing medication dose. Note, however, when increasing dose, the efficacy increases, but potential side effects may increase as well. If a patient is improving with at least 50% improvement in symptoms, consider augmenting the current medication with a second medication with a different mechanism of action. If a patient is experiencing less than 50% improvement in their symptoms, consider switching to another antidepressant with a different mechanism of action or a medication in a different class.

Generally, antidepressants should not be abruptly discontinued, but should be gradually tapered (or cross tapered) to avoid "discontinuation syndrome". This is particularly true when discontinuing a medication with a short half-life such as paroxetine, and less common with medications with longer half-lives, such as fluoxetine. Symptoms of "discontinuation syndrome" can include flu-like symptoms, i.e., nausea, vomiting, diaphoresis, headache, and sleep disturbances. Less common symptoms include tremors, imbalance/vertigo, dysphoria, and anxiety.

Since Maria is complaining of ongoing mood/cognitive symptoms, is concerned about weight gain associated with mirtazapine, and is having less than 50% response after more than 6 weeks of treatment, it is reasonable to consider switching mirtazapine to a medication that may offer more improvement in her cognitive functioning as well as unremitting mood symptoms.

When switching or augmenting antidepressant pharmacotherapy the first consideration should be choice of another antidepressant of a different class or mechanism of action. In Maria's case, our first consideration is an antidepressant from a different class. Since Maria is taking an SSRI, the next step may be switching to a serotonin-norepinephrine reuptake inhibitor (SNRI), a norepinephrine-dopamine reuptake inhibitor (NDRI), or a serotonin modulator (SMS).

The choice of class of medication should take into consideration mechanism of action, receptor binding profile, and side effect profile. The goal of therapy is complete remission of symptoms. If energy and motivation are prominent residual symptoms, a more activating medication such as bupropion may be the best choice. On the other hand if insomnia and difficulty sleeping are problematic, a medication such as mirtazapine, which is more sedating, may be a logical choice.

There is growing evidence for the use of augmenting agents in major depressive disorder. When there is at least a 50% response, but failure to reach remission, the following strategies may be considered:

- Lithium
- T3 (thyroid hormone)
- Buspirone
- TCAs
- Second generation antipsychotics (SGAs)

The following SGAs have an indication for augmentation in the treatment of MDD: aripiprazole, brexpiprazole, olanzapine, and quetiapine.

Augmentation of one serotonergic agent with another must be done with caution because of the risk of causing "serotonin syndrome", which is a medical emergency. Serotonin syndrome is a relatively rare adverse event associated with treatment with multiple serotonergic agents including antidepressants (SSRIs, SNRIs, MAOIs), triptans, dextromethorphan, metoclopramide, SGAs, and others. Symptoms of "serotonin syndrome" include: hypertension, tachycardia, hyperthermia, hyperreflexia, agitation, diaphoresis, tremor, and mydriasis (pupil dilation).[33]

Case Continues

You and Maria discuss the potential advantages and disadvantages of switching or augmenting her current antidepressant therapy. Given Maria's incomplete response (PHQ-9 score decreased from 12 to 9) at maximal dose therapy, and her remaining cognitive symptoms (poor concentration), you both decide that switching from mirtazapine to vortioxetine is the best option at this point. Given this, the correct answer to this question is D. As well, Maria is pleased that this medication is not specifically associated with weight gain. While she is not on other serotonergic medications, she is counseled to discuss and remind other healthcare providers about her medication, should she begin a new medication.

In addition to this change, you continue to support wellness measures that have been shown to improve depressive symptoms. These include exercise, mindfulness training, socialization practices, sleep hygiene, and diet/nutritional tracking and counseling.[34] You recommend a mindfulness training mobile app that your other patients have found helpful.

Maria returns in 2 weeks to assess tolerability and safety concerns (i.e. thoughts of self-harm or suicidal ideation). Four weeks later, she returns to reassess her mood. Her PHQ-9 scores have improved from 12 to 6, and she reports no bothersome adverse side effects. While she has mild nausea, she states she can tolerate this in the light of slightly improved concentration and mild weight loss. Together you decide to increase her dose of vortioxetine to further improve her symptoms, with the understanding that you can decrease dose or change medications later. At this later follow up visit, you continue to measure her response to treatment and monitor for residual symptoms and side effects.

