210: Q&A with Dr. Michael Cummings

David Puder, M.D.

INTRO

Dr Puder: Welcome back to the Psychiatry and Psychotherapy Podcast. I am joined today with Dr. Michael Cummings. He is a pivotal person in this podcast series and his deep dives on psychopharmacology. I send out to my email list if you have gone on my website, you're on my email list and so I sent out, please send me your questions, and I will pitch them Dr. Cummings. This is a cornucopia of questions. It's all over the place. If you like this, you can let me know and if you want to do this again, if we get enough of those positive things, we'll do it again. So here we go. You're ready, Dr. Cummings?

Dr Cummings: I am happy to be back and we'll see what happens.

Dr Puder: Some of these will be rapid fire. Some of them maybe will speak more and I asked people if they wanted me to list their names or not. So if I do, I've gotten their permission. and so we have no conflicts of interest here, Dr. Cummings, to report.

Schizophrenia

Here are our questions on schizophrenia: An anonymous listener from Iowa, “I listened to all your podcasts and repeated them. I've learned more from you than my professors. Please speak about treating with two long acting injectables (LAIs). I have a patients with severe psychosis who absolutely will not take any oral. I have cases that become life threatening because the patient believes food and medical treatment are contaminated and refuses them. These are individuals in psychiatric facilities long term. I've had people on Haldol 200 milligrams every two weeks. I've worked with fluphenazine injections, but I've never dosed more than 75 milligrams every two weeks.

Dr Cummings: Okay, essentially this question deals with the issue of polypharmacy. There's nothing inherently forbidden about giving to long acting injectable antipsychotics. The question is whether the combination is rational or irrational. The first step of course, would be to check the single antipsychotic To be sure that it is optimal. While dose can tell you something about optimal treatment, it's very limited because of the variation people have and rate of metabolism for drugs. The better way to assess optimal treatment is to measure the plasma concentration. For example, haloperidol has an optimal range of two to 18 nanograms per milliliter fluphenazine has an optimal range of around one nanograms per milliliter to four nanograms per milliliter. So the first step would be to check to be sure that your single drug is optimal. Usually in a resistant patient, meaning near the upper end of the optimal plasma concentration range for that drug. If the patient fails to respond adequately to an optimal single agent, then the next step is to look for an agent that offers complementary mechanisms of action. For example, combining

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haloperidol and fluphenazine would make very little sense because they offer essentially very potent D2 receptor antagonism but not much else. An example of something that would be a more rational combination would be haloperidol and olanzapine. In particular, olanzapine at its higher plasma concentration ranges 120 to 150 nanograms per milliliter and begins to give you modest glutamate modulation in addition to dopamine blockade. Combining that with haloperidol could give you a robust D2 blockade plus at least a weaker version of glutamate modulation that is weaker than clozapine's glutamate modulation. Such a combination in oral form has indeed been demonstrated to provide modestly superior antipsychotic effects. One would expect that giving both drugs in long-acting injectable form would produce the same results so that although that has not been specifically tested. One thing you would not want to do would be to combine a dopamine antagonist, like haloperidol, with a partial agonist such as aripiprazole, and that's because they are aripiprazole has a much higher binding affinity for the D2 receptor and will essentially displace the haloperidol so that the haloperidol becomes an inactive drug if the aripiprazole is occupying the vast majority of the D2 receptors.

Dr Puder: Excellent and of course, if they're willing to do clozapine that would be even better.

Clozapine

Okay, anonymous listener from Manitoba, who says, “I have listened to all episodes with Dr. Cummings, and they are my favorite. And I'm very grateful for his wisdom and deep knowledge.” By the way, if Dr. Cummings is your favorite, my ego is totally okay with that. He's one of my favorites too.

Dr Cummings: On the other hand, I'm blushing.

Dr Puder: So this person asks, I would like to ask if there are any relative or absolute contraindications to try clozapine for treatment resistant schizophrenia, and whether there are specific factors that would make it unlikely that Clozapine would be effective. The reason I'm asking is that I see a lot of reluctance by psychiatrists to consider clozapine even for the most treatment resistant patients.

