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Exploring the Clinical Treatments of Schizophrenia

Ashley Baker:
Welcome to *NeuroFrontiers* on ReachMD. I'm Psychiatric Nurse Practitioner Ashley Baker, and I'm speaking with Dr. Nabil Ali, who is an Assistant Consulting Professor in the Department of Psychiatry and Behavioral Sciences at Duke University School of Medicine in Durham, North Carolina. Today, he's here to discuss current treatment options for schizophrenia.

Dr. Ali, welcome to the program.

Dr. Ali:
Thank you.

Ashley Baker:
Let's jump right in, Dr. Ali. What class of medications treat schizophrenia, particularly psychosis, and how and why do they work?

Dr. Ali:
All right. Well, the class of medications that treat schizophrenia and/or psychosis related to any other underlying condition are the antipsychotic medications. The main reason that they work, although it's a little bit of an oversimplification, is dopamine blockade, which is thought to play a significant role in particularly the positive symptoms of schizophrenia, the auditory hallucinations, the paranoid delusions, etc. The reason I say it's an oversimplification is a lot of the antipsychotic medications that we have now involve other neurotransmitters, in particular the serotonergic system. And some of our most effective ones have less dopamine blockade and more involvement of other pathways—for example, clozapine.

Ashley Baker:
So there are first-generation antipsychotics and second-generation antipsychotics. How is their psychopharmacology different? You did touch upon the serotonin component of the newer antipsychotics. Can you get into a little bit more detail or give different examples of why the psychopharmacology is different?

Dr. Ali:
Yeah, sure thing. The classic divides between typical and atypical really is a historic divide, and clozapine and medications since clozapine are atypicals, and anything prior to the use of clozapine, are atypicals. And the reason they're called atypicals, clozapine atypical to the other medications at the time didn't seem to result in extrapyramidal symptoms or Parkinsonism or dyskinesias. And so the medications used to be titrated to Parkinsonism and then pulled back, and that was considered the effective dose.

The way I try to conceptualize it and the way I try to teach my residents and students is to think of it more as high potency versus low potency. And there are low-potency typical antipsychotics that tend to have less D2 blockade and so are less likely to cause Parkinsonism but may be more likely to cause the metabolic syndrome and orthostasis that some of the atypicals are known to cause, whereas the atypicals, risperidone, paliperidone, are examples of high-D2-blocking agents that may be more likely to cause Parkinsonism than some of their atypical cohorts but may be less likely to cause metabolic derangement or autonomic dysfunction.

Ashley Baker:
Is there space still for the older antipsychotics? What are some examples of when we may go back to using Haldol or something that is much older than some of the newer medications we see now?

Dr. Ali:
Yeah. I mean, I think if you're more concerned with metabolic disturbance than you are with Parkinsonism based on patients' history or

the side effect profile of their prior medication trials then you may want to go with a higher potency typical agent; or really if someone is treatment refractory to multiple medication trials or another reason why you may go with an older agent is dependent on costs or they're more likely to be able to come in a long-acting injectable form, which is really important for compliance and being able to sustain remission when that's achieved.

Ashley Baker:
So on the contrary, can you give me some examples of when we may opt for the newest medications on the market? Or do you see a space for some of the newer medications coming out?

Dr. Ali:
Yeah. I mean, I think on the opposite end of that spectrum if someone has had a history of abnormal movements, whether that to be Parkinsonism or hyperkinetic movements like dyskinesias then moving towards the atypical or lower potency agents have a bigger role to play. And that could be anything from clozapine, olanzapine, quetiapine that are less likely to cause iatrogenic movement disorders or tardive dyskinesia over time.

Ashley Baker:
And so in addition to antipsychotics, can you speak to any other treatments that you find to have good evidence and really be able to help treat schizophrenia in patients?

Dr. Ali:
Yeah. I mean, I think one of the things that we're always trying to find are ways to have people who are otherwise treatment refractory, to be able to get them to have a good outcome. And so in randomized controlled studies, mirtazapine as an augmentation to clozapine have shown good evidence. Aripiprazole, which has a different mechanism of action than clozapine, shows good evidence. Probably, the thing that's most efficacious when someone is clozapine refractory is combining clozapine with electroconvulsive therapy. And that's something that may not necessarily be something that we should use as a last resort but may use in our armamentarium a little bit sooner than we think otherwise because it is very effective, has low side effect profiles in terms of long-term sequelae. And really, the main thing that we worry about for the short term is things like short-term memory loss, which can be part of an acute psychotic episode where if someone is actively hallucinating, they're going to be unable to concentrate and form memory anyway, and so the benefit of ECT may significantly outweigh the risk in that kind of situation.

Ashley Baker:
Super interesting point. In your experience, how quickly can someone recover from an episode of psychosis or catatonia or whatever you're trying to treat with the ECT? How many treatments do you typically see? What would be a good turnaround?

Dr. Ali:
Yeah. That's the thing that patients or their guardian always wants to know is how long it's going to take because I think the lay notion of ECT or even the non-psychiatry and neurology notion of ECT is it's a one-time thing and that they get better, but it really is a treatment course. And what I try to tell patients is really I can't predict how long it may take. They're their best own measure of that, and so what we do is we monitor for improvements, for sustained gradual improvements that eventually plateaus on average nine to 12, but some people may need to up to 18 to 20, but some people may get better within five or six. And so if they've had prior ECT courses, that's probably the best estimate as to how many they would need, but it really is based on their own clinical response.

