Optimizing Therapy Selection and Sequencing in Schizophrenia

Dawn I. Velligan, PhD,[a] and Sanjai Rao, MD[b]

Clinical practice guidelines in schizophrenia broadly align in recommending antipsychotic pharmacotherapies in patients with first-episode psychosis.[1] That said, selecting the optimal choice in real-world settings can prove challenging, as no findings to date have established superiority for a specific agent within this treatment class. Because the efficacy of first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs) appear similar, health care providers must consider alternative variables when formulating treatment plans. Among the most relevant factors for patients and care providers to consider are treatment-related adverse events. Although SGAs are generally preferred over FGAs, the latter may be more suitable for treatment recipients willing to tolerate extrapyramidal side effects over metabolic adverse events.[2] Olanzapine, a widely prescribed SGA, induces a 7% or greater weight gain from baseline in 80% of patients with schizophrenia.[3] The magnitude of weight gain seen with SGAs is positively correlated with each agent's binding affinity for 5-HT_{2A} receptors expressed in the nervous system. Beyond increasing mortality, SGA-associated weight gain can prompt patients to discontinue treatment entirely, even if such a choice results in the return of psychotic symptoms.[4]

One promising strategy to counter weight gain from olanzapine is to pair the agent with samidorphan, a μ-opioid receptor antagonist. In a double-blind, 24-week, phase 3 study, investigators compared weight gain among adult patients with schizophrenia receiving combination olanzapine/samidorphan and olanzapine monotherapy. At 24 weeks, significantly fewer patients in the combination therapy arm experienced weight gain in excess of 10% from baseline (17.8%) than those receiving olanzapine monotherapy (29.8%). Antipsychotic efficacy was similar, along with the frequency of somnolence, dry mouth, increased appetite, and other treatment-related adverse events.[5]

Metformin, a first-line medication in the treatment of type 2 diabetes, is concurrently emerging as a strategy to counteract weight gain induced from SGAs. In a randomized, placebo-controlled study, researchers noted that add-on metformin (1,000 mg/d) significantly affected body mass index and insulin resistance in patients with a first episode of schizophrenia.[6] These findings corroborate those of a later meta-analysis[7] of 12 published studies assessing weight gain in schizophrenia patients treated with antipsychotics and adjunctive metformin. Pooled data from these investigations suggest that the mean difference in weight between those receiving antipsychotics and adjunctive metformin and placebo is −3.27 kg; insulin resistance index values, on average, declined by 1.49.[7]

The anticonvulsant topiramate additionally warrants consideration in patients with schizophrenia who are experiencing antipsychotic-induced weight gain. Findings from a related meta-analysis indicate that the agent is well tolerated in patients, with researchers detecting no difference in the frequency of side effects between participants receiving topiramate and placebo.[8]

Although options to address antipsychotic-associated weight gain and schizophrenia are generally growing in number, treatment-resistant disease remains problematic in routine practice. According to one study, approximately one-third (34%) of patients with schizophrenia are treatment-resistant, which is defined by the persistence of symptoms despite 2 or more trials of antipsychotic medications adequately dosed and taken with documented adherence.[9] In this setting, clinicians tend to underutilize clozapine—the only medication approved for use in patients with treatment-resistant schizophrenia.[9] Accumulated evidence from decades of study indicates that clozapine outperforms SGAs and FGAs in alleviating overall symptoms and relapse rates in both treatment-resistant and non–treatment-resistant subpopulations.[10] That said, diverse adverse events ranging from sedation and hypersalivation to cardiomyopathy and seizure temper gains from medication and restrict its wider adoption. Until alternatives supplant clozapine as a standard of care in the treatment-resistant setting, clinicians must recognize the benefits of clozapine and cultivate a greater understanding of how to manage its serious, treatment-related adverse events.[9]

[a]Division of Schizophrenia and Related Disorders, Department of Psychiatry and Behavioral Sciences, The University of Texas Health Science Center at San Antonio, San Antonio, Texas

[b]University of California San Diego and VA San Diego Healthcare System, San Diego, California

J Clin Psychiatry 2023;84(1):MS21078COM9

To cite: Velligan DI, Rao S. Optimizing therapy selection and sequencing in schizophrenia. *J Clin Psychiatry.* 2023;84(1):MS21078COM9.

To share: https://doi.org/10.4088/JCP.MS21078COM9.

This COMMENTARY section of The Journal of Clinical Psychiatry *presents highlights of the teleconference series "Revisiting the Relapse and Remission Roller Coaster: Safety and Efficacy of Novel Schizophrenia Treatments," which was held on September 13, 2022. This report was prepared and independently developed by the CME Institute of Physicians Postgraduate Press, Inc., and was supported by an educational grant from Alkermes, Inc. and Sunovion Pharmaceuticals, Inc.*

Scan QR code to watch the experts discuss topics highlighted in this article.

Even after clozapine initiation, between 40% and 70% of patients with treatment-resistant schizophrenia will exhibit a poor response to medication. To date, medication augmentation strategies for clozapine have failed, and few options exist to prevent patients from experiencing severe symptoms and hospitalization.[11] A pair of studies[12,13] conducted in the 2010s yielded findings supporting the use of electroconvulsive therapy in clozapine-resistant patients, but other researchers have concluded that it cannot improve response rates to clozapine.[11] Taken together, these treatment gaps support the development and eventual integration of novel therapies into the armamentarium that can supplement the efficacy of existing treatments or replace current standards of care that have unacceptable tolerability profiles. Such alternatives are essential in ongoing efforts to increase the proportion of patients with schizophrenia capable of achieving a full recovery.

Caregiver Perspective

"It seems that deciding to take medication is one thing for diagnosed people, but deciding to ensure that it is taken exactly as prescribed at the exact right time is another issue entirely. My brother is proof that it is extremely difficult to keep track of many different medications simultaneously. . . . A single mismanaged dose can potentially lead to weeks of hardship. . . . Going without has caused a lot of unnecessary hardship for my brother, and it's possible that some of his visits to the emergency room for psychological distress could have been avoided entirely."[14]

Published online: January 18, 2023.

Relevant financial relationships: **Dr Velligan** has served as a consultant for Merck, Alkermes, Otsuka, and Janssen; received grant/research support from Biogen; received honoraria from Janssen and Otsuka; and served on the advisory boards for Merck, Janssen, Otsuka, and Alkermes. **Dr Rao** has served as a consultant for Janssen and Alkermes and received honoraria from Janssen, Alkermes, Otsuka, and Neurocrine.

Funding/support: Financial support for preparation and dissemination of this commentary was provided by Alkermes, Inc. and Sunovion Pharmaceuticals, Inc.

REFERENCES

1. National Collaborating Centre for Mental Health (UK). *Psychosis and Schizophrenia in Adults: Treatment and Management*. London: National Institute for Health and Care Excellence (UK); 2014.
2. Maroney M. An update on current treatment strategies and emerging agents for the management of schizophrenia. *Am J Manag Care*. 2020;26(suppl):S55–S61.
3. Fitzgerald I, O'Dwyer S, Brooks M, et al. Worth the weight? olanzapine prescribing in schizophrenia: a review of weight gain and other cardiometabolic side effects of olanzapine. *Front Psychiatry*. 2021;12:730769.
4. Rasmussen H, Ebdrup BH, Oranje B, et al. Neocortical serotonin2A receptor binding predicts quetiapine associated weight gain in antipsychotic-naive first-episode schizophrenia patients. *Int J Neuropsychopharmacol*. 2014;17(11):1729–1736.
5. Correll CU, Newcomer JW, Silverman B, et al. Effects of olanzapine combined with samidorphan on weight gain in schizophrenia: a 24-week phase 3 study. *Am J Psychiatry*. 2020;177(12):1168–1178.
6. Wang M, Tong JH, Zhu G, et al. Metformin for treatment of antipsychotic-induced weight gain: a randomized, placebo-controlled study. *Schizophr Res*. 2012;138(1):54–57.
7. de Silva VA, Suraweera C, Ratnatunga SS, et al. Metformin in prevention and treatment of antipsychotic induced weight gain: a systematic review and meta-analysis. *BMC Psychiatry*. 2016;16(1):341.
8. Goh KK, Chen C-H, Lu M-L. Topiramate mitigates weight gain in antipsychotic-treated patients with schizophrenia: meta-analysis of randomised controlled trials. *Int J Psychiatry Clin Pract*. 2019;23(1):14–32.
9. Potkin SG, Kane JM, Correll CU, et al. The neurobiology of treatment-resistant schizophrenia: paths to antipsychotic resistance and a roadmap for future research. *NPJ Schizophr*. 2020;6(1):1.
10. Wagner E, Siafis S, Fernando P, et al. Efficacy and safety of clozapine in psychotic disorders: a systematic quantitative meta-review. *Transl Psychiatry*. 2021;11(1):487.
11. Chakrabarti S. Clozapine resistant schizophrenia: newer avenues of management. *World J Psychiatry*. 2021;11(8):429–448.
12. Petrides G, Malur C, Braga RJ, et al. Electroconvulsive therapy augmentation in clozapine-resistant schizophrenia: a prospective, randomized study. *Am J Psychiatry*. 2015;172(1):52–58.
13. Wang G, Zheng W, Li X-B, et al. ECT augmentation of clozapine for clozapine-resistant schizophrenia: a meta-analysis of randomized controlled trials. *J Psychiatr Res*. 2018;105:23–32.
14. Treatment plans: lessons learned. Family and Caregiver Schizophrenia Discussion Forum. Schizophrenia.com. Published May 2019. Accessed December 6, 2022. https://family.schizophrenia.com/t/treatment-plans-lessons-learned/7788