

# A Patient-Clinician Discussion of Current Challenges in Schizophrenia Part I: Addressing Daily Functioning and Cognitive Impairments Associated with Schizophrenia [Podcast]

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Dr Philip D. Harvey is Leonard M. Miller Professor of Psychiatry, vice chair for research, and director of the Division of Psychology at the University of Miami Miller School of Medicine, and has also received a number of awards for research and has authored over 1,000 scientific papers and abstracts and written over 60 book chapters.

Mr Carlos A. Larrauri, MSN, is a mental health clinician, and member of the National Alliance on Mental Illness (NAMI) Board of Directors who was diagnosed with schizophrenia at 23 years of age. He has previously published on cognition and functioning in schizophrenia with Dr Harvey, and is currently pursuing a law degree at the University of Michigan Law School, and a concurrent master's in public administration at the Harvard Kennedy School, where he is a Zuckerman Fellow at Harvard's Center for Public Leadership. He also writes original music and performs in the band FogDog alongside Mr Matthew Racher, whose music can be heard in this podcast.

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**Abstract:** Dr John M. Kane discusses cognitive impairments in schizophrenia with fellow expert Dr Philip D. Harvey and patient advocate and mental health clinician, Mr Carlos A. Larrauri, who was diagnosed with schizophrenia. The podcast aims to raise awareness of the unmet need to address cognitive impairments associated with schizophrenia (CIAS) as well as the challenges/opportunities faced by patients and clinicians regarding assessments and treatments. The authors emphasize the importance of a treatment focus on daily functioning, in parallel with cognitive symptoms, to mitigate impairments and improve overall outcomes. Mr Larrauri presents the patient perspective and shares his experiences of how psychosocial support and cognitive training can benefit recovery and help patients achieve their goals.

**Keywords:** schizophrenia, cognition, cognitive impairments, functioning, clinician and patient perspectives, peer support, cognitive assessment, cognitive treatment

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## Podcast Speakers

Carlos A Larrauri (CL); Philip D Harvey (PH); John M Kane (JK)

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## Chapter I: General Introduction [00.00]

**JK:** Welcome to the podcast entitled “*A patient-clinician discussion of current challenges in schizophrenia: Part One, addressing daily functioning and cognitive impairments associated with schizophrenia*”, which we’re going to be referring to as CIAS. This podcast is aimed at clinicians treating schizophrenia across the globe, their patients and caregivers. The authors of this podcast manuscript meet criteria for authorship as recommended by the

International Committee of Medical Journal Editors. Writing, editorial support and formatting assistance with earlier talking points and the final transcript were provided by Fishawack, which was contracted and funded by Boehringer Ingelheim Pharmaceuticals Inc. for the services. Boehringer Ingelheim was given the opportunity to review earlier talking points and the final transcript for medical and scientific accuracy, as well as intellectual property considerations.

My name is John Kane, and I'm a professor of Psychiatry and Molecular Medicine at the Donald and Barbara Zucker School of Medicine at Hofstra Northwell. I would like to introduce my co-authors, Dr Philip Harvey, who's Professor of Psychiatry, and Director of the Division of Psychology at the University of Miami Miller School of Medicine. And Mr Carlos Larrauri, a patient advocate and psychiatric nurse practitioner, who has previously received a diagnosis of schizophrenia, and who will share the patient perspective with us on this podcast.

The specific aims are to raise awareness of how cognitive impairments associated with schizophrenia, which we will refer to as CIAS can present as a cluster of symptoms in patients, and to highlight the experience of people living with CIAS, the unmet clinical needs, and to emphasize the importance of focusing on improving daily functioning in parallel with cognitive symptom improvement in patients. We also want to provide guidance on clinical assessment methods for CIAS and the relationship to daily functioning. We want to describe current and potential future treatments for CIAS and emphasize the benefits of available cognitive training as add-on therapy to address cognition and functioning. Cognitive enhancement may facilitate learning of new skills, but improved cognition does not necessarily equate to improved function. We want to discuss the impact of current treatments on patient outcomes, and summarize the current challenges and potential future directions.