And what I tend to see is if someone has catatonia and psychosis, the catatonia improves quicker, and then we start to see an emergence of psychosis that we may have not seen before. It's sort of the opposite of what may happen with an antipsychotic where if someone counterintuitively is getting worse on an antipsychotic, then it should really increase your index of suspicion that they may be in the state of catatonia where D2 blockade can exacerbate that, and so that may be a time where you may refer someone to ECT quicker than you would otherwise.

Ashley Baker:
And looking at the course of ECT, what can patients expect in terms of frequency? Is it a few times a week, every day, once a week? What would that typically look like?

Dr. Ali:
Yeah. So the typical acute course is two to three times a week here in the United States. Three times is standard. In England, it's two times a week until they reached that plateau. At that point, unlike for depression where if you treat weekly after that plateau for four weeks, it insignificantly reduces the likelihood of relapse. With psychosis or schizophrenia, you require a longer taper. And so what we do is we go from weekly if they're doing well to every two weeks. If they continue to do well, do it every three weeks. If they continue to do well, once a month. At that point, it's probably reasonable to trial them off of it. However, what we see not infrequently is when we

spread it out, say, from two weeks to three weeks, symptoms reemerge at which point you want to go to the longest duration between treatments where people are relatively stable.

Ashley Baker:
For those just tuning in, you're listening to *NeuroFrontiers* on ReachMD. I'm Psychiatric Nurse Practitioner Ashley Baker, and I'm speaking with Dr. Nabil Ali about current treatment options for schizophrenia.

So just to get a little bit deeper into the antipsychotic treatment regimen, can you speak just a little bit to why somebody may have really a lackluster or no response on certain antipsychotics but then the trial of another antipsychotic there could be a rapid turnaround? Do we know enough about how the medications work and about the disease process and treatment that we know why one med might work and one may not?

Dr. Ali:
I think, hopefully, eventually, we will have a better idea when we really get into the pharmacogenetics of this. One example coming from the neurology end of things is we just recently discovered the zonisamide gene, essentially, that allows for people of Parkinsonism to respond better to zonisamide than they would otherwise, and so we have this medication. We didn't know about the gene until after the creation of the medication. And so if we have a better idea of the pharmacogenetics, we may be able to more quickly be able to find which medications work better for a particular person.

Right now, we have to go with clues like family history and what family members have responded to or obviously their own personal history if they had a good response to a prior medication trial or based on, again, side effect profile. If someone has more, either Parkinsonism or dysautonomia or metabolic syndrome, try to avoid medications that are going to exacerbate that, or if they have more negative symptoms, which our antipsychotic medications aren't that great at targeting, we may want to avoid worsening that with more higher potency D2-blocking agents.

Ashley Baker:
And what about special populations, like the elderly, pediatrics, other specific patient groups? What else should we be mindful of there?

Dr. Ali:
I think we need to be mindful of the dosing. And so if you're not as familiar with treating pediatric or geriatric patients, low and slow is always a good thing to work with. And so they may not require as high doses, or they may not tolerate as high the doses. One particular patient population, I think people who are on the autism spectrum disorder who require an antipsychotic either for psychosis or behavioral dysregulation, risperidone has significant evidence behind it, and it's actually FDA approved, whereas some of the other antipsychotics aren't necessarily as well studied in that particular population.

Ashley Baker:
Bringing this to clinical practice, both inpatient and outpatient, what are the barriers to patients starting the newer medications, whether they're inpatient or needing something in the outpatient?

Dr. Ali:
I think the biggest barrier is cost. The newer medications tend to be more expensive because the pharmaceutical companies need to make the money back in the research that they spend for it. Before they go either off-label or generic, they tend to not be affordable for a lot of our patients that do have severe and persistent mental illness that hampers their fiscal independence. And so unless you're in an outpatient clinic where you have access to free samples, that may be a hard medication to put someone on early on.

Ashley Baker:
Before we close today, are there any final takeaways that you'd like our audience to know about antipsychotics, ECT, and the clinical treatment of schizophrenia?

Dr. Ali:
Yeah. I mean, I think the main takeaway is not to have one particular medication that you stick by at all times. It really is dependent on patient profile, their personal histories, their side effects, other side effect profiles, comorbidities, and to have an open mind in terms of your treatment algorithm. And again, I think to not consider ECT really something that's as a last resort, particularly when someone has some symptoms of catatonia or is really suffering from their illness and needs to have more rapid improvements than what may take weeks to months with medication.

Ashley Baker:
This has been a super informative discussion on current treatment options for schizophrenia. I'd like to thank my guest, Dr. Nabil Ali, for sharing his insights.

Dr. Ali, it was wonderful speaking with you today.

Dr. Ali:
Thank you. My pleasure.

Ashley Baker:
For ReachMD, I'm Ashley Baker. To access this and other episodes in our series, visit *NeuroFrontiers* on reachmd.com, where you can Be Part of the Knowledge. Thanks for listening.