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COMMENTARY

A Patient-Clinician Discussion of Current Challenges in Schizophrenia Part 2: Negative Symptoms in Schizophrenia [Podcast]

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Dr William Carpenter, MD, is a professor of psychiatry at the University of Maryland School of Medicine, is Editor-in-Chief for Schizophrenia Bulletin. Dr Carpenter's main research focus is in the area of schizophrenia, and was awarded The Rhoda and Bernard Sarnat International Prize in Mental Health (Institute of Medicine of the National Academy of Sciences, 2013), the Schizophrenia International Research Society (SIRS) Lifetime Achievement Award (SIRS, 2019) and the Pardes Humanitarian Prize in Mental Health (Brain and Behaviour Research Foundation, 2019).

Mr Matthew Racher is a Certified Recovery Peer Specialist and dedicated advocate for people living with schizophrenia, who is currently studying for his Master of Social Work (MSW) in Miami, Florida. Mr Racher's aim is to draw upon his own lived experience in recovery from schizophrenia to help others manage and overcome their own mental health challenges. Alongside his involvement in Miami-Dade's local National Alliance on Mental Illness (NAMI) affiliate, he is also a keen and talented musician, who performs in the band FogDog alongside Mr Carlos Larrauri and whose music can be heard in this podcast.

Abstract: Dr John Kane discusses negative symptoms in schizophrenia alongside fellow expert, Dr William Carpenter, and Mr Matthew Racher, a Certified Recovery Peer Specialist and dedicated advocate for people living with schizophrenia, who is currently studying for his Master of Social Work (MSW) in Miami, Florida. In this podcast, the authors discuss challenges and opportunities faced by patients and clinicians in the assessment and treatment of negative symptoms. They also touch upon emerging therapeutic strategies, with the aim of raising awareness of the unmet therapeutic needs of those living with negative symptoms. Mr Racher provides a unique patient perspective to this discussion, drawing on his own daily experiences of living with negative symptoms, as well as offering positive insights from his recovery from schizophrenia.

Keywords: schizophrenia, negative symptoms, clinician and patient perspectives, peer support, psychosocial support, clinical assessment, treatments

Podcast Speakers

Matthew Racher (MR); William Carpenter (WC); John M Kane (JK)

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Chapter 1: General Introduction [00.00]

JK: Welcome to the podcast entitled "*A patient-clinician discussion of current challenges in schizophrenia. Part 2: negative symptoms in schizophrenia*". 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

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Pharmaceuticals Inc. for these services. Boehringer Ingelheim Pharmaceuticals 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'd like to introduce my co-authors, Dr William Carpenter, who is Professor of Psychiatry at the University of Maryland School of Medicine, and Mr Matthew Racher, a patient advocate and certified peer specialist who has previously received a diagnosis of schizophrenia. Mr Racher will share the unique patient perspective with us on this podcast.

The podcast aims to raise awareness within the mental health community of the negative symptoms associated with schizophrenia. In this discussion, we briefly explore the following topics relating to negative symptoms: the clinical presentation, and prevalence of negative symptoms; the neuropathology of negative symptoms; the burden of negative symptoms for patients and caregivers from a patient perspective; current treatment strategies and novel therapeutic approaches to manage the symptoms; and the current unmet clinical need for patients with regards to the management of negative symptoms. And first, let's discuss how negative symptoms are defined.

Chapter 2: Defining Negative Symptoms [02.35]

WC: The negative symptoms include issues like diminished emotional expression. An example is expression of emotions in the face, a failure to make eye contact, prosody, diminished movement of the hands, face, and head when speaking (Figure 1).[1,2] And it also causes effects, such as clinical negative symptoms, when the patient shows little interest in participating in activities, in work or in social engagement. They sit for long periods of time, or be isolated from others during that time.

MR: So yeah, as a patient, an individual living in recovery from schizophrenia, I've experienced negative symptoms. The one I immediately noticed was along the lines of anhedonia, loss of interest in pleasure, and playing guitar, and singing. I noticed that the activities that I once enjoyed doing, that I once felt very connected to or engaged with, I started to feel this sense of lack of pleasure in pursuing. I believe it's important for clinicians to evaluate symptoms that diminish emotional expression, and anhedonia, as these contribute to the framework of diagnostics.

JK: It's not common for clinicians to use rating scales in clinical practice, although I think that would be ideal. But as you suggest, I think clinicians really need to evaluate patients for symptoms like diminished emotional expression, and avolition and really understand how those contribute to diagnostic framework. And we should be asking patients about their interests, their social interactions, motivation, and at the same time we need to look for blunted affect and poor rapport and alogia, and I think, when possible, it's really important that caregivers, or significant others, should also be asked about patient activities, motivation, social interaction, etc. Will, are negative symptoms identifiable early in the course of illness?

