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Released: 08/28/2025
Valid until: 08/28/2026
Time needed to complete: 60 minutes

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Advances in the Treatment of Neuropsychiatric Symptoms of Alzheimer's Disease: Early Recognition, Diagnosis, and Innovative Emerging Therapies

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Chapter 1

Dr. Sabbagh:
And good morning, everyone. I hope you're waking up, and welcome to our symposium on Advances in the Treatment of Neuropsychiatric Symptoms of Alzheimer's Disease: Early Recognition, Diagnosis, and Innovative Emerging Therapies. I'm Marwan Sabbagh, professor of neurology at the Barrow Neurological Institute. I am joined by a very, very distinguished faculty, including Professor Alireza Atri, who's the chief medical officer at Banner Research, and Chris Correll, who is the professor of psychiatry and molecular medicine at Hofstra, and also in New York.

Thank you. So these are our disclosures.

Our learning objectives today are to identify the clinical features of neuropsychiatric symptoms associated with Alzheimer's disease. This is becoming a bigger issue, as you will discuss today. And to improve the early recognition and diagnostic accuracy in clinical settings. We want to evaluate the clinical risks and therapeutic benefits of off-label antipsychotic use, because, in reality, that's been where we've spent most of our time treating neuropsychiatric symptoms, and explain the underlying neuropathophysiology of neuropsychiatric symptoms associated with Alzheimer's disease. Finally, we want to evaluate available evidence from clinical trials supporting the safety and efficacy of emerging therapeutic agents targeting the NPS associated with Alzheimer's disease.

Chapter 2

Dr. Sabbagh:
So we're going to open with a few introductory slides before we go into individual presentation. So the first thing we're going to do is just have a little discussion on improving diagnostic accuracy and identifying neuropsychiatric symptoms due to Alzheimer's disease.

This first question is to you, Dr. Atri. We're now seeing this idea of antecedent symptom clusters before what we would say is a formal diagnosis, so kind of minus the years before diagnosis. What's been your experience about these clusters?

Dr. Atri:
Yes. So thanks, Marwan. Good morning, everybody. Thank you for coming today. And by the way, this is CE. These are the slides that we got together, and they're all yours, so you can download them, et cetera. And so, yeah, Marwan, so that's something we see all the time. I think as a subspecialist, when a patient comes to me, even as we're evaluating for Alzheimer's disease and cognitive impairment, it's very, very common for me to see them on medicines. Maybe a third to half can already be on an SSRI or something else already.

Somebody already recognized there's something going on, whether there was apathy or they thought the apathy was actually depression.

Dr. Sabbagh:
Right.

Dr. Atri:
And this goes back. This is Jost and Grossberg, et al. You can see it's way back in the '90s, and this went all the way to autopsy. And it's pretty clear. People recognize that those changes in behavior more, and they don't think necessarily that this could be a neurogenic process.

Dr. Sabbagh:
And you and I are part of the ADRC and we often talk about the MBI, this new construct. Can you tell everybody about this new construct called MBI?

Dr. Atri:
Yeah. So we can see there's the Psychogeriatric Association has a new criterium. Our Canadian colleague and friend, Zahinoor Ismail, is the lead author for those. But just like you have the construct of mild cognitive impairment that is a condition, is a syndrome, it's not telling you what the underlying diagnosis or the cause or the contributors are, you can think of MBI as another construct, where you were, essentially, a person who has not had those features. They've not had lifelong, for example, agitation, aggression, depression, et cetera, develops these symptoms in later life, that they're not explained by something else, like an illness, et cetera. And this can be, again, oftentimes—it's being studied—but it seems to be a very clear prodrome for neurodegeneration.

Dr. Sabbagh:
So MBI is mild behavioral impairment, which appears to be a parallel construct of MCI. Chris, we kind of cluster things, and you being the psychiatrist amongst us, this is kind of more in your familiarity of clustering of the neuropsychiatric symptoms. Can you kind of comment on how a psychiatrist would look at this, as opposed to a dementia neurologist?

Dr. Correll:
Yeah. I'm not sure we're looking at this so differently, but these are symptoms that we're all very familiar with across different diagnoses. So these are transdiagnostic symptoms, which could be prodromal, as you're mentioning, for multiple diseases or could become syndromal. And we would cluster them into those that are like minus symptoms, so like apathy, there is not enough of it where they have social withdrawal, lack of interest and motivation. But as you've said, that could be depression.

Dr. Sabbagh:
Right.

Dr. Correll:
It could be also, maybe, social anxiety. It could be secondary to paranoia, so you have to then also see are people withdrawing because they're afraid, because they may have also sensory impairments.

Sleep is, I think, a big thing because that's both a marker but maybe also contributor of behavioral dysregulation. We all know that ourselves, when we haven't slept well, that that really makes us much more thin-skinned and there's less of a buffer. Irritability, aggression, I mean, sometimes this is seen early on as an accentuation of the personality, but that can also go totally awry. Then psychomotor behaviors. People get a little restless, walk around. That can be quite disruptive because we need to keep them safe and also other people around them. And then the suprathreshold symptoms, where people, I think, get really concerned, is when it becomes

aggression toward objects, self, or others or then frank psychosis. But even psychosis can be hidden, correct? So it might be a little milder or people keep it to themselves. It takes a while to even realize something that's not as mild anymore. But these symptoms are often the ones that have the consequence that family members have to take off work, stay home, try to keep patients safe, but also the family, or reduce the transition into a higher level of care.