Dr Cummings: First clozapine is the gold standard for treatment resistant psychotic illness. The likelihood of a person with treatment resistant schizophrenia responding to clozapine is typically in the 40-60% range, the likelihood that they will respond to a dopamine antagonist, or dopamine partial agonist is somewhere south of 7%. So fairly bad response rates for everything except clozapine. Clozapine does start to lose efficacy after the person has been treatment resistant for more than 2.8 years. That's from a Japanese study by Yamashiro. In which they looked at what happens long term if you don't give Clozapine. There are other articles that have

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been published about the effects of delaying clozapine treatment. There are no absolute contraindications. People can be rechallenged after things like myocarditis, and even after things like severe neutropenia. It calls for a great deal of careful monitoring, and a very, very slow titration in both of those clinical contexts. Because Clozapine for many patients is their only viable option. The FDA removed severe neutropenia as an absolute contraindication. Basically saying, if the clinician believes that the benefit is more likely than harm then yes, but with obvious caution. Obviously with caution given that severe neutropenia, or myocarditis can both be life threatening.

Dr Puder: Yep, excellent. So in summary, more providers should have less reluctance to use clozapine and remember that constipation kills more people than neutropenia, right?

Dr Cummings: Yes. by a factor of almost 10. People don't appreciate that after someone has been on Clozapine for two years, the risk of death due to severe neutropenia is down in the less than one per 10,000 range, so it's statistically tiny. With respect to the constipation issue, one thing to be sure of for anybody that you treat with clozapine, is to be sure they're on a good bowel regimen. Which can be starting with an osmotic laxative, such as polyethylene glycol. If that's not sufficient, add a stimulant laxative, such as sennosides. If that combination isn't sufficient, replace the sennoside with a secretagogue, like linaclotide or prucalopride, that will avoid the issue of constipation or bowel obstruction in the vast majority of patients also be sure that you don't load the person with other drugs that are anticholinergic 50 milligrams of Clozapine is roughly equivalent, in anticholinergic effects to one milligram of Benztropine.

New Antipsychotics

Dr Puder: That's a lot. That's a lot of anticholinergic power. Okay, anonymous listener asks, What do you have to look forward to in the world of new antipsychotics? Are there any new classes of medications that work differently than those other D2 two meds? any hope of long acting injectables for clozapine? Anything to help with negative symptoms and cognition? Okay, should we take an episode on that?

Dr Cummings: I started saying that's about an episode and a half there. The main area that's currently of interest in research for a new mechanism to control schizophrenic symptoms is modulation of M4 muscarinic receptors. The first drug likely to be available in that area is xanomeline. It's an M4 agonist. By the way, Clozapine is also an M4 agonist. Basically, this is a way of presynaptically modulating the release of dopamine in the ventral tegmental area. So rather than trying to block dopamine postsynaptically, this would be an attempt to modulate the release of dopamine in this specific circuit presynaptically. There are also allosteric receptors involved in that pathway and there's some research looking at trace amine-associated receptor (TAAR) molecules to modulate the same circuit. Those are a little further away as potential

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drugs. Will there be a long acting injectable version of clozapine? It will be difficult because of the doses of Clozapine required, and consequently, the volume involved, but I know there are a couple of people interested in that area. I'm not sure how far along they've gotten with the physical chemistry aspects of looking at, for example, subcutaneous gels that could contain an adequate amount of Clozapine. Not in the United States, but in other countries, there is an immediate release injectable form of Clozapine available. In the UK and Australia, and may be available in other Commonwealth countries, as well. Doses are not high enough for maintenance treatment, but are large enough to permit initiation of clozapine.

CYP Inducers and Inhibitors

Dr Puder: Interesting. Okay, Kaden Page (M1 at RUSM), and a longtime listener, who has successfully entered his first year of medical school.

Dr. Cummings: Congratulations!

Dr. Puder: Yes, congratulations, Page. And he says that Dr. Cummings is the Yoda of psychiatry.

Dr. Cummings: Can I say, “Honored I am”

Dr. Puder: Can you speak more to the mechanism in which CYP inducers and inhibitors work? For example, how the interaction between fluvoxamine and Clozapine works and what it does in the body and what the effects are?

Dr Cummings: Let me briefly start back at the beginning. We have CYP enzymes–five large families of them. The first number in the name represents the family. The second is a group within that family and then the last number is the specific enzyme in that group. So for example, 1A2 is family number one group A enzyme number two in that group. Fluvoxamine inhibits 1A2, which is the principal metabolic pathway for clozapine and can consequently increase clozapine by as much as 500 to 1,000%. Which is why if you're going to do that, to inhibit clozapine metabolism, you need to be very careful about dosing and effect because you can make somebody very toxic very quickly. The way inhibition works is that the molecule you're giving, which is an inhibitor, directly binds to the enzyme and blocks its activity. You know, the enzyme has to attach to a substrate, alter the substrate and then release the substrate. If you have a molecule present that binds to the enzyme and then basically, like a bad houseguest refuses to go away. That enzyme can't move on to do anything else and that's what fluvoxamine does to 1A2.