## Chapter 2: Defining CIAS as a Cluster of Symptoms [03:15]

- JK:** So first, we want to talk about the course, the profile of the course and severity of cognitive symptoms, which endure over time. I think being overwhelmed by information not being able to make sense of conversations; not being able to plan and organize; thoughts getting jumbled up; difficulty paying attention and not getting distracted; poor memory; difficulty perceiving and using emotions; difficulty comprehending key features of social situations and intentions are some of the things that we see in this context. Let me ask Carlos to comment on symptoms and course and what your own experience has been.
- CL:** Sure, in my experience, cognitive symptoms may take a more degenerate course without an early intervention. Dr Harvey once used the metaphor of a rubber band to explain cognitive symptoms that I thought explained it quite clearly. The more you stretch out the rubber band, the more it loses its original elasticity. Likewise, the more psychotic episodes you have, the more residual cognitive symptoms and impairments may remain.
- PH:** Despite the relationship between symptoms and cognitive impairments, cognitive impairments may be the first sign of risk for the illness. They can be identified prior to the onset of psychotic symptoms. And they are more severe in people who eventually get a diagnosis of schizophrenia than those who don't, among people who look like they might have a prodrome.
- CL:** This was my experience. I think the cognitive symptoms weren't identifiable before psychotic symptoms were present. As you mentioned, during the prodrome, or the high-risk clinical state, I had trouble concentrating and completing routine academic assignments. I initially recognized this was not normal and went to see a school psychologist. But they failed to identify this as a cognitive deficit associated with schizophrenia, and hence, it was not addressed. However, I had a friend from high school who was with me at college, and she was able to identify that my behavior had changed in a way that was beyond normal stress of school or substance misuse. She communicated with my Mom, and from there we began the process of getting professional help. It took about six to nine months to finally get the right diagnosis, and family had noticed during this time that I had trouble staying focused, that I would space out a lot or lose attention during conversations. I was also disorganized in my thought process.
- JK:** So, you know, we see the association between cognitive symptoms and other dimensions in schizophrenia, such as negative symptoms and positive symptoms, but there are differences that we need to keep in mind. Negative symptoms include a seeming lack of interest in the world, not wanting to interact with other people that we describe as social withdrawal, an inability to feel or express pleasure, anhedonia, an inability to act spontaneously, a decreased sense of purpose or lack of motivation, which we call avolition, not talking much or alogia, and positive symptoms include delusions and hallucinations, so there are really important differences between those domains, and cognitive symptoms.

Cognitive symptoms are a cluster of symptoms that present across multiple disorders, consider it a biotype. The nature of cognitive symptoms in schizophrenia overlap, to a degree, with other cognitive disorders... dementia, or bipolar disorder or major depressive disorder, and may share genomic risk characteristics. Hence, the broader transdiagnostic context of cognitive impairments should also be considered.

- PH:** But we've got to keep in mind, there are some differences. Psychiatric conditions have signatures that are similar to each other, but quite different from cortical dementia. Here we're going to focus on cognitive impairments as they present in schizophrenia. The major differences from cortical dementia include rapid forgetting, in dementia syndromes, which is not seen in schizophrenia. And probably the hallmark cognitive impairment in dementia is the inability to retrieve information, even if you have a cue or a prompt. And in some studies, people with schizophrenia have normal performance on memory tests, if they receive prompts or cues, and are only impaired if they have to retrieve the information without any external contexts. The differences with bipolar disorder are relatively minor. These impairments are present in euthymic individuals and in relatives. But it may very well be that the biggest difference between schizophrenia and bipolar disorder is a question of severity, and not the profile of impairment. And many studies have found that they correlate similarly with disability. So, it may be that the main difference between schizophrenia and bipolar disorder, in terms of cognition in the population as a whole, may be differences in premorbid functioning; if someone has had better premorbid functioning, they may wind up, even if they deteriorate, having better performance than someone whose abilities were not as good. So, we're going to focus on some of the features that are seen in cognitive impairment in schizophrenia.
- JK:** And this can be seen in the infographic that is included in our presentation (Figure 1).<sup>1,2</sup>

### Chapter 3: Current Challenges and Unmet Needs [09:00]

- JK:** So, what about the worldwide prevalence of schizophrenia and how cognitive disorders fit into that?
- PH:** Yeah, it looks like the worldwide prevalence of schizophrenia is about 1%.<sup>3</sup> It doesn't seem to vary much across different nations and cultures. There are cultural impacts on everyday functioning because some places provide more or less opportunities; the prevalence of the diagnosed condition seems to be the same. At least 70% of people with schizophrenia have current cognitive impairment that would meet criteria for being significant.<sup>4,5</sup> It may be higher, because that doesn't consider premorbid functioning. The challenge, of course, is to get an adequate assessment of cognitive functioning, as well as diagnosis. Cognitive impairments are best measured with performance-based tests. It turns out that one of the features of schizophrenia and related conditions is also a challenge in self-assessment, which is a cognitive ability, and self-reported information from the patient has questionable validity in some circumstances.<sup>6</sup> Parents, caregivers, or high contact clinicians have actually been shown to be able to get really good information about people's cognitive performance. The challenge, of course, is that although, compared to other neuropsychological assessments, the assessment for schizophrenia is relatively abbreviated, but it's still really long. And given the time allocated for doing assessments, the 75 minutes required to do the Matrix Consensus Cognitive Battery, referred to as the MCCB, may just be too long. If you have a scheduled session of 20 minutes, you don't have 75 minutes to do testing.<sup>7</sup> Abbreviated in-person batteries, particularly ones that were developed specifically to assess schizophrenia, probably have similar validity and are related to the results from the MCCB. It seems appealing to use a computerized cognitive battery such as CogState, or CanTab.<sup>7</sup> But the fact is, those are not really self-administrable assessments. They require tester training, and many clinical practices don't have the time or staff members with the right training to do that kind of assessment. Plus, it costs a lot of money too. So, there's an acquisition cost, and there's typically both a licensing and test delivery costs.
- PH:** COVID-19 has definitely accelerated the development of web-based neuroscience informed cognitive assessments.<sup>8-10</sup> But the barriers for implementation sometimes include lack of access to the Internet, and challenges in digital literacy.<sup>9</sup> So, what happens is, it doesn't really matter if you've got a really good cognitive assessment that can be delivered remotely; if you've got someone who can't access the Internet and doesn't know how to log on to their computer, it will still be challenging to deliver that remotely. So, what we need to do is think about clinical assessments and interventions that address associated functional impairments that are critical to overall outcomes. Findings of large, prospective studies and people with schizophrenia have shown that several elements of real-world functioning are not routinely assessed and targeted by intervention programs and community mental health services.<sup>11,12</sup> So, what happens is, the focus is commonly on symptom reduction, which is actually, in many cases less of a challenge, and less on focusing on functioning and reducing disability. Personalized interventions aimed at promoting cognitive functioning and independent living have to be a critical part of management because, after all, despite the emptying of the state hospitals in the 1950s, associated

with the availability of antipsychotic treatment, the overall outcome, focusing on functioning, getting married, having a job, living independently hasn't improved much. So patient access to cognitive rehabilitation and functional rehabilitation services is critical.

Another thing to keep in mind is that antipsychotics, despite their excellent efficacy in many patients for reducing psychosis, don't improve cognitive functioning.<sup>13</sup> So, there's a number of novel treatments in clinical development. Some of them focused on our knowledge of cognition in the general population and the knowledge of the importance of neurotransmitter manipulations, others based on their importance in schizophrenia. So, GABA and glutamate modulators, such as the GlyT1 inhibitors are being investigated; muscarinic agonist targeting the M1 and M4 receptors are in development; phosphodiesterase inhibitors, PDE inhibitors, also interact with glutamate and are being investigated.<sup>14</sup> Dopamine agonists have been evaluated. The challenge, of course, is that you really want to stimulate the dopamine D1 receptor and many compounds that hit D1 are too large to cross the blood-brain barrier. And studies of IV administration of D1 agonists have not been remarkably successful.