Dr. Sabbagh:
So in the bottom left we have depression and some people always, particularly in primary care, we'll just say that is kind of pseudodementia. Do you both—I'm talking now to you—is it an antecedent symptom? Is it a risk factor? How would you look at depression, specifically?

Dr. Correll:
Yeah. So in our terminology, pseudodementia would really relate to the cognition that people are so slowed down and that it's not only physical movement that doesn't work. It's also concentration and cognition. But I think we don't know exactly the pathways.

There's obviously a lot more depression early in life, but that is a marker of having a neuropsychiatric vulnerability, and sometimes this is a prodrome to psychosis, late onset, but also to Alzheimer's, showing that there's neural network disintegration, and that can then have multiple downstream effects depending on what other neurodevelopmental pathologies are ongoing in the brain and obviously also the genetic underpinnings.

Dr. Sabbagh:
And hallucinations. Ali, do you always think of a Lewy body when you see hallucinations? Or could you see hallucinations in other conditions?

Dr. Atri:
You can see it in other conditions, but yes, Lewy body's, for our trade, comes to mind right away. And Alzheimer's disease pathology is the most common in older people but it is very rarely you find pure pathology of Alzheimer's disease. So even with Alzheimer's disease, 15% to 20% will have some Lewy body somewhere. So some people are a little bit more—

Dr. Sabbagh:
It's not that rare.

Dr. Atri:
It's not that rare. And then even with vascular. Yeah, so.

Dr. Sabbagh:
So we understand that it's associated with adverse outcomes, too. Ali, you and I know that that is a marker. So the happy demented, I used to like to say the happy demented stay home; it is the agitated dementia with the high neuropsychiatric symptoms that have accelerated decline and more morbidity and mortality. What's been your experience?

Dr. Atri:
Yeah, it's very, very difficult. I'll tell you my experience both as somebody who first was a care partner for my aunt, who was like a mother or a grandmother to us and lived with us on my mom's side, and then with my dad. I'm a cognitive neurologist and I think about cognition, function, behavior, but I can tell you behavior is the most difficult thing.

Dr. Sabbagh:
Right.

Dr. Atri:
Because cognition you can support; function you can support, if someone is not resistive. And seeing my dad change, and it was very, very difficult. And so, yes, it's associated with negative outcomes. Poor outcomes and probably a stage of a disease that shows that you're going to go downhill. And morbidity, mortality. People who are in nursing homes end up having more falls, fractures, and they don't get medical care either as much because they're resistive.

Dr. Sabbagh:
We know that a patient with neuropsychiatric symptoms will stay in acute care twice as long and long-term care 3 times as long, so it is a huge driver of cost, morbidity and mortality, and increased medication use.

So we would agree, for the majority, that it's grouped into clusters of apathy, agitation, and psychosis, which may overlap in presentation.

Chapter 3

Dr. Sabbagh:
So I'm going to kind of give you some of the neurochemical aspects of the neuropsychiatric beyond dopamine, the pathophysiologic drivers of neuropsychiatric symptoms. So I think I've already made the argument that neuropsychiatric symptoms are common. As you see here, one estimate puts it at almost 100% of people will develop some neuropsychiatric symptoms. It doesn't have to be psychosis. To be very clear on this, it could be anxiety, depression, apathy, and aggression, but the cluster is all of them. And when you see it, of course, you see it's a driver, as we already talked about, and when it is, it's also there's limited therapies or we have struggled with limited therapies. We've struggled with underdiagnosis and socioeconomic burden. So this is a feedback loop.

We understand that it kind of falls into several things that kind of work together. We think at the top. So cognitive neurology thinks of normal cognition, mild cognate, and dementia, but we understand that there's an interplay. Psychosis tends to occur, at least hallucinations and delusions in Alzheimer's dementia, in the more moderate stage, but we see other psychiatric symptoms emerging earlier.

And when you see early emergence of neuropsychiatric symptoms, you need to be thinking about medical issues, infection. First thing I always do is I check a urine every time, because I've diagnosed more UTIs than I could ever care to say, and I'm a neurologist and I've diagnosed a lot of UTIs. And so we need to look at medical issues, we need to look at epigenomic and transcriptomic issue environment, but we also need to look at circuitry. So I'm going to walk through some of these elements now.

So psychosis is the element of hallucinations and delusions. When we talk about psychosis, we're really talking about hallucinations and delusions. And we're going to talk a lot about the neurochemical aspects, including dysregulation of serotonin, dopamine, and glutamate. But we also know that that doesn't just occur in isolation. We also know there's synaptic dysregulation. You get neuroinflammatory response, you get abnormal responses from astrocytes, microglia, and oligodendrocytes, and mitochondria might be damaged, and you get oxidative stress.