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Dr Puder: So basically, fluvoxamine, the bad houseguest, comes in and then doesn't let 1A2 break down clozapine. Because clozapine is so dependent on 1A2, clozapine jumps up 500 to 1,000%.

Dr Cummings: Yes, it can. If somebody gives a what would be a fully antidepressant dose of fluvoxamine. You can use fluvoxamine at tiny doses to increase clozapine plasma concentrations. For example, in a rapid metabolizer, but you need to be very careful about that. Because somebody else might come along and go "oh, that's not enough antidepressant" and give the person a dose that will get them into toxic territory with clozapine.

CYP inducers are substances that are metabolized by the target enzyme but also cause the liver to go,"oh, we need to work harder to get rid of that", and therefore the hepatocytes wrap up the synthesis of that particular enzyme, so that you simply physically have more of the enzyme and that, in other words, the synthesis has been induced and more of whatever that enzyme metabolizes will be done away with more quickly because there are more copies of the enzyme present to attach to and metabolize that particular substrate.

Dr Puder: Very cool. Well, I think I'll shout out to Kaden Page. I think his first couple emails to me were where he was listening to your episodes and he was taking notes and he figured out that one of his–he was on an inpatient unit as like a helper, he wasn't in med school yet–he was catching some side effects in patients and he was emailing me about it. And I was like, "wow, this is a bright kid". So shout out to him.

Antipsychotic Polypharmacy

Dr. Puder: A listener asks, I work in an inpatient psychiatric unit. Sometimes we have patients who still have pretty significant psychotic symptoms despite up titration of a single antipsychotic, usually Risperdal or Zyprexa. I know that technically, response could be up to six weeks, but we never have that much time to wait for improvement. In these sorts of cases, do you recommend combining antipsychotics during their hospital stay to try to get better symptom control? If so, what combinations would you recommend? This question is assuming that we can't do clozapine for practical reasons such as homelessness, non-compliance, etc.

Dr Cummings: Again, this brings us back to the polypharmacy issue. There is data out there suggesting that polypharmacy is modestly more effective than monotherapy. Provided, as we said before, that you choose drugs that offer complementary mechanisms of action. Again, for example, it would make no sense to combine two drugs like haloperidol and fluphenazine that have essentially identical activity profiles. The one mentioned here haloperidol and olanzapine is a very common combination, because the olanzapine offers a second mechanism of action

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that haloperidol does not. So you may get essentially a better antipsychotic effect. One important issue with time of response: if you're giving a drug and you're titrating it, the effect you're going to see from that drug, you'll see about 80% of the response in the first two weeks. So, you don't need to wait six weeks to titrate again. If you give somebody what you think is the therapeutic amount of the drug, you're above the minimum response threshold, and you wait two weeks, what you see is about 80% of what you're going to get. So if it's not adequate, you can go ahead and titrate further. That will shorten the amount of time that you're waiting. I know in a lot of inpatient, acute inpatient settings, even that timeframe is too long. I was talking with the local county hospital, here where I work. Their average length of stay these days is 3.5. days–just barely enough time to initiate treatment. Certainly not enough time to complete treatment, which speaks to the importance of step down and day hospital programs after acute hospitalization.

Dr Puder: I'd be curious what you think about, let's say someone was on Abilify Maintena so aripiprazole injection? What augmenting strategies would you give if, like 400 wasn't completely bringing them out of psychosis?

Dr Cummings: If 400 milligrams of Maintena a month is roughly equivalent to 20 milligrams of oral aripiprazole. Frankly, no one has demonstrated much of a difference between 15 milligrams of aripiprazole a day and any higher dose and that's because it has such a high binding affinity. Augmenting the partial agonist is very difficult because of the very high receptor affinity. I certainly would not choose, for example, the dopamine antagonists because they won't ever see the D2 receptor, for the most part. If there's any evidence, for example of bipolar diathesis, then I would certainly be looking at addition of a mood stabilizer, most likely lithium or valproic acid. Unless the patient is female and at risk of pregnancy. I would also consider other drugs such as SSRIs for negative symptoms. Beyond that, there's not a lot. One of the things I always encourage people to do if they're thinking about starting a long acting injectable partial agonist, either Maintena or Aristada, be really, really, really sure that person is a responder to aripiprazole before making that commitment. Because the washout time for the long acting injectables is incredibly long.