Chapter 3: Clinician and Patient Perspectives of Negative Symptoms [04.49]

WC: So, that varies for many patients, they begin well in advance of manifestation of the psychotic symptoms and it may be part of their developmental history.[2,3] But there are others that develop it after the onset of the psychosis component, schizophrenia, and develop over time following that.

JK: Matt, what was what was your experience? How did you first encounter this sort of negative symptoms?

MR: Well, I recall, I was hospitalized for psychosis, for a severe episode in 2011, and shortly after this experience I started to become more keen on noticing how I had this blunted affect, almost these feelings of, how I stated earlier, a lack of interest in things that were once pleasurable to me or activities. You know, music is very important to me. I recall playing and gigging as a musician and playing in a live music scenario, and I experienced these symptoms more intensely. I experienced feelings of self-doubt, inadequacy, I get other self-critical thoughts and perceptions of myself. And these were specifically triggered during music gigs and social gatherings.

JK: So, from what we've been discussing, it's clear that negative symptoms can contribute to poor functional outcome for patients.[4–6] So a really, really important domain. But at the same time, I think we have to keep in mind that learned helplessness and demoralization can also affect daily functioning and should be distinguished from negative symptoms. But about 60% of patients with schizophrenia will experience clinically-relevant negative symptoms which require treatment.[1,7] I think it's fair to say that the positive symptoms often receive more attention from health care providers, while negative symptoms may go undetected. So, it's really important

to establish the relevant functional assessments, and clinicians need to feel more comfortable with assessing these types of symptoms. I think the subjective experience is important to recognize and there's value in affirming this experience from a clinical standpoint. The correct diagnosis is really key. Negative symptoms may go undetected within our current system of care, due to limited resources and barriers to accessing resources. I think one challenge for individuals in treatment, that is, you know, post-psychosis or crisis-stabilization, is really a system-wide deficit in providing access to evidence-based treatment and psychosocial care. That's something that we really, really need to address. It's very important that these symptoms are recognized. The association between negative symptom severity and functional outcomes can affect many aspects of a person's life, including work and education, social functioning and integration, and the overall quality of life.[4,6]

Chapter 4: The Burden of Negative Symptoms [08.06]

JK: So, let's talk for a minute about how symptoms can impact on a patient's ability to live independently and to carry out activities related to daily living or maintaining interpersonal relationships. Matt, how did that affect you in terms of, you know, work and social situations?

MR: Well, looking back, I recall, this feeling of kind of being this outsider. The negative symptoms I experienced led to this intense amount of anxiety within work situations and social settings. I recall, working certain jobs and going into work and feeling this sense of challenge in engaging, in going to work, and communicating with coworkers, and being able to carry out certain tasks. Often-times I'd experience this anxiety and it will trigger me to shut down and not remain engaged, and this got in the way of certain work-related activities. I feel this intense sense of isolation, and it's the experience of feeling anhedonia, or this disconnection.

JK: Will, negative symptoms can also impact on other symptom domains. Can you comment on that?

WC: So, the burden of negative symptoms is very substantial. They can be long-lasting, they can be up there early in the course of schizophrenia and be long-lasting. There's physical and emotional manifestations of them.[8–10] It creates a situation where patients are less likely to be fully employed, or less likely to be engaging in the activities that are rewarding to them, they tend to become more isolated. And it's been a very difficult one to approach clinically, because we don't have strong therapeutic effects with most of the negative symptoms. There's much work left to be done in the development of the therapeutic approaches.

Chapter 5: The Neurobiology of Negative Symptoms [10.26]

JK: And that kind of isolation that you refer to, that can lead to things like substance abuse, right? And that then can trigger another psychotic episode, and we have a sort of vicious cycle. So negative symptoms are a heterogeneous group of symptoms with complex neurobiology.[1] And there's really no single underlying biological explanation for their occurrence, but it's thought to involve the dysfunction of several neurotransmitter systems or circuits, as well as potentially inflammatory contribution. The dopaminergic theory or hypothesis that negative symptoms arise as a result of hypo-dopaminergic signaling in the frontal lobe has been a mainstay.[11] Also, N-methyl-d-aspartate, or NMDA, receptor dysfunction is also thought to be implicated, since NMDA receptor antagonism induces psychotic and negative symptoms in healthy individuals and exacerbates those symptoms in patients.[12] There's also some evidence pointing to a potential correlation between alterations of peripheral inflammatory markers and negative symptoms;[13,14] though there's really no definitive link between the immune system and the development of negative symptoms.