I want to spend a moment talking about this slide here. We talked a little bit about the neurotransmitters. In Alzheimer's disease, we know that are neural anatomical changes, and I'll talk about those in a second, but we see the serotonin pathways are altered. So amyloid pathology reduces serotonin, which then alters the signaling in the limbic system. And if you look at the glutaminergic system, we see that the oligomers affects glutamate reuptake, which causes NMDA receptor hyperactivation. And then if you also look at the dopamine pathways, because of alterations of serotonin and glutamate, you get ventral technol nigro alterations and dopaminergic disinhibition.

In hallucinations, you tend to see a lot of changes in the temporal lobe and in the occipital lobe, and in delusions, you tend to see a lot of changes in the frontal lobe and the cingulate gyrus. So we anatomically know that different parts of the brain are driving different aspects of neuropsychiatric symptoms; it's not a global thing. So and when we look at it, we understand that we already talked about some of the neurotransmitter changes, but we also know that these changes occur at the cellular level, at the cortical level, and that they're alterations of genetic and epigenetic factors that are driving some of these, upregulation, downregulation, alterations in methylations, et cetera. So it is an interaction. Originally when we were thinking about this, we were really just thinking about the neurotransmitter changes, but now we're starting to think of this in a much more broad sense with epigenetic impact.

I like this slide. It's a busy slide. But let me just tell you that the anterior cingulate is common in agitation, irritability, disinhibition, and eating disturbances. And when you look at the delusions, you see here changes in the orbital frontal areas, the superior temporal areas, as well as occipital areas.

And hallucinations, you see changes in the left superior frontal lobe. This would be hallucinations, right here, left superior frontal lobe,

occipital lobe, and the dorsal lateral cortex. So I'm just saying that each of them have specific neuroanatomical changes that seem to drive the neuropsychiatric symptoms.

When we look at it, we know that the inferior parietal lobe, hippocampus, and frontal subcortical regions are associated with this network that it drives both cognition and neuropsychiatric symptoms. But interestingly enough, what we know now is that we can start to look at specific areas of the brain that are accumulates. For example, with amyloid, posterior parietal on the right seems to be associated with increased levels of neuropsychiatric symptoms. Same with tau. We know that biparietal tau accumulation and temporal tau accumulation is associated with neuropsychiatric symptoms. And then you see that there are gray matter volumetric loss is in specific areas of the brain.

So again, when we start to break down neuropsychiatric symptoms, we realize that there's neurochemical changes, epigenetic changes, neurotransmitter changes, and we are now starting to see specific areas of neuroanatomical changes, both at the MRI and PET levels.

This is showing you that the disruptive parietal frontal circuit drives psychosis. We know that you've seen gray matter volume loss in the right dorsolateral, prefrontal cortex and ventral cortex. This map is showing you, actually, just pretty much the posterior parietal regions right here, but what, in fact, causes impairment in reality monitoring, attention regulation, and cognitive control. And so we now can map out neuroanatomically where parts of the brain that are driving these specific neuropsychiatric symptoms. And when we look at it on things like FDG PET, where we see a couple of things that—I just want to, before I talk about FDG PET, is that adiponectin levels are increased, which could be a biomarker. I don't know if it will become a biomarker, but it could be a biomarker because we certainly see it elevated in psychosis and NPS. But we also start to see, when we look at FDG PET, frontal and temporal lobe changes, and we see this also on heat maps, as well.

When we look at tau pathology, we now identify that tau pathology in specific areas. It’s not just having tau, but where the tau is, and we specifically identify that it's in the parietal lobe and the temporal lobe. And when we see these changes in them, we're more likely to see the emergence of neuropsychiatric symptoms. as seen on tau PET. So I'm just trying to make the argument that neuroanatomical regions are specialized and we start to be identifying specific areas of the brain that are associated with neuropsychiatric symptoms.

Chapter 4

Dr. Atri:
Thanks, Marwan.

Okay, everybody. So again, the slides are there. This is going to be referenced for you. You can go back to them. I'm just going to give you a little gist of things. This will be a little bit more practical.

So this is a difficult problem. And I think one of the things is I approach it the same way as I approach sort of, like the general framework for somebody that comes to me for Alzheimer's and related dementias. It’s really, really important to actually have a timely diagnosis and detection. Management is multifactorial, but it's really predicated on a foundation of knowledge and appreciation, not just by the patient but also the care partner and the team. And we have limited pharmacology, but ultimately, we have to have an alliance with the dyad of the care partner and the patient. Only when we have all those together and we're proactive about it will this work. So we can make the most amazing care plans but if they're not implemented and we don't get feedback and communication, it won't work.

So the foundation of managing any Alzheimer's disease, and including neuropsychiatric symptoms, is behavior and knowledge. Both allowing them to understand that the general evolution, giving them a vocabulary about things, because people don't appreciate, for example, that this may be part of the illness.

And they may not recognize the behaviors as manifestations of anxiety, for example, or aggression, or psychosis. And always thinking about triggers. As Marwan was mentioning. Whether that's psychosocial, environmental, or biological. Making sure that the activities are just right and meaningful, not too much stimulation, not too little stimulation, having a safe environment, and providing enough social contacts in the right way. And almost learning to communicate in a new language with somebody as they're changing.

So Marwan touched on the fact that even though we’re neurologists, we do a lot of urology without putting foleys in. And so a lot of UTIs can be triggered, so very early on, educating people about the medical conditions that can trigger neuropsychiatric symptoms, including

metabolic derangements, dehydration. Christoph mentioned sleep, very, very important, pain, constipation, infections, and drugs, including alcohol. Too much or too little. So I really want to be proactive, and so this is something from very early on that we try to counsel the patient and the family members to hydrate. I try to really look at sleep hygiene, pain, constipation. And so being proactive to recognize this may be emerging and to diagnose it and treated it is really, really important.

The other foundation is basically—this is formalized in the DICE approach. You can go to the website. Even if you have care partners, they can go in there, learn at the DICE website. But basically, teaching them to be able to describe the challenges and the behavior, kind of the who, the what, the where, and the how. How to investigate it and think about the triggers to create a plan that's multifactorial and then to evaluate the plan.

Now, this is for reference for you to think about the steps later on. But basically, what you'll see is that at every step, one of the first things you're doing in that red box is triaging. Is this going to be a safety risk right now for the patient or someone else? If it is, then you have to take immediate action. You may not even have to go to investigate/create. You may have to do something right away. And that's where our options are kind of limited right now. That's one of the places our options are limited. We go to pharmacology, but what happens, oftentimes, is we're confounding, basically, for calmness. We basically sedate people. It's a knife edge.

And you can see, as you're investigating it, each time you're thinking about safety. You're also thinking about is there really actually depression or anxiety that's diagnosable.

So oftentimes to do that, we've reached for antipsychotics, and that's what we have. It's a long tradition. You can see on the right side, here, whether it's used to be typicals and now atypicals. But basically, you're dodging a bullet. You're playing with fire a bit.

But what options do we have? I mean, I think that's one of the difficulties is the options can be difficult. So you have to be proactive in many ways. So the risk versus relief associated with whether it's agitation and aggression in AD, it's a challenging balance. Or psychosis. So psychosis in the US has an FDA black box warning. It says that there's an increased risk of mortality for the elderly patients with dementia-related psychosis. And I'm going to give you some bullet points and then I'll flash some slides for each one of them as reference material. Okay?

So basically, there's a modest effect size, usually Cohen's d around 0.2-ish at the group level. Again, when we see these studies, remember it's for a group. And we're individuals, so your mileage may vary. But for the group, it's modest.

Brexpiprazole in the US is the only drug that is approved. You'll hear more about it, and that's for agitation associated with AD dementia. And risperidone is also used in Europe for short periods of time for severe, refractory psychosis, agitation, and aggression. And it's, I think, available in Canada. But as you'll see, there's mortality risk with these drugs, whether they're typical or atypical. Mortality risk goes up. There's cognitive decline. There's stroke, cardiovascular risk factors that come in. And the longer you're on it, the worse it is, probably. And there's risks of sedation, of edema. You're sitting around, you're sedated, you aspirate. There's parkinsonism. People become stiff. They have difficulty walking and balancing, then they may fall and have injuries. So it could be this vicious spiral.

So for reference for you, you can see here that here's a bunch of different drugs, aripiprazole, olanzapine, quetiapine, risperidone. And there's a small, statistically, oftentimes, benefit with these drugs, but again, the risks are higher. For risperidone, you can see that for psychosis, the cones, these are about 0.2 small effect size. For agitation, about 0.2 also. And this slide sort of summarizes things for you. Again, all neuropsychiatric symptoms, about 0.2. Psychosis, less, except for risperidone, a little bit better. And for agitation, for olanzapine and risperidone a bit better, but of course that's the one that—brexpiprazole, it finally has a FDA label.

And then, in general, there's a harm risk to these things, and it depends on the dose and how long. But in general, things like there is a number needed to harm, including for death, for falls, and they vary.

So I'm just flashing for you just the fact that you give up something. You're trying to sedate somebody, really to make them calm, but oftentimes you also suppress cognition, as you can see here on the MMSE.

And increased risk of cerebrovascular risk factors. And Bill, Dr. Brooks, you can see that Brodaty is the first one over there, your colleague. And so well-known risk of cerebrovascular events and the meta-analysis by the FDA or Lon Schneider, all of them suggest that there's at least a 1.7 increased risk in mortality with neuroleptics. The absolute risk, again, may be small but it increases over time.

And it's more, even, with the typicals than the atypicals.

This is our colleague, Clive Ballard, and basically, you can see that if you're on an antipsychotic and you stay on it for a long time, you can see basically once you develop really severe symptoms, you risk mortality. So that's the darker green. But then the lighter green is being on the antipsychotics. And you can see that after 3 1/2 years or so, 50% alive versus like 25%. So there's an increased mortality risk.

What about brexpiprazole? So brexpiprazole, as I mentioned, is titrated up to about 2 mg over 3 weeks. So in the trials, really, 2 to 3 mg is the right dose. Below that, really, not so much. And it's not an acute drug. So whether its benefits come out in 10 or 12 weeks, in the first 4 weeks maybe not necessarily. So if someone is immediately dangerous, this is not the drug. And we have a gap there.

It was FDA-approved a couple of years ago, specifically for agitation associated with dementia. Not for psychosis, for agitation. And at the individual level, even though the cohen's d's are actually modest or moderate, 0.25 to 0.35, they're a little bit higher for this than some of the other drugs. At the individual level, actually, there may be some responders. So there's a 50% greater likelihood that someone is actually going to respond a fair bit on the CGI, which is a 7-point severity scale, getting better by 2 points. And remember, in these trials, placebo is actually very good. So getting that attention actually is good. So this is above placebo.

The overall risk and benefits seem to be pretty good. There's a low likelihood of cognitive suppression. It didn't show up, so that's good. Parkinsonism and falls, again, not so much of a signal. So really, on the efficacy side, maybe a little bit more efficacy, but maybe a little bit less risk. And that actually, if you have better efficacy, people may stay on the drug for longer to get the benefit. And what we don't know is the long-term mortality. And of course, for other antipsychotics, to review, again, modest effect sizes, but probably higher risks, potentially.

There really haven't been head-to-head studies. But long-term risk with this stuff, with these drugs, are not known.

So what happened in the US was, basically, there was a mandate to try to get people off of antipsychotics. And basically, what happened was that people substituted. So in nursing homes, you had less antipsychotic use, but then things like neuroleptics, things like anticonvulsant use, went up. And guess what? And the total number of people getting psychotropics didn't go down. So they were basically switched over to another drug where there is really no evidence base and there's risks.

And here are the risks, for example, of these drugs relative to antidepressants. So the risks are higher. The number needed to harm are higher than antidepressants. But even antidepressants have some issues with them. And Christoph's going to talk a little bit more about what's emerging, but one of the things that happened in the US is that this study came out a few years ago for citalopram for agitation. It was a 9-week study and there seemed to be some benefit. But you had to go up to about 30 mg, right? And the problem was, in that short of time, you lost about a point on the MMSE and the QT went up. And the effective dose, really, was mostly targeted at 30 mg. And for elderly, probably 20 is enough. And so people started giving this out, handing it out like candy.

And then, the S-CitAD study was done. I was part of this group. It just got published this year. It was so much handed out like candy in the US, that we couldn't recruit for the study. You could see, it was an underpowered study. What it unfortunately showed was that, actually, we saw conduction delays. Even in the cousin of citalopram, escitalopram, which is thought to be a little bit more benign. And so we need options. And that's what it comes down to is that the prevalence of NPS is high; the burden of it is high. The unmet need is still great, even though we have some drugs that are approved for short-term periods or in the US we have brexpiprazole specifically for agitation. Future research really needs to look at other mechanisms, comparison studies, et cetera, and this is a good lead-in for Christoph.

Chapter 5

Dr. Correll:
Well done. Now, we want to take the last step, the third step here in this discussion, and then invite your questions. You've heard that there is a lot of stuff going on in the brain and in people's lives that is really difficult, burden for patients but also caregivers and society, that we have very limited options right now. The medications that work actually have a black box and can have detrimental outcomes. So where do we stand with one treatment approved for agitation, nothing at the moment for psychosis. Although antipsychotics were obviously developed for psychosis, they seemed to have a lower effect size, at least half the effect size as what we've seen in

schizophrenia, where the effect size is about 0.4. And we need to be better than that. Risperidone about 0.55, olanzapine 0.56. That doesn't translate into efficacy in Alzheimer's disease. Is that because it's more fluctuating? Because these patients are more helped with environmental cues and structure, as we've heard? So that tells us something. We need to do that. But all of us are struggling with the patients, where that is not possible.

So where do we go from here? This is one network meta-analysis. Remember, a network meta-analysis tries to take advantage of all the trials that are there, including indirect comparisons, which are generally against placebo because there are very, very few treatments that are head-to-head comparisons. And there are lots of lines left and right. But as you know, in a meta-analysis, whenever the 95% confidence interval crosses this vertical line, that means it's not statistically significant. There are only 2 lines that don't kiss or cross that line, and one is dextromethorphan-quinidine, which is a drug that was in development 10, 15 years ago. Had a very promising phase 2 study. I'll show you some of the results. It doesn't have the phase 3 study in this meta-analysis because the program was then discontinued.

We'll talk a new edition of dextromethorphan, now not with quinidine, which is really just added to reduce the breakdown of the medication. It's now combined with bupropion, and we'll see where that goes.

And at the two-thirds down, you have risperidone, what we all heard about, has an effect size that's small, about 0.2, but has all of the detrimental effects. So it's not for lack of trying, as you can see. There are, I don't know, maybe 20 drugs here, memantine and others that are used primarily for dementia. And none of them seem to really go beyond the placebo effect, except for isolated differences.