Social Media Trends Promoting Deprescribing

Dr Puder: Excellent. Okay. Here's a question from an anonymous, New York psychiatrist who calls Dr. Cummings the John Oliver of psychiatry. There seems to be a rise in popular media (TikTok, YouTube) of psychiatric professionals critical of Psychopharmacology and intervening in mental health care with medications. For example, a TikTok doctor, making rounds on the 40 pages with videos critical of SSRIs and benzodiazepines. His TikTok and YouTube channels have recently featured a prominent English psychiatrist and research expert on deprescribing. What do you make of these criticisms? Are they new/newly revisited? Does popular media

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attention to deprescribing and the overuse of mental health medications do more harm than good? Is it better for patients to observe the psychiatrist debating these issues online as being more harmful to the overall goals in the field profession? How would you recommend talking to patients who have been de-influenced after consuming this media?

Dr Cummings: This is not new. The use of medications has been debated since the introduction of chlorpromazine and to some extent before that with the use of the barbiturates. I think criticism in one sense is founded and that sometimes people get carried away with expecting things from medications that medications cannot deliver. I'm very careful to educate both the people I consult with and patients that medications are tools. They are there to improve certain symptoms and symptom complexes. They are, in psychiatry, generally not curative. That is, they don't change the person's underlying genetics or epigenetics sufficiently to make them a completely different person. I also caution people not to expect pharmacology to address complex issues in the person's life, either past or present; and, to adopt a more balanced view of medication versus psychotherapy. In fact, more often it should be medication plus psychotherapy.

Dr Puder: You know, someone who was critical of the podcast recently, said, “why is there so much psychotherapy stuff on here? This is not a good podcast for us, prescribers.”

It's like, to call yourself a “prescriber”. First of all, like can we talk about that? Are we just “prescribers”, really?

Dr Cummings: I certainly hope not. You know, I am a psychopharmacologist. As people can tell, I spend a lot of time thinking about molecules and neural circuits. I can tell you that there is no pill that is going to cure or fix any complex issue in your life. The pill may help you. But there's still work to be done beyond that and I think that when people forget that that's where a lot of the criticism arises from, “Oh, here take this pill and everything will be 100% okay ". That's nonsense. You know, life is complicated. Life is often difficult; and calls for responses beyond symptom reduction.

Dr Puder: So…yeah, I think I would say, you know, to any psychiatrists who are venturing to make TikTok videos and put out stuff on social media, you have to think through how we can present ourselves in an accurate, nuanced way. And it's difficult. And I think, fear mongering medication side effects, without a sort of a buttressing of why we're using them or how we're using them or when they're helpful or not helpful, I would say is, is probably not helpful for the field. I don't know. Any thoughts on that?

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Dr Cummings:Yeah, I would say you know, the approach always has to be balanced and nuanced. Again, medications are tools. They always have both benefits and risks. Those need to be explored with the patient, discussed. and choices made carefully.

Brain imaging and Mental Health

Dr Puder: Okay, let's move on. Jacob, who owns his own practice in Wyoming, says “Dr. Cummings is magical. I wish that even a minority of clinicians in the field of mental health were able to study and learn from Dr. Cummings on a regular basis, as we are. His knowledge base is more godly than is standard; and that is both terrifying and enlightening.” Okay, so he uses the information to support his treatment teams. Let me move on to his question. “What is your opinion of when a patient qualifies for the need for brain imaging, or formative and summative evaluations and treatment using a type of brain imaging and mental health?”

Dr Cummings: For most patients with at least severe mental disorders, major depressive disorder, schizophrenia, bipolar illness. Certainly I'm very much one in favor of the patient at the outset of treatment receiving a fairly thorough workup. a good physical, neurologic exam, lab profile, and if they've never had a brain image done, then a MRI without contrast is not unreasonable. and I say this because there are a whole host of both medical and neurological illnesses that can present initially with psychiatric symptoms. We need not to be missing those. I'm very much not one of those psychiatrists who was of the opinion that, "Oh, psychiatrists should never touch their patient". I do a physical exam and at least a focused neurological exam on almost every patient I see. Just to be sure nothing is being missed. I'm also a firm believer that psychiatric offices should own things like scales given that we give drugs that cause people to gain weight, and so forth. In other words, we need to be physicians first. So I have a fairly low threshold for ordering an MRI even if I am perfectly aware that the overall yield is likely to be low. But every now and then you find something that you weren't expecting or the patient wasn't expecting and occasionally it’s helpful in terms of directing their treatment.

