The Position of Clozapine in Patients With Treatment-Resistant Schizophrenia:

Reply to Mattes

To the Editor: Dr Mattes[1] expresses concerns about my review[2] on challenges to the supremacy of clozapine in patients with treatment-resistant schizophrenia (TRS). He observes that industry-linked considerations may drive the choice of antipsychotic away from clozapine for patients with schizophrenia, that challenges related to hematological monitoring may further reduce the enthusiasm to prescribe clozapine, and that psychiatrists in the US, including those in training, already seldom prescribe clozapine. He rightly feels that readers might be even further discouraged by my article.[2]

In response, I continue to assert that, going by evidence, an up to 3-month trial of olanzapine or risperidone, if not already conducted, may be worth considering before turning to clozapine; my nuanced reasoning was presented in my article from the section titled "Appraisal of the Recent Meta-Analyses" onward, with special emphasis on the section titled "Suggestions," and I will not repeat the arguments here.

Importantly, Dr Mattes adds that, in his experience, patients treated with clozapine get closer to normality; and that, whereas olanzapine or risperidone may elicit clinical response, benefit with clozapine might be greater. These observations are perhaps shared by most psychiatrists experienced with clozapine. Regrettably, we do not have randomized clinical trials with long-term follow-up that provide data on health-related quality of life, subjective well-being, and patient-related outcome measures that can capture the "closer to normality" effect over and above benefits captured in psychopathology ratings.

Doing such studies could prove challenging, and so we must take comfort with the recognition that clozapine has been considered a game-changer for schizophrenia patients for over 3 decades and is still the go-to drug for TRS in schizophrenia treatment guidelines.

At a personal level, I see the same benefits with clozapine that Dr Mattes does, but the challenge that I face when prescribing the drug is not related to industry promotions or the need for monitoring blood counts; rather, it's the greater risk of common adverse effects, especially sedation, weight gain, and the metabolic syndrome, that is daunting.

References

1. Mattes JA. Rationale for clozapine trial. *J Clin Psychiatry*. 2026;87(1):25lr16256.
2. Andrade C. The superiority of clozapine over second-generation antipsychotics in patients with treatment-resistant schizophrenia: room for doubt. *J Clin Psychiatry*. 2025;86(3):25f16038.

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