Now, this is the dextromethorphan-quinidine study. Dextromethorphan is a complex agent. You may all know it. It's an antitussive and it's used a lot in kids for cough, but it's also washed out very, very quickly. You need to block its breakdown through the cytochrome P450 2D6 in order to maintain it, and I'll show you a slide later down the road, in order to have more of it. It's then an interesting compound. It's an NMDA antagonist, it's a sigma 1 agonist, and it also interacts with serotonin and adrenaline.

This is an unusual study design that was chosen that basically tries to take advantage of placebo nonresponders. So you see that there are 2 stages. It's a 10-week study, but it's two 5-week components of it. The first one is a traditional head-to-head study, placebo-controlled. And in that first component, there was actually, a statistically significant advantage of dextromethorphan-quinidine. And then the placebo nonresponders are taken and re-randomized. So you're enriching now, for nonresponse to placebo and you can see that there is an even greater difference. And then the 2 phases are put together.

Now, this is obviously enrichment on the nonresponse to placebo, and we have no idea whether the FDA would actually accept such a design or would just take the first half of that study design.

Now, we've heard about serotonergic agents, that they're used a lot. And again, the quinidine-dextromethorphan combination was stopped because a large phase 3 study wasn't able to replicate that in a placebo-controlled parallel design. Here you see, well, when you put everything together, and that's the advantage and the disadvantage of meta-analysis. You put apples, oranges, brussels sprouts in terms of patients, in terms of designs, in terms of outcome, you may push this over the finish line. That's the upper forest plot. But then it becomes more complicated. There are studies that have a high risk of bias. Maybe there's functional unblinding. It's very clear who's on what. Maybe you just take the people who finished this study. So this is a survivor bias. You don't analyze patients that are dropped out early. You don't do an intent-to-treat analysis. Or there are other reasons. Maybe it's not fully blinded.

If you then take out the high-dose citalopram studies, as Ali was saying, this is something that's not even FDA-approved. It would be off-patent, off-label. That's also not significant. But we're talking about agitation, aren't we? So when you just take that outcome and bring back everything else, high dose, high risk, even then, there is no significant advantage. So that means serotonergic augmentation doesn't seem to really cut it for agitation. At least, in our average patients in meta-analysis.

Now, this is the new addition of dextromethorphan, coupled now with bupropion. On the right-hand side, so you see what happens to DM, dextromethorphan, when you don't put a metabolic inhibitor to it. It's basically very low levels and washed out. But once you put bupropion into it, like quinidine was in the past, then you keep the blood level up. And that combination then gives you a neurotransmitter optimization or influence that is not restricted to one neurotransmitter. And with my 30 years of psychopharmacology experience, it seems that, to me at least, that the rich pharmacology—previously we called them dirty drugs—but rich pharmacology, when you have multiple neural transmitters that talk to each other in concert, may have better efficacy. I mean, we tried to do this

clinically by putting multiple things together because the brain is a very malleable and also resilient organ. When you put some pressure on one end or you block something, there's counter regulation. So it's much better to have something that already has multiple neurotransmitters that potentially then work in concert.

As I mentioned, dextromethorphan is an NMDA receptor antagonist, but it's at the same time also a sigma 1 agonist, which has some antidepressant capacity, and it also interacts with noradrenaline, dopamine and serotonin. So what are the data? This is one phase 2/phase 3 trial because it has enough numbers and is designed to be also a registrational kind of trial. One dose of dextromethorphan with bupropion titrated over 2 weeks with a lower dose, that was AXS-05, 30 mg dextromethorphan and 105 bupropion twice a day. Generally, for antidepressant effect, we need more than 210 mg. And then it was increased for weeks 3 to 5 to 45 mg twice a day, plus 105 mg of bupropion. But you don't know, maybe it's just the bupropion. We've seen that maybe citalopram does something, so placebo alone is not the right comparison. You need a pseudo placebo or an active comparator just to make sure it's not the bupropion that does the trick here.

Broad inclusion criteria. So 65 to 90 years. You see that they have a diagnosis of agitation and also an MMSE between 10 and 24 and have an NPI-AA score of greater or equal to 4. What did this study show? Bupropion alone doesn't do anything; it's like placebo. But when you add dextromethorphan to it and keep it up in the brain and the blood levels, then there is a significant effect that starts to touch the 0.05 line at Week 2, when, remember, it's just the lower dose. But then as of Week 3, it actually becomes statistically significant.

Looking at the acute study, generally, the FDA wants 2 acute studies because it's an all-comers. Here, a different approach was chosen, and the second study was done; that's a relapse prevention study. Now, we want to know whether people who respond also stay stable, but it's an enrichment design.

That means you're only following people who have already benefited. And you can see that in the table, that patients had, for example, a CMAI score of almost 71 in the beginning, and that dropped during the open-label stabilization to 40s, low 40s.