Chapter 6: Current Clinical Practice [11.54]

JK: Currently, there are no FDA-approved drugs, specifically targeting negative symptoms. Some antipsychotic medications have data to support their use in primary negative symptoms, for example, cariprazine and low dose amisulpride, but keeping in mind that amisulpride is not available in the United States.[15,16] Concomitant antidepressants have shown to have modest efficacy;[17] social skills training and cognitive remediation have also been shown to have some benefit, particularly CBT (cognitive behavioral therapy).[18,19] Will, can you comment on the results of some recent trials?

WC: This has been interesting, and it's been a very difficult thing to achieve, but there's been a result of recent trial that demonstrates the potential for roluperidone in the treatment of negative symptoms and improving everyday functioning in patients with schizophrenia.[20] This drug is an antagonist of 5-hydroxytryptamine, sigma, and α-adrenergic receptors.

PANSS-derived Negative Symptom Factor Scores were lower, that is they were improved for roluperidone at 64 mg compared to the placebo and this can be found, as published in Schizophrenia Bulletin in 2022, with Davidson et al as authors.[20] These results demonstrate that this is a compound, and its unique mechanism of action may pave the way for the development of new improved treatments for negative symptoms that differ from the current approved antipsychotic drugs.

JK: Matt, what are your thoughts about that?

MR: Yes, it's definitely hopeful to think about new treatments coming down the pipeline as far as being able to effectively treat negative symptoms. Current treatments may effectively address positive symptoms, which in turn leads to enhanced positive recovery outcomes when coupled with the appropriate psychosocial services. Specifically, hallucinations or delusions are mitigated by medication if adhered to over time. Yet, the negative symptoms including the personal experience of lack of pleasure in daily activities and goals, reduced motivation to set and slowly achieve these goals, and the resulting satisfaction experienced over time for achieving these goals; all these aspects can be appropriately addressed with sustained social connections provided by different peer support groups and networks, work opportunities or job skills, training opportunities, engaging in meaningful activities such as going back to school and pursuing a course of therapy with a licensed clinician, and of course having family support and peer support alongside to help during that journey.

JK: Just one thing to keep in mind is the potential of secondary negative symptoms and, although antipsychotic medications can be very helpful in the treatment of positive symptoms, they can also lead to secondary negative symptoms due to drug-induced Parkinsonism, and things like that.[2] But I think it's really important that we spend some time talking about the difference between the patient and the clinical perspective, in terms of, you know, how we go about managing negative symptoms. Matt, do you have more thoughts about that?

MR: Yes, absolutely. So, from the patient-peer perspective, you know, the difference between the patient-clinician perspective, I agree is important, very critical for symptom management. You know, I recall, certain descriptions of symptoms that I experienced can differ from clinical descriptors, and this oftentimes can make negative symptoms sometimes difficult to quantify for clinicians. One example is the negative symptoms I had experienced would often lead me to provide short, non-descriptive responses to questions asked by clinicians. You know, I felt as though the negative symptoms perpetuated a deep sense of disconnection from myself resulting in the short, often straight-to-the-point answers; I may have stated something, when asked 'how am I feeling today?', I may have stated, you know, 'I'm good', or 'doing okay', when, in reality, there was a lot more to discuss in the clinical setting, and in other therapeutic settings. I was unable to express the sense of disconnection I felt from within myself, my thoughts, my feelings, illness-related concerns I had, and you know, other symptoms can also interfere with the patient-clinician communication process. I recall early in the course of my recovery, I experienced intense symptoms of different expressions of paranoia. When meeting with care providers, I felt as though I had to be mindful of and careful as to how I answered questions, and this was a result of the paranoia and delusions I was going through early on in my recovery. I would provide vague answers to avoid any potentially "perceived negative consequences" that could stem from my responses. In reality, the providers I met with were simply conducting clinical assessments to see how to best treat my psychosis and schizophrenia.

Chapter 7: Future Clinical Perspectives [17.14]

JK: So, while we await further drug development and further development of strategies, I think the evidence right now suggests that there are benefits of psychosocial strategies, particularly cognitive behavior therapy.[18,19] Will, can you comment on clinical trials and what you see going forward?

WC: Well, there seems to be a renewed interest and more confidence that successful development can be there. There are a number of ongoing Phase I to IV clinical trials, that are investigating different treatment options, with improvements in negative symptoms as the primary endpoint.[15,20] So, we can be hopeful that we'll be developing new information, new approaches through a better understanding of how the drugs may affect the negative symptoms per se.

JK: So yeah, while we look forward to new developments, I think we need to emphasize how important it is for clinicians to be able to recognize, primary versus secondary negative symptoms when considering treatment options. It's important because there are treatments for some secondary negative symptoms. Secondary symptoms, which can respond to treatment occur in association with, or results from, positive symptoms, affective symptoms, or medication side effects, sometimes environmental deprivation, or other treatment or illness related factors. And so, we need to be able to identify

both primary and secondary negative symptoms. We need to think about the benefits of non-pharmacotherapeutic approaches alongside traditional medication approaches, such as psychosocial rehabilitation and cognitive remediation. And more studies are needed to determine the best real-world strategies which might involve combinations of different approaches. At the moment, recognition and assessment are lacking as well, and I think more training of mental health professionals and more support for these strategies is also really important.

MR: Yeah, absolutely, thank you. And I was going to add to that, that I remember early on in my recovery, it was important to have family support system or peer support system as well. I want to highlight the importance of supporting caregivers and family; without the support of my family early on, I may not have been able to make it to a different psychosocial groups and peer support groups. Having a family network to encourage me and motivate me to go to these groups helps me connect with different advocacy groups such as NAMI; these groups help to normalize the experience and add a sense of community and a sense of meaning to the recovery journey. And I truly believe that having the experience normalized really helps engage in different recovery services and clinical services.

Chapter 8: Conclusions [20.34]

JK: Yeah, that's, really important. So, in conclusion, I think we'd say that negative symptoms are really a core feature of schizophrenia. However, there's an urgent, unmet clinical need to effectively treat these symptoms. The socio-economic burden associated with schizophrenia is enormous. There are ongoing trials to develop therapies in this area, though combination treatment strategies with non-pharmacological approaches should also be explored. And critically important, is that compassion and social support are really vital in aiding successful recovery in patients. So, I want to thank my colleagues, for joining me in this podcast and thank you all for listening.

Music Introduction [21:25]

Carlos Larrauri: You will now be hearing music from FogDog, original music by Matthew Racher and Carlos Larrauri. 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 Matthew Racher and Carlos Larrauri, 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

Disclosure

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Brain affected by schizophrenia

Abnormal neurochemical signaling

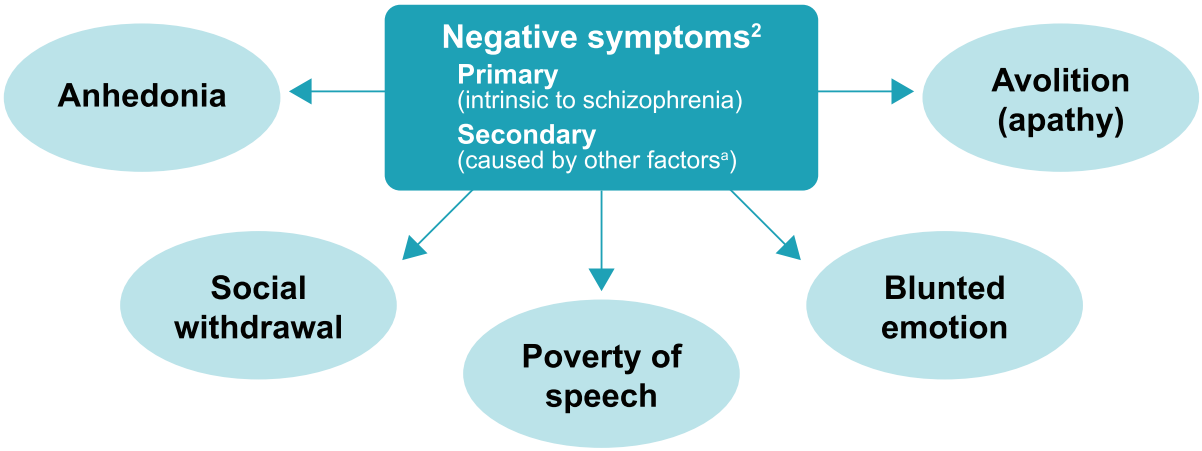
↓

Disrupted brain activity

↓

Impairment

- Schizophrenia is a neurodevelopmental disorder affecting <1% of the global population
- People with schizophrenia often experience changes in behavior and cognitive processes that commence in early adulthood (often years before onset of schizophrenia)
- The symptoms of schizophrenia fall into three categories: positive, negative and cognitive
- In the late stages, negative and cognitive symptoms may prevent patients from living independent lives and impose economic burdens on both families and society[1]



Current treatments for schizophrenia include a combination of pharmacotherapy, cognitive rehabilitation and psychosocial support.

There is an unmet need to develop therapies to address the negative symptoms of schizophrenia.

Figure 1 Negative symptoms associated with schizophrenia.
Notes: [a]Symptoms occurring as a result of positive symptoms, comorbid depression, side effects of antipsychotics, substance abuse, or social isolation. Data from Wu et al[1] and Mosolov et al.[2]

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