Conclusions

The burden of MDD in the U.S. remains large and has a massive impact on individuals affected, their families, and society. PAs are on the front line of treating this common condition. They play a critical role in recognizing, diagnosing, and treating patients with major depressive disorder. Key to appropriate treatment is the use of objective measurement of response: measurement-based care (MBC). The PHQ-9 is commonly used to track MDD symptoms as it reflects the DSM-5 criteria for major depressive disorder. In patients with a partial response, doses of medications may be maximized first. Afterwards, if response is still inadequate and patients do not achieve remission of symptoms (less than 50% improvement), one may consider switching medications; however,

if there is a partial response (greater than 50% improvement) without complete remission, one can consider augmenting with other agents, which may include other classes of medications. When choosing subsequent treatment options, consider side effect profile and remaining residual symptoms, such as energy level, sexual side effects, and weight gain. Wellness interventions have been shown to improve depression as well. These interventions include exercise, mindfulness training, socialization practices, sleep hygiene, and diet tracking/counseling. At times, even with the best treatment, some patients will require specialist referral either for psychotherapy or other psychopharmaceutical treatment options. To ensure the safety of patients, providers should feel comfortable working together not just to decrease depression, but to target complete depression remission.

CLINICAL PEARL

We hope you have enjoyed this *eCase Challenge*, and that you have increased your knowledge and confidence in assessing and treating patients with major depressive disorder.

Major depressive disorder is common in the primary care setting. Unfortunately, research still shows that it is underrecognized and undertreated. Steps to improve recognition and treatment response include the use of validated scales for tracking mood, such as the PHQ-9.

In terms of treatment, being aware of treatment response, but also next steps in treatment, are crucial for adequately treating patients with major depressive disorder. Several algorithms for treating depression exist.

Their key principles include (1) regular follow-up with closer follow-up after switching medication or increasing dose, (2) increasing dose for partial responders, and (3) switching or augmenting, as appropriate, if patient experiences intolerable side effects or is still not responding sufficiently.

Treatment choices include SSRIs, SNRIs, such as duloxetine, and NDRIs, such as bupropion, or neuromodulator, such as vortioxetine. Augmenting agents include antidepressants of a different class, lithium, and second-generation antipsychotics.

When assessing treatment response, it is important to ask about adherence.

Wellness interventions also benefit patients, with objective improvements in depression scores through simple interventions, such as walking, mindfulness mediation, social connectedness practice, and food and alcohol intake tracking.

As well, it is important to rule out other potential medical causes of depressive symptoms, such as thyroid disease or medications themselves, such as anticonvulsants, corticosteroids and some cardiovascular medications.

Thank you again for your participation in this *eCase Challenge*.

References:

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Association; 2013.
2. CDC. Suicide rising across the US. Centers for Disease Control and Prevention. Published November 27, 2018. Accessed October 12, 2020. https://www.cdc.gov/vitalsigns/suicide/index.html
3. Hasin DS, Sarvet AL, Meyers JL, et al. Epidemiology of Adult DSM-5 Major Depressive Disorder and Its Specifiers in the United States. *JAMA Psychiatry*. 2018;75(4):336-346.
4. Weissman MM, Gershon ES, Kidd KK, et al. Psychiatric disorders in the relatives of probands with affective disorders. The Yale University--National Institute of Mental Health Collaborative Study. *Arch Gen Psychiatry*. 1984;41(1)13-21.
5. Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: review and meta-analysis. *Am J Psychiatry*. 2000;157(10):1552-1562.
6. Reeves WC, Strine TW, Pratt LA, et al. Mental illness surveillance among adults in the United States. *MMWR supplements*. 2011;60(3):1-29.
7. Marcus SC, Olfson M. National trends in the treatment for depression from 1998 to 2007. *Arch Gen Psychiatry*. 2010;67(12):1265-1273.
8. Bishop TF, Press MJ, Keyhani S, Pincus HA. Acceptance of insurance by psychiatrists and the implications for access to mental health care. *JAMA Psychiatry*. 2014;71(2):176-181.
9. Boyd JW, Linsenmeyer A, Woolhandler S, Himmelstein DU, Nardin R. The crisis in mental health care: a preliminary study of access to psychiatric care in Boston. *Ann Emerg Med*. 2011;58(2):218-219.
10. Rhodes KV, Vieth TL, Kushner H, Levy H, Asplin BR. Referral without access: for psychiatric services, wait for the beep. *Ann Emerg Med*. 2009;54(2):272-278.
11. Malowney M, Keltz S, Fischer D, Boyd JW. Availability of outpatient care from psychiatrists: a simulated-patient study in three U.S. cities. *Psychiatr Serv*. 2015;66(1):94-96.
12. Fortney JC, Unützer J, Wrenn G, et al. A Tipping Point for Measurement-Based Care. *Psychiatr Serv*. 2017;68(2):179-188.
13. Scott K, Lewis CC. Using Measurement-Based Care to Enhance Any Treatment. *Cogn Behav Pract*. 2015;22(1):49-59.
14. Trivedi MH, Daly EJ. Measurement-based care for refractory depression: a clinical decision support model for clinical research and practice. *Drug Alcohol Depend*. 2007;88 Suppl 2:S61-71.