Dr Puder: Do you think that there's ever a role for a SPECT (single-photon emission computerized tomography) of the brain?

Dr Cummings: There can be in cases where you suspect for example, something that's fairly rare, like nonconvulsive Status Epilepticus. I actually had such a patient, when I worked for the VA. Frankly, all of us had thought he was schizophrenic, except that every time we gave him an antipsychotic, he got substantially worse. And when we got a SPECT scanner. (This speaks to how far back this goes.) We did a SPECT scan and sure enough, he had a hot focus (hot metabolically) deep in the frontal lobe. We put him on valproic acid, and suddenly his psychosis went away. So yes, these days, Positron Emission Tomography (PET) has replaced SPECT

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scans in many settings, simply because it provides a more accurate, detailed three dimensional image of the brain.

Dr Puder: Okay, so there are certain types of clinics, we won't name names, that use this type of thing often, just for routine evaluation. Is this what we're talking about?

Dr Cummings: No, no. SPECT scan would not be for routine evaluation. SPECT scan would be if you suspect that there's an underlying organic cause going on. Usually something like non-convulsive status, or

Dr Puder: Wouldn't you just get an EEG for like, if you thought a seizure was going on?

Dr Cummings: Nonconvulsive deep epileptiform foci may not show up on a surface EEG and that's because the focus is very deep seated. In this guy's case, it was in the anterior basal ganglia. Well, there's a lot of tissue between that and the cortex and what you're seeing in a standard EEG is primarily the electrical activity of the cortex. If the cortex is fully active it may mask more subtle underlying metabolic hotspots.

Dr Puder: I appreciate your nuance here. The very rare use of it. Okay, so what would be the symptoms of this deep seizure that's ongoing?

Dr Cummings: Usually, in this case, the presentation was of cognitive disorganization. Occasionally, visual hallucinosis. The tip off in this particular case, though, was the worsening whenever exposed to a drug that would lower seizure threshold, like an antipsychotic. Which was the tip off; and this guy's case, it was not a case of he didn't respond to the antipsychotic, even minor doses would make him substantially worse. Which was, of course, not the expected outcome. It's like that old saying when you hear hoofbeats go look for horses, but every now and then you find a zebra.

Dr Puder: Okay Awesome. This is great. Okay, that's like so, no one can say that they didn't learn anything from this episode after learning that. I'm pretty sure everyone learned from that.

Dopamine Agonists

Okay. Ryan states, “He's probably the most brilliant and articulate man I've ever heard speak. I often revisit Dr. Cummings’ episode list because I know everything with him will be a gem.” Okay, so here's his question: Do dopamine partial agonists over-compete dopamine antagonists

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at the D2? Would aripiprazole, for example, preclude further D2 blockade from other antipsychotics? If so, if a patient is on a long acting Abilify (aripiprazole), and experienced breakthrough psychosis, what would be the best strategy to manage their condition?

Dr Cummings: Usually, in those cases where the partial agonist is not proven to be an adequate medication, it's often the case that you're forced to discontinue the long acting injectable partial agonist because if you're truly giving the partial agonist at a therapeutic dose, the odds are you're occupying well, more than 80% of the D2 receptors with the partial agonist. So your antagonist is not going to have much of a target. You can go ahead and initiate an antagonist, stop the partial agonist, and of course it will then gradually wash out. With Maintena, for example, however, the half-life, on average, is 46 and a half days. If you do the math, that means complete washout is going to be 232 and a half days. So, a long time. But it will be going away the entire time and every time the aripiprazole falls off the D2 receptor, that means that receptor is now available for your dopamine antagonist. Just be aware that the antagonist may not have much of an effect initially. And of course, we can always come to the gold standard of antipsychotic treatment, Clozapine, which can be used with partial agonists, because it does not provide its antipsychotic benefit by blocking dopamine. The two known mechanisms, so far, are glutamate modulation at NMDA (N-methyl-D-aspartate) receptors; and, likely, stimulation of M4 muscarinic receptors in the ventral tegmental. Neither of which is directly affected by a dopamine partial agonist.