Serotonin antagonists have been examined as well, and these agents may have cognitive benefits.<sup>15</sup> But I think that what happens is, recently there have been a number of developments with positive effects of agents in this general domain of non-dopaminergic agents that are hitting other receptors that may be important. The current antipsychotic therapies, even long-acting injectable ones that do a very good job of stopping relapse and keeping people out of trouble, don't offer direct therapeutic benefits for cognitive impairment.<sup>13</sup> You may find that daily functioning is improved, but it's not improved through an improvement in cognitive functioning. So, it may very well be that what long-acting antipsychotic treatment does, is reduce some of the deficits associated with disorganized behavior, without improving the fundamental core challenges associated with cognitive impairment. In terms of developing treatments for cognitive impairment, antipsychotic maintenance therapy may interfere with treatment effects. There have been a number of studies that have shown that agents that don't work in people with schizophrenia receiving antipsychotics, work in schizophrenia spectrum conditions like schizotypal personality disorder, where maintenance antipsychotic therapy isn't delivered.<sup>16-18</sup> Lack of access to formal performance-based assessments and clinical trials are critical. Relying on self-report may be inaccurate, and informants may not be available. After all, among the symptoms of schizophrenia, are social withdrawal associated with the negative symptoms that Dr Kane talked about. Requiring someone to have an informant may actually be too high a bar for many studies. Patients are non-adherent occasionally to the medication. They're not necessarily more non-adherent than the general population, but the consequences are quicker. We need to reserve judgments on apparently ineffective treatments, as medication non-adherence may very well cover up the real effects. Interventions aimed at improving medication adherence would improve the outcomes of treatment. It has turned out that even in studies of cognitive-enhancing agents with relatively benign side effect profiles, non-adherence was very common, and very challenging; and this has to be something that we address going forward. If you never take the medication, you don't perceive the benefit that you're getting from it, so there's no motivation to continue.

## Chapter 4: The Patient Perspective [16.41]

**JK:** Carlos, can you give us your perspective on some of these challenges and current treatment?

**CL:** That's right, I can't stress enough the importance of getting sleep to protect cognitive functioning. And more broadly, it's important to patients, for them to understand that in addition to medical treatments, there's a variety of coping mechanisms that will help them in the recovery. So, I find that, for me, at least cognitive function, likely deteriorates in a more pronounced fashion without enough sleep, you know, I used to be able to stay out late and function. I also find it more difficult to switch attention between tasks. Let's say I'm on my phone and trying to pay attention to a conversation at the same time, switching attention becomes more difficult. I also find the ability to retain information that I read or heard decreases. If I'm taking an exam the next day after not sleeping, I might have to reread a question prompt one, two, or three times. And sometimes there's a longer latency in responding to auditory stimuli. I've had people call my name and maybe a couple of seconds go by before I respond. And all these things happen when I don't get enough sleep. But of course, there's ways to cope and one of them is modifying one's environment. For example, one way to cope with cognitive symptoms is for me to seek low distraction settings. I actually gravitate towards libraries or quiet places or private rooms, and sometimes wear noise cancelling earphones or earplugs. In addition, mitigating the effects of pressure are important. For example, triggering anxiety or positive symptoms such as hallucinations can also make it more difficult to focus.

**CL:** Cognitive interventions, including cognitive remediation tools are helpful, but they can also include creative pursuits such as playing instruments, improvising, running, etc. For example, I enjoy jamming as a musician and

that requires activities such as reading other people's facial expressions, body language, and social cues. This means having to pay attention and respond in real time to dynamic changes in music and social expression. Also, being mentally engaged with school or employment can help as well as avoiding substance use, such as alcohol and marijuana, which impair cognitive performance. Early intervention is important to mitigate cognitive impairments; with Dr Harvey's rubber band metaphor, multiple relapses loosen the rubber band, creating more residual cognitive impairments. I also think it's important to stress that it takes time to heal from a psychotic episode, it may take a couple of years or longer for someone to return to their prior baseline cognitive performance. It's like someone having to do physical therapy for months before they regain full functioning of their muscle or limbs. So, it's important for families and patients to give themselves the grace and space to take those baby steps in the beginning, but at the same time, not to settle for less or have a defeatist attitude. Stigma and discrimination may cause others to believe you're capable of less, but this is not necessarily true.

## Chapter 5: Future Therapeutic Opportunities - A Clinician's Perspective [19:46]

- PH:** So, we do have a couple of best-practice suggestions based on the impressions of people who are living with schizophrenia as well as our own research-based data that we've collected. It's really critical to supplement self-reported data with more objective data to get a diagnosis. Caregiver data can help you discriminate between a challenge in motivation and a lack of competence. If someone can do something, but doesn't, then that would require a different intervention than if they're trying to do something, but they're unable to succeed. People with schizophrenia often have difficulty using reward-related information to adaptively guide future behavior;<sup>19</sup> they may require some reminders and suggestions to be brought back on task. It's important to emphasize that cognitive assessment should not be a required prerequisite for cognitive enhancement therapies. We don't require a full positive and negative syndrome scale score before administering an antipsychotic. Essentially everyone with a schizophrenia diagnosis has some level of impairment. So, focus should be instead on improving patient's functioning; get as much information as possible about what they're doing, find out what their perceived limitations are, try to find out if they perceive limitations that others don't, or if they're misestimating in the other direction.
- PH:** Technology may be very helpful for the assessment of functioning, both passively such as with Fitbit or GPS information, or actively using the sort of interactive paging system on a smart device.<sup>20-22</sup> Combining pharmacological and nonpharmacological such as cognitive training, and psychosocial interventions, can help improve functioning in patients.<sup>23,24</sup> Improving cognition alone, is not going to teach you skills. If you get 15 extra IQ points out of the cognitive enhancement that you receive, you're still not going to be able to speak French if you've never spoken it before. And you're not going to be able to go on a job interview unless you know how to do that either. So, functional skills have to be learned, and cognitive enhancement makes that much easier. A lot of emerging digital smartphone technologies can be used to improve medication adherence, provide broader access to psychosocial support, while also monitoring functional activity that would imminently impact on the accuracy of clinical data.<sup>25</sup> I think it's helpful to monitor the efficacy of medications and eventually improve clinical outcomes, both daily functioning and cognition. The success of adherence monitoring may not always be as good as expected, but any kind of monitoring is good. And evaluation of people's functioning may get them to pay more attention to themselves and what they're actually doing.

## Chapter 6: Future Therapeutic Opportunities - A Patient's Perspective [22:33]

- JK:** So, Carlos, what about patients' self-advocacy?
- CL:** Dr Kane, patients' self-advocacy is a key component of recovery. For example, I found that advocating for academic accommodations, such as a quiet testing space or extra time on high-stakes exams, has allowed me to play on a level playing field. These measures allow people with schizophrenia to perform to the best of their abilities by reducing the likelihood of symptoms interfering. Furthermore, workplace accommodations, such as hybrid, or remote work, provide greater flexibility in relation to working hours and the timing of necessary breaks during the workday. For those with cognitive impairments, the capacity to control and adapt to one's working environment, would enhance performance and help them perform their job duties. What I'd like to say is that current medications are often necessary, but they may also be insufficient to help people achieve their goals; peer support, therapy, cognitive remediation, and other tools are necessary and important for us to share and use. As mentioned earlier, it's important to engage the brain in mentally-stimulating school or employment to improve

cognitive functioning. The brain is like a muscle where one must either use it or lose it, and it needs to be exercised after psychosis to heal. Lastly, platforms that provide patients access to peer support and shared experiences is particularly helpful so people can learn from others' perspectives.