15. Harding KJK, Rush AJ, Arbuckle M, Trivedi MH, Pincus HA. Measurement-based care in psychiatric practice: a policy framework for implementation. *J Clin Psychiatry*. 2011;72(8):1136-1143.
16. Guo T, Xiang Y-T, Xiao L, et al. Measurement-Based Care Versus Standard Care for Major Depression: A Randomized Controlled Trial With Blind Raters. *Am J Psychiatry*. 2015;172(10):1004-1013.
17. Aboraya A, Nasrallah HA, Elswick DE, et al. Measurement-based Care in Psychiatry-Past, Present, and Future. *Innov Clin Neurosci*. 2018;15(11-12):13-26.
18. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16(9):606-613.
19. Williams N. The Mood Disorder Questionnaire. *Occup Med (Lond)*. 2017;67(2):165-166.
20. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res*. 1982;17(1):37-49.
21. Greenberg SA. How to try this: the Geriatric Depression Scale: Short Form. *Am J Nurs*. 2007;107(10):60-69; quiz 69-70.
22. Trivedi MH, Greer TL. Cognitive dysfunction in unipolar depression: implications for treatment. *J Affect Disord*. 2014;152-154:19-27.
23. Poletti S, Sferrazza Papa G, Locatelli C, Colombo C, Benedetti F. Neuropsychological deficits in bipolar depression persist after successful antidepressant treatment. *J Affect Disord*. 2014;156:144-149.
24. Wagner S, Doering B, Helmreich I, Lieb K, Tadić A. A meta-analysis of executive dysfunctions in unipolar major depressive disorder without psychotic symptoms and their changes during antidepressant treatment. *Acta Psychiatr Scand*. 2012;125(4):281-292.
25. Herrera-Guzmán I, Gudayol-Ferré E, Herrera-Guzmán D, Guàrdia-Olmos J, Hinojosa-Calvo E, Herrera-Abarca JE. Effects of selective serotonin reuptake and dual serotonergic-noradrenergic reuptake treatments on memory and mental processing speed in patients with major depressive disorder. *J Psychiatr Res*. 2009;43(9):855-863.
26. Frampton JE. Vortioxetine: A Review in Cognitive Dysfunction in Depression. *Drugs*. 2016;76(17):1675-1682.
27. Herrera-Guzmán I, Gudayol-Ferré E, Herrera-Abarca JE, et al. Major Depressive Disorder in recovery and neuropsychological functioning: effects of selective serotonin reuptake inhibitor and dual inhibitor depression treatments on residual cognitive deficits in patients with Major Depressive Disorder in recovery. *J Affect Disord*. 2010;123(1-3):341-350.
28. Michelson D, Amsterdam JD, Quitkin FM, et al. Changes in weight during a 1-year trial of fluoxetine. *Am J Psychiatry*. 1999;156(8):1170-1176.
29. Masand PS. Weight gain associated with psychotropic drugs. *Expert Opin Pharmacother*. 2000;1(3):377-389.
30. Fava M. Weight gain and antidepressants. *J Clin Psychiatry*. 2000;61 Suppl 11:37-41.
31. Ornoy A, Weinstein-Fudim L, Ergaz Z. Antidepressants, Antipsychotics, and Mood Stabilizers in Pregnancy: What Do We Know and How Should We Treat Pregnant Women with Depression. *Birth Defects Res*. 2017;109(12):933-956.
32. Anderson KN, Lind JN, Simeone RM, et al. Maternal Use of Specific Antidepressant Medications During Early Pregnancy and the Risk of Selected Birth Defects. *JAMA Psychiatry*. Published online August 5, 2020.
33. Tormoehlen LM, Rusyniak DE. Neuroleptic malignant syndrome and serotonin syndrome. *Handb Clin Neurol*. 2018;157:663-675.
34. Jain R, Jain S. *The Science and Practice of Wellness: Interventions for Happiness, Enthusiasm, Resilience, and Optimism (HERO)*. W. W. Norton & Company; 2020.