Now, that's an interesting question. Do people who respond to the drug, then, should they be on it, or do they lose the effect? But it's not necessarily giving us the assurance that, yes, I can give it to all-comers and always win against placebo. So it's a question whether the FDA, in such a high-need stage or area of dementia-related agitation will accept that as the second study. But it was significant in terms of maintaining patients pretty well when the medication was added and continued versus it was withdrawn. And it's not just the withdrawal effects. You don't see all of the relapses early, so that assures us it's really the drug effect itself. And when looking at the relapses over that 6-month study, you can see it's 7.5% versus 25.9%. That's like a 13%, 15% difference or so. 7%. So it's an NNT, number-needed-to-treat, of about 6 or 7 it's below 10, which is definitely something that's clinically relevant.

But there's something else on the horizon. You may know that on the 26th of September last year, a revolution occurred in schizophrenia. Maybe not your area, but we have the first and currently only modulator of a different system than postsynaptic doping blockade that's approved for schizophrenia. We've waited for 7 decades for that. And again, that was also not for lack of trying. There have been multiple mechanisms that have been explored and exploited, but here now, we have muscarinic agonism, M1 and M4 agonism, and that is called xanomeline. Xanomeline is then paired with trospium, which is a peripherally restricted anticholinergic, and I'll tell you about that in a minute.

Just let's briefly review what the cholinergic system consists of. So we have the nicotinic receptor system. We're not talking much about this today. It's related most likely to cognition. Alpha 7 receptors have been exploited in the past, and encenicline, which failed later down the road. These are fast ion-gated channel receptors. We're talking about the muscarinic receptors that are basically G-protein-coupled receptors. There is a downstream effect, which has a lot to do with the second messenger cascades. There are 5 muscarinic receptors. The odd ones, 1, 3, 5, are postsynaptic. When you stimulate them, it's a go. The even ones, 2 and 4, are presynaptic, and when you stimulate them, it's a stop because these are autoreceptors.

Also, these receptors can either have a pocket that's orthosteric, where our endogenous neurotransmitter goes, that's acetylcholine, and then it's either a stop or a break. Or you can have an allosteric pocket, which is much more specific for each of the 5 receptors, and it's almost like a bystander pocket. When you go there and you stimulate, it's called a positive allosteric modulator. So you're enhancing binding of the endogenous neurotransmitter and also the transmission.

Or you have a negative allosteric modulator.

Why are we talking about M1, M4? Because these receptors are concentrated in areas where we think neurobehavioral abnormalities emerge and psychosis resides. And you see that at the top, here. Whereas M2, and also 3 and 5, are more related to peripheral side effects or effects which are a lot gastrointestinal.

So here is a brief schematic why an M1/M4 agent would work for psychosis. I'll walk you through this very briefly. Basically, we have that bottom up and inside out, M4 effect on psychosis. There is a hindbrain to midbrain transmission of acetylcholine. Acetylcholine and dopamine are friends. When they meet, there is a party. There's a lot of dopamine going up. So by stimulating M4, the autoreceptor, you're reducing acetylcholine input into the midbrain, ventral tegmental area, which then reduces presynaptic dopamine output.

There's also a localized M4 receptor through a cholinergic interneuron in the associative striatum, where we think psychosis reside. So specifically there. That's inside out. You stimulate M4, you're reducing dopamine output. And then there's a top-down effect where you stimulate M1. Now, this is not an autoreceptor, it's a go, but it sits on a GABAergic interneuron. And we think that for psychosis and behavioral dysregulation, there's an EI imbalance, excitation-inhibition. Too little GABA inhibition, too much excitation, glutamate. Glutamate and dopamine are also friends. Too much glutamate, too much dopamine. So by stimulating M1, you're stimulating GABA. GABA then reduces glutamate input into the midbrain, and that reduces output in the associative striatum.

So you see, now, this is an orchestration of different neurotransmitters, not just dopamine or glutamate or acetylcholine. And at least in schizophrenia, this has led to approval for psychosis. But we know this molecule. We have known it since the ‘90s. Eli Lilly tried to develop this not for agitation or psychosis, but for cognition because it increases acetylcholine in the frontal lobe. That's where the M1 stimulation is. And actually, it worked in the 1990s, at least in the protocol or completer analysis, there was better cognitive improvement with xanomeline alone. But it wasn't titrated; it wasn’t also coupled with the peripheral anticholinergic.

But what was seen without expecting it, dose-dependent up to 225 mg. Here, the approval of xanomeline trospium is a 125 twice a day. And you can see that basically, there is a decreased dose-dependent in the severity of the patients that have an increase in the severity of either neurobehavioral or psychotic symptoms. Similarly, there's also a lower percentage of patients that, over the 6-month study, had new onset of neurobehavioral or psychotic symptoms, and a dose-dependent greater percentage of people have a full resolution of these symptoms. So when you see something that's unexpected, that's dose-dependent, effect sizes of 0.8 and larger, you really have something

But it was untenable and it was then shelved because, at the same time, Lilly had olanzapine, which worked very well. And here, we have side effects of gastrointestinal problems, particularly, nausea, like 50% vomiting, and people had also syncope and loss of consciousness.

Now, the KarXT, that xanomeline-trospium combination, that takes advantage of the central effects of xanomeline, has some titration, but also curbs the peripheral effects by having trospium in there, which has also been around for decades for overactive bladder.