## Chapter 7: Conclusions [24:01]

**JK:** I think to summarize all of this, you know, we'd have to say that despite being a core feature of schizophrenia, that cognitive impairment really represents an area of great clinical unmet need, with no approved pharmacologic therapies to treat it. Improved daily functioning, associated with cognitive improvement, and facilitation of patients' self-advocacy, really should be prioritized. Novel pharmacologic treatments in clinical development have the potential to facilitate improved patient outcomes, if combined with other strategies, such as cognitive training programs and psychosocial interventions that encourage peer support and the sharing of experiences among patients.<sup>23,24</sup> Treatments in development, as you've heard, include inhibitors of the glycine transporter, drugs that show preferential agonism of the muscarinic receptors, type 1 and type 4. So, there are a lot of, I think, promising developments that we look forward to. And I want to thank Phil and Carlos for excellent summaries of a very important and complex area. We hope that this has been helpful to the listeners, and we very much appreciate your attention.

## Music Introduction [25:19]

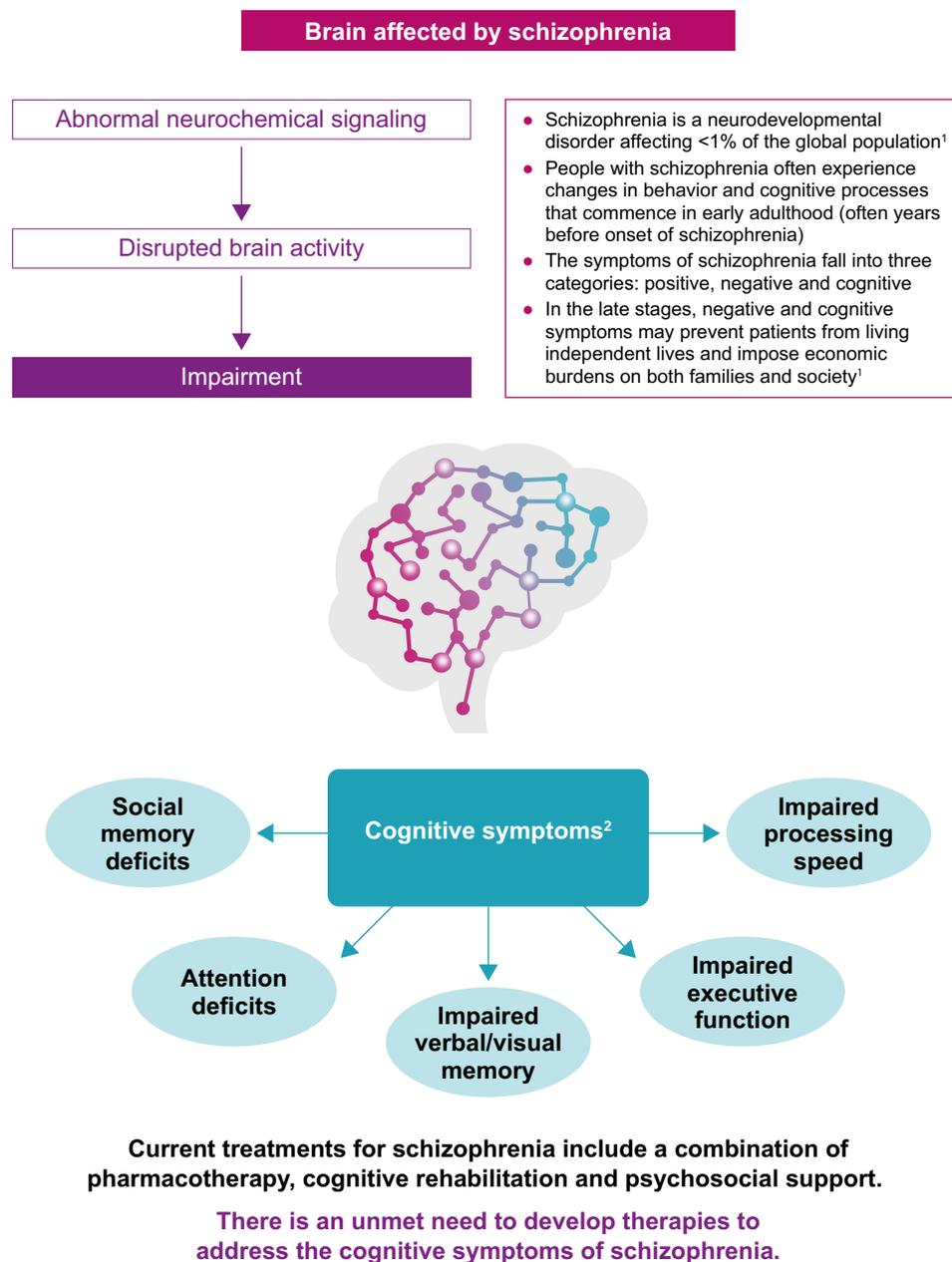
**CL:** You will now be hearing music from FogDog, original music by Carlos Larrauri and Mathew Racher. The definition of fog dog is a light that breaks through a fog bank, and they hope their music storytelling and advocacy is a source of hope and recovery for those in need.