Dr Puder: I did a polypharm episode without you, Dr. Cummings; and one thing we looked at was, the combination of clozapine and aripiprazole will actually make sense. And there's some good data to support that.

Dr Cummings: Yes, indeed, there have been some studies published that demonstrate the clozapine plus aripiprazole has a more robust augmentation effect than many other combinations.

Depression

Dr Puder: All right. We're gonna move on to some questions about depression. Doctor Severin Hahn from Hamburg, Germany, in his second year of psychiatry training. He really appreciates you. He said, he has an entire note of little wisdoms from you, that he uses, and he wishes you could be his personal mentor. He said, “where do you see me lies in the treatment algorithm of depression? How would you treat depression in an algorithm including more exotic options like MAOIs, pramipexole, eszopiclone,SAM-E, T three, etc. Specifically, in what order? Which specific antidepressant first and so on? Would you do including lithium, atypical antipsychotics, thyroid medications.

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Dr Cummings: Okay. This could indeed be another entire episode. In brief, however, usually these days antidepressant treatments start with either an SSRI, an SSRIs/5-HT1A drugs, such as vortioxetine or vilazodone, or an SNRI, meaning venlafaxine, duloxetine, or in most of the world milnacipran or levomilnacipran, or bupropion. Basically, if you have a person who does not respond to adequate trials of those medications at some times greater than the typical dose, then it may be time to think about would this person perhaps respond better to a tricyclic antidepressant? Although there is data now suggesting that the tricyclics are not necessarily superior to the SNRIs, if they're truly equivalently dosed. Beyond that, though, you do have the monoamine oxidase inhibitors. And frankly, the MAO inhibitors are likely somewhat better antidepressants than any of the drugs up to this point. And the reason for that is, is that most of our antidepressant drugs directly affect either serotonin or norepinephrine, or both. The MAO Inhibitors go a step beyond that and affect norepinephrine, serotonin and dopamine. Because the MOA otherwise block the degradation of all the monoamines. We sometimes forget that dopamine also plays a role in depression. The reason of course that these never became widely popular drugs is because of the risk of hypertensive crisis known in the 1960s as the cheese reaction because it was triggered by age cheese. Foods are not typically that much of a problem. Because tyramine levels are limited in food.The more dangerous interaction is between the MAO inhibitors and direct sympathomimetic stimulants (ie cold medications). Those can cause severe hypertensive crisis and death. Consequently, these have become unpopular, but we should not forget them. In cases of very refractory major depressive disorder, or severe anxiety disorders, the MAO inhibitors are a little more effective than all of the other antidepressants that we have. Of course, the other thing we can do for people with refractory depressive illness is electroconvulsive therapy (ECT). ECT is still more effective than any of the pharmacological interventions.

We also now have transcranial magnetic stimulation (TMS) and vagus nerve stimulation as well for chronic recurrent depression. And I think we sometimes still forget that in addition to pharmacotherapy for depressive disorders, things like exercise, lifestyle, cognitive behavioral therapy (CBT) or related psychotherapies are incredibly important. Again, this is an area where you do not expect the medication to fix all the problems in the person's life.

Antidepressant Plasma Levels

Dr Puder: Awesome. Dr. Hahn also asks, “What do you make of measuring antidepressant plasma levels?”

Dr Cummings: I think that can be useful in the sense that while the antidepressants don't, in most cases, have as well defined plasma concentration ranges for example,as the antipsychotics or lithium do.There are some general indications. For example, if you want to

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know if the person is actually taking the drug, a blood level can help you with that. If you want to identify whether they are a rapid metabolizer of the drug. Blood levels can also be helpful with that, so that you can at least figure out if you're getting the amount of antidepressant that you're expecting in the person from the dose that you're prescribing. A plasma concentration is an excellent way to know that.

Dr Puder: He also asks, “if you're treating a depression that also has some external stressor that's very large, that likely causes the depression, or a personality disorder that's prevalent in the mix of things, would you use the same algorithm as pure major depressive disorder?”

Dr Cummings: I would use the same algorithm however, there would be a very large emphasis on use of psychotherapy.