These are the drugs that are currently being investigated for Alzheimer's agitation, and you can see that the muscarinic modulators, there are now 12 or 13 that are currently in development for schizophrenia. Xanomeline-trospium is currently tested for psychosis in Alzheimer's disease, so we'll see, hopefully, many more options there.

Chapter 6

Dr. Sabbagh:
So we have a few minutes to have some questions and the first question. If there's any online, please go ahead and put them in. While we're waiting for questions to come in, some discussions about psychosis versus agitation. I know this is a nosological question. We struggle with this. Companies struggle with this. Can you comment on it, Chris?

Dr. Correll:
Yeah, and I'm interested to hear your take on it. Obviously, there's a lot of overlap, and we've seen that in the studies with pimavanserin. They were actually positive for psychosis, but there was a lot, also, agitation improvement. And sometimes, nosologically, it's hard to differentiate. There might be psychosis underlying agitation.

But I think it's a little bit of a pseudo accuracy to try to separate them.

Dr. Sabbagh:
Right.

Dr. Correll:
So having this as a mixed basket and still, like we have the PANSS, the Positive and Negative Syndrome Scale, that gives us treatment for schizophrenia. We're not treating positive symptoms only. Wouldn't it be nice to have also some wraparound of either psychosis or agitation? We can do subanalysis. We do that in schizophrenia, positive and negative symptoms, but I think it's a little bit too pseudo-specific. I don't know what you guys think.

Dr. Sabbagh:
There are lumpers and splitters, and I see that you can have agitation without psychosis, but clearly psychosis can drive agitation. Your thoughts?

Dr. Atri:
Yeah. And it's sometimes it's hard to know what's going on in the head. What are they actually thinking. Like you were saying, they could be sitting around stewing and having delusions and hallucinations and other things, and that's driving them, and they're not going to tell you. And, again, we're talking mostly about AD today, but with Lewy body, it's amazing, isn't it, Marwan? I mean, with Lewy body, they come to you, and you ask the family members, have they ever had any hallucinations or anything like that? And the family, no, no, no. And then you ask the patient, and they say, oh, yeah, for 12 years I've been, you know, at night, when I go to sleep, I see these things and stuff. The spouse is like, why didn't you tell me? There's something—it's amazing. We'll maybe figure it out. There's some network that allows people to sort of suppress that for so long. So, yeah.

Dr. Correll:
And it's stigmatized, correct? I mean, I'm not crazy.

Dr. Atri:
It's stigmatized, but there's something else. They almost live with it. And so it's a long-winded answer to say we don't know what's going on in there, what's driving that.

Dr. Sabbagh:
So something that we deal with is the caregiver, really, is ill equipped and can kind of exacerbate the agitation because they don't know how to respond. What strategies would you say you recommend in a situation like this?

Dr. Atri:
Oh, gosh. Well, come to our Harvard dementia course. We have a whole day on this. We have 3 1/2 days on stuff but one day just for neuropsychiatric symptoms, pretty much. And yeah, there's so many different strategies. I mean, I think keeping things simple. That new language of being able to talk to somebody and react to them in a calm, reassuring way, even though inside, it's very, very tough. And it's sometimes like stand-up comedy. You have to very quickly devise a plan about what to do.

I remember my dad. I was the closest to him in so many ways. He lived with us for 10 years. So I was the lightning rod for most things. But he was such a calm person that I'd seen him raise his voice twice in my whole life. Usually, if you sat next to him, your blood pressure went down. He was so calm. I remember, he was, like, agitated. He couldn't find his hat. It was when we were in Boston. It was cold. He's looking everywhere. He comes to me, he goes, who's taken it. Right? And it was on his head. And so I tried to, in a very light way, sort of say that's on your head, and then he looks at me and he goes, well, who put it there? Right? So then you have to be able to sort of manage that. So, so much of it is learning to sort of manage the situations and manage your own blood pressure and not react.

Dr. Sabbagh:
Do you believe—this is to you, Christoph—that the advent of the xanomeline and new dextromethorphan-bupropion would mean earlier treatment of agitation and psychosis than has been in current ADP, before patients progressed to more severe symptoms?

Dr. Correll:
That's an interesting question. Since you guys are coining now this MBI, minimal or mild behavioral impairment concept, these drugs are pretty well tolerated. So wouldn't that be a better way to start early and keep these symptoms down? The question is, will that then help also maybe delay some of the other pathophysiology or the neuropathophysiological changes? But I think it will prolong people being in lower levels of care and also improve quality of care and quality of life, for sure.

Dr. Atri:
I'd like to add to that. In general, I think once you lose a function or something becomes really established, it becomes very hard. So once, for example, the delusions or the psychosis even takes hold, it becomes more resistant and harder. So I think having that proactive ability to sort of suss it out early and intervene in any way you can is important.

Dr. Correll:
That's a really important point because in psychosis, the duration of untreated psychosis predicts poor outcome. And the brain is a learning machine. It gets easier and easier to flip into the states, yeah.

Dr. Sabbagh:
I want to thank both of you for joining me today. I think it was a very productive discussion.

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