## Acknowledgements

The music from this podcast was provided by Carlos Larrauri and Matthew Racher, patient advocates and authors from their band FogDog. The song is entitled 'You Are Not Alone' and the full version can be found at the following link; <https://open.spotify.com/track/5sn07Tk9xzo7dL14F8N9ty?si=3f371663626f42c5>.

## Disclosures

The authors of this podcast manuscript meet criteria for authorship as recommended by the International Committee of Medical Journal Editors. Writing, editorial support, and formatting assistance with earlier talking points and the final transcript were provided by Lieve Desbonnet PhD of Fishawack Communications Ltd, part of Fishawack Health, which was contracted and funded by Boehringer Ingelheim Pharmaceuticals, Inc., for these services. Boehringer Ingelheim Pharmaceuticals, Inc. was given the opportunity to review earlier talking points and the final transcript for medical and scientific accuracy as well as intellectual property considerations. Speakers on this podcast speak on personal behalf, independently of Boehringer Ingelheim. **CL** has received presentation/speaker fees from Biogen, Intracellular Therapies, Karuna and The Center for Patient Advocacy Leaders; he has also received fees from Boehringer Ingelheim for development of a video on schizophrenia; personal fees from Klick Health, Alkermes, K Therapy/Health, Janssen, Discern Health, Neurocrine, paid travel expenses from Boehringer Ingelheim for a poster presentation, outside the submitted work. **PH** has received consulting fees or travel reimbursement from Alkermes, Boehringer Ingelheim Inc., Intra Cellular Therapies, Karuna Pharma, Minerva Neuroscience, Otsuka America, Roche, Sanofi Pharma, Sunovion Pharma, Takeda Pharma, and Teva Pharma; Royalties from WCG Clinical Outcomes; Intellectual property from iFunction, and a research grant from Takeda Pharma and from the Stanley Medical Research Foundation. **JK** has received consulting fees or honoraria for lectures from Alkermes, Boehringer Ingelheim, Cerevel, Dainipon Sumitomo, Intracellular Therapies, Janssen, Lundbeck, Merck, Newron, Otsuka, Roche, Saladax, Sunovion, and Teva; he has received research support from Lundbeck, Otsuka, Janssen and Sunovion, and is a shareholder in Health Rhythms, LB Pharma, MedinCell, North Shore Therapeutics and Vanguard Research Group; personal fees from Allergan, Click Therapeutics, HLS, Indivior, Johnson & Johnson, Minerva, Neurocrine, Novartis, NW Pharmatech, UpToDate. The authors report no other conflicts of interest in this work.



**Figure 1** Cognitive impairments associated with schizophrenia.

**Note:** Data from Wu Q et al<sup>1</sup> and Kharawala et al.<sup>2</sup>

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