Cariprazine

Dr Puder: Chris from Ohio says he loves learning from you. And he asks, “Vraylar (cariprazine), which is FDA approved for use with antidepressants to treat depression. He says, I believe they are now marketing more towards this market and would like to be viewed as a monotherapy for depression and more first in line than an SSRI. What are your thoughts on this?”

Dr Cummings: Cariprazine is an interesting drug and is one of the partial agonist antipsychotics. And you're right, drug companies like to market drugs for mood disorders because, frankly, that's a larger population, more potential customers. Cariprazine does have significant antidepressant and anti-manic effects. It's one of the few drugs that, like lithium, can be effective for both the manic and depressive polls of bipolar illness. And it differs from the other partial agonists in that in addition to being fairly robust antagonists or partial agonists to D2 receptors, it also has a significant and even more robust interaction with D3 receptors which alter dopamine activity, particularly in the frontal cortex. I'm not sure I'm willing to go as far as saying that cariprazine should be used as an antidepressant monotherapy. But, it probably is one of the more robust augmenting agents currently for major depression or for bipolar illness; and it may prove itself as monotherapy, but I haven't seen a good head to head comparison across groups comparing standard antidepressant treatment with cariprazine monotherapy. All of the studies I've seen, it’s been used as an augmenting agent.

Dr Puder: Same person further says, you know, he's never seen studies that look at the risk for this medication and TD (tardive dyskinesia). What's your educated guess to the risk, given its mechanism of action?

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Dr Cummings: You're right, there are not good studies regarding cariprazine and TD. In fact, there are not good studies looking at aripiprazole and brexpiprazole and TD. Since these do decrease dopamine signaling, it is almost certain that in some patients they will induce neurologic side effects including things like acute dystonia or Parkinsonism. Albeit at much lower rates than the first generation antagonists. and my guess is you'll also see tardive dyskinesia arise in some patients. Again, it's very likely the most common patient will be elderly female patient with a mood disorder.

Controversy of SSRI Efficacy

Dr Puder: Okay, an anonymous fan of Dr. Cummings says, "big fan, a very big fan. And I've listened to his episodes with Dr. Puder many times. I even have his book on treatment resistant psychotic disorders. He is so knowledgeable but more than that, I trust him." And this person's question is the STAR*D Trial has been re-examined and current controversy seems to lean towards the belief that SSRI medications are ineffective or lacking more than before. SSRIs have been the go to medications for many disorders. And personally, I have seen them work well. How do you view the controversy? And do we need to rethink SSRI use if the controversy warranted?"

Dr Cummings: I think the controversy has more to do with our understanding of things like major depression and anxiety disorders. Early on, people simplistically thought depression is a lack of monoamine neurotransmitter and that turned out frankly, not to be the case. We've talked about before on this podcast that things like major depression and anxiety disorders are likely based on primary dysfunction in the limbic circuits that get beyond the modulatory ability of the monoamine neurotransmitters and that sets an inherent limit on how effective things like the SSRIs can be. If you look at trials of antidepressants, while the numbers don't match precisely, they are relatively uniform in that if you look at, well how many people in a depressed sample or an anxious sample show a 50% reduction in symptoms severity. It's about two thirds. Meaning two thirds get better and one third don't get better by that much. How many of those people achieve full remission? Then you're talking about numbers down around one third. And I think that's what people have recognized is that while these medications do have a positive benefit, achieving remission only in one out of three cases, is not as satisfying an outcome as people would like. And I think again, this speaks to the issue that while the medications are effective and helpful, and in many cases life saving, they should not be the entirety of treatment.

Dr Puder: Yeah, and I think he's kind of hinting that the STAR*D Trial has been re-examined. Is there anything that you've seen on this?

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Dr Cummings: It's more a case of the STAR*D Trial has been debated. Which of course is not uncommon. Almost every major study that occurs then has subsequent smaller studies that examine various aspects of it, and there's typically in the literature and ongoing debate. That certainly has been the case with the STAR*D Trial. There was a somewhat provocatively titled study about a year ago that the title was, and I'm paraphrasing here, something along the lines of why aren't the SSRIs effective? Which of course, was an overstatement, but it was, I think it was phrased that way to essentially get attention. They went through the same thing that I just noted that in the vast majority of people with major depressive disorder or with severe anxiety disorders, the SSRIs are helpful. Two thirds of people get a 50% reduction in symptoms, and one third actually go into remission. But that's a less than completely satisfying outcome. You know, in the ideal world, of course, we'd like medication that the person takes once and they're cured. We don't have a lot that functions like that.

