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Commentary

Optimising clozapine use through expert consensus: commentary, Wagner & Hasan

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Delphi; psychotic disorders/schizophrenia; clozapine; treatment-resistance; antipsychotics.

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Reply

We are grateful to Dr De Léon for his excellently written comment on our work,[1] which thoughtfully revisits long-standing barriers as well as emerging insights into clozapine-associated myocarditis. As outlined by Dr De Léon, many aspects of clozapine's safety are related to aspects that cannot be easily investigated in clinical trials or meta-analyses. He described the impact of ancestry on the risk of myocarditis that needs to be acknowledged not only for this cardiac side-effect but also for agranulocytosis. Moreover, he introduced skilfully the views of different psychiatrists and emphasised the importance of a bottom-up expert approach such as presented in our Delphi study.

Clozapine remains the most effective antipsychotic in psychiatry, and strengthening the evidence base to guide its safe and optimal use has substantial potential to reduce mortality and symptom burden. Importantly, previous collaborative efforts – most notably expert consensus statements – have already translated into meaningful regulatory change, including revisions to the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) requirements for haematological monitoring of clozapine.[2,3] This illustrates how coordinated, evidence-informed guidance can directly improve access to and the safety of this uniquely effective treatment.

Beyond its clinical efficacy, clozapine is increasingly recognised for its distinct pharmacological profile. Its effectiveness in treatment-resistant schizophrenia may, in part, be attributable to partial agonism at the muscarinic M4 receptor,[4] highlighting muscarinic signalling as a therapeutic mechanism that extends beyond the traditional antipsychotic concept of blocking dopamine D2-receptors.[5] Notably, this mechanism overlaps in principle with that of newer non-dopaminergic antipsychotics, including xanomeline–trospium, which received FDA approval in September 2024,[6] as well as emraclidine, a selective M4 agonist that ultimately failed in phase 2 trials.[7] These developments underscore that the mechanistic space occupied by clozapine remains highly relevant within contemporary drug development efforts.

In an era of rapidly evolving disease models and therapeutic paradigms in schizophrenia research, we argue that optimising the use of established, highly effective medications such as clozapine is at least as critical as the pursuit of novel agents. This is particularly pertinent given the apparent convergence of mechanisms between clozapine and emerging non-dopaminergic treatments.

Within this context, Delphi methodologies offer a particularly well-suited approach to addressing persistent evidence gaps, especially in the relatively under-investigated domain of treatment-resistant schizophrenia. By systematically integrating expert judgement where empirical data remain limited, Delphi processes can help generate pragmatic, consensus-based guidance that complements ongoing mechanistic and clinical research.

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E.W. drafted the manuscript. A.H. critically revised the manuscript for important intellectual content. Both authors approved the final version.

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Declaration of interest

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