CME POST-TEST: Participants must: 1) read the educational objectives and faculty disclosures; 2) study the educational materials; 3) complete the post assessments in Learning Central. See page 2 for further information.

Question #1

What is the Mood Disorder Questionnaire used to screen for?

A. Bipolar disorder
B. Major depressive disorder
C. Personality disorders
D. Postpartum depression

Question #2

Which of the following medication classes is associated with improvements in cognitive functioning in major depressive disorder (MDD)?

A. Norepinephrine-dopamine reuptake inhibitors (NDRI)
B. Serotonin modulators and stimulators (SMS)
C. Serotonin and norepinephrine reuptake inhibitors (SNRI)
D. Selective serotonin reuptake inhibitors (SSRI)

Question #3

A patient taking an SNRI and St John's Wort presents with hypertension, tachycardia, hyperthermia, clonus, hyperreflexia, and mydriasis that has manifested over the past 18 hours. What is the best diagnosis of the given options?

A. MDMA intoxication
B. Neuroleptic malignant syndrome
C. Serotonin syndrome
D. Benzodiazepine withdrawal

Question #4

Which of the following is NOT a class of antidepressants one should generally use as an augmenting agent?

A. Monoamine oxidase inhibitor (MAOI)
B. Norepinephrine-dopamine reuptake inhibitor (NDRI)
C. Serotonin modulators and stimulator (SMS)
D. Selective serotonin reuptake inhibitor (SSRI)

Question #5

Which of the following is NOT generally considered to be an augmenting agent in MDD?

A. Buspirone
B. Lithium
C. Second generation antipsychotics
D. Stimulant medications

Question #6

Which class of medications is more frequently associated with antidepressant discontinuation syndrome?

A. Longer-acting antidepressants
B. Shorter-acting antidepressants
C. Buspirone
D. Second generation antipsychotics

Question #7

Which of the following medications is associated with a risk of serotonin syndrome if used in combination with other serotonergic medications?

A. Cocaine
B. Proton-pump inhibitors (PPIs)
C. Second generation antipsychotics
D. Triptans

Question #8

Which of the following classes of antidepressants is most appropriate to augment with for treatment of major depressive disorder (MDD)?

A. Monoamine oxidase inhibitors (MAOI)
B. Second generation antipsychotics (SGA)
C. Anxiolytics
D. Serotonin-norepinephrine neuromodulators

Question #9

Which of the following SSRIs is more frequently associated with antidepressant discontinuation syndrome?

A. Citalopram
B. Escitalopram
C. Fluoxetine
D. Paroxetine

Question #10

A 54-year-old male accountant, who was diagnosed with MDD, returns to the primary care clinic for a follow-up appointment. He was started on a selective serotonin reuptake inhibitor (SSRI); however, this was discontinued after six weeks because of problems with sexual functioning. He was switched to bupropion, current dose of 450 mg PO daily. His PHQ-9 at the beginning of treatment was 14. At this follow-up appointment, his PHQ is 6. He reports no troublesome side effects other than depressed mood. He denies alcohol or illicit substance use and takes no other prescribed medications. In view of ongoing depressed mood, the most appropriate next step in treatment is which of the following:?

A. Augment with a 2nd generation antipsychotic
B. Continue treatment with bupropion for 6 weeks
C. Taper bupropion and refer for cognitive behavioral therapy
D. Switch to a mood stabilizer

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