Dr Puder: Yep. And that's why I think, in my actual clinical practice, it looks a lot like okay, they got 50% reduction in their symptoms, it's probably what we're gonna get from an antidepressant. Now we're going to highly encourage them to get out of bed and you know, do some behavioral activation, get some exercise, start some therapy. You know, things that maybe when they were severely depressed, they couldn't do or had a high resistance to it.

Loss of Medication Efficacy Over Time

Dr. Puder: Okay, let's jump to the next question. Scott Cannady, a senior policy adviser of the Virginia Medicaid program, says, “do SSRIs, SNRIs, and other medications for depression lose their clinical effectiveness after years of use?”

Dr Cummings: They can. And this is something that speaks not to necessarily a defect in the medication, but to the fact that many psychiatric illnesses such as bipolar illness, schizophrenia, major depression recurrent are themselves progressive in nature. For example, with major depressive disorder, the overall risk in the population is around 6-8%. But if somebody has had one episode of major depressive disorder, their ongoing risk for a second episode is up around 50%; and it keeps going up the more episodes they have. That speaks to, I think, an evolving underlying abnormality in the way their limbic system functions that can become increasingly resistant to medication. Certainly if you look at the elderly, depressed population, especially those who've had a lifelong history of recurrent major depression, they often reach a point where they become pharmaco-resistant. That is, they reach a point where they don't respond to antidepressants at all. And indeed, they often wind up on things like maintenance ECT as a result.

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Dr Puder: We're gonna get through depression and maybe we'll have to do a second recording for the next series. On anxiety, bipolar, ADHD, and so on.

Dr Cummings: Yeah, I was gonna say, otherwise, this could be a marathon podcast.

Dr Puder: Well, maybe we'll put them all together. You know, we'll just kind of glue them all together. It'd be like a six hour episode.

Adjunctive Prescribing with Antipsychotics (58:00)

Dr. Puder: When initiating an antidepressant for unipolar depression, does concomitant prescription of an antipsychotic accelerate response times.

Dr Cummings: That has been looked at, because people have been trying to accelerate the antidepressants for as long as the antidepressants have been around. And indeed, you know, there's now one product on the market that is a combination of bupropion and dextromethorphan for that very purpose. In its pivotal trial, the dextromethorphan addition got a superior response at two weeks, but then by six weeks, the superiority had vanished because the bupropion monotherapy caught up.

Adding an antipsychotic can accelerate antidepressant response particularly for those antipsychotics that have proven themselves to be augmenting agents in terms of antidepressant effects. Whether to routinely use an antipsychotic outside of psychotic depression however, I think warrants careful consideration of potential adverse effects. Because you're adding a whole new class of medication that may involve adverse effects the person who would not have from antidepressant monotherapy. Most of the acceleration study with antidepressants frankly, have not been that impressive. We're talking about shortening the response time by two or three weeks.

Conclusion

Dr Puder: Awesome. Yeah. So I think this is a good place. To stop. Maybe what I'll do is schedule a part two, and we'll have some people add some questions. This could go on forever. This could be an ongoing Q&A with Dr. Cummings. So if you have a question, I'll put up another email when this episode leaves and you can add your question to the Google Form. And I'll try to put it together for the next episode. Dr. Cummings, it's been a pleasure. I think you are well loved in this community here, across the world. And I didn't expect this to be as popular as it has

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been, but I think we're nearing or have reached 8 million downloads. And that's more than I expected. And so yeah, any final thoughts?

Dr Cummings: I know one person said I was magical. I did like the Harry Potter series. However, I don't own a magic wand.

Dr Puder:Your magic wand is your brain. Someone asked you, I don't think we got to it, how do you study or how do you learn so much or like what's your process?

Dr Cummings: Basically, we can discuss it at some point in greater detail. But basically, I look for new information two ways. I have a number of the major journal table of contents sent to me, which I basically just scan those to see what sort of new and upcoming, what's the current focus of research so that's more or less a cross sectional sample, if you will. And then in certain areas, as I get interested in a particular topic or something appears to be becoming important, I'll do a literature search on that and then look at the research in one particular area, vertically. So in short, that's, that's how I look for information.

Dr Puder: All right. We will leave it there for today. Thank you guys for listening and thank you, Dr. Cummings. As always

Dr. Cummings: Thank you. Bye bye

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