BJPsych | The British Journal of Psychiatry (2025)
227, 2, 574–575. doi: 10.1192/bjp.2024.255

Letter

Host microbiota in clozapine-induced ileus and pneumonia among people with schizophrenia

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Key words
Adverse events; clozapine; gut-lung axis; host microbiota; mortality.

In their recent study, Partanen et al[1] investigated the substantial burden of ileus and pneumonia in people with schizophrenia treated with clozapine, using data from the longitudinal FinnGen biobank project. The study analysed 2659 people with schizophrenia and evaluated 2157 diseases and health-related events. Among these, 27 events were significantly associated with clozapine use and categorised into five groups: gastrointestinal hypomotility, seizures, pneumonia, other acute respiratory tract infections and tachycardia. Notably, the cumulative incidence of ileus and pneumonia was 5.3 and 29.5%, respectively, both conditions being significantly linked to higher mortality in clozapine users. The authors concluded that clozapine-induced ileus and pneumonia are more common and associated with greater mortality risks than previously reported.[1]

Although the exact mechanisms underlying clozapine-induced ileus and pneumonia remain unclear, the author suggests that abnormalities in the host microbiota may contribute to these adverse events. Emerging evidence suggests that gut microbiota dysbiosis may play a role in the development of psychiatric disorders, including schizophrenia, and that restoring the microbiota balance could offer therapeutic potential.[2,3] Partanen et al[1] reported that constipation and pneumonia were significantly more common in clozapine users compared with other adverse events. Recent studies also indicate that clozapine alters the gut microbiota composition in treatment-resistant people with schizophrenia, reinforcing the potential link between dysbiosis and these conditions.[4] Dysbiosis disrupts the balance between beneficial and harmful bacteria in the gastrointestinal tract, impairing motility and contributing to constipation.[5] A bidirectional Mendelian randomisation study recently demonstrated a causal relationship between gut microbiota dysbiosis and constipation.[6] Collectively, these findings suggest that clozapine and its metabolites may reduce beneficial bacteria that promote intestinal motility while increasing harmful microbes, leading to slower gastrointestinal transit and worsening constipation. This dysbiosis, combined with clozapine's effects on cholinergic, serotonergic and dopaminergic pathways, exacerbates gastrointestinal hypomotility, resulting in constipation and potentially progressing to ileus.

In addition to the gut, the lungs, though less abundant in microbiota, also harbour microbial communities that may be influenced by gut microbiota.[2] The gut–lung axis refers to the bidirectional communication between the gut and lungs, mediated by the immune system, microbiota and their metabolites. A study demonstrated that antibiotic-induced microbiome depletion improved lipopolysaccharide-induced acute lung injury via the gut–lung axis.[7] In a healthy state, a balanced gut microbiota supports lung immunity by influencing immune cell development and reducing inflammation. Conversely, lung infections and inflammation can alter the gut microbiota, potentially disrupting intestinal barrier function. In disease, dysbiosis in either the gut or lungs can contribute to respiratory or gastrointestinal disorders, highlighting the interconnectedness of these systems in maintaining health and controlling inflammation.[8,9] Given the role of the gut–lung axis in health and disease, clozapine-induced gut microbiota dysbiosis may not only contribute to gastrointestinal hypomotility but also affect lung microbiota, potentially worsening respiratory health and increasing the risk of pneumonia. This, in turn, may elevate mortality risks in clozapine users.

In conclusion, further research is needed to confirm the role of host microbiota, particularly the gut–lung axis, in clozapine-treated people with schizophrenia. A deeper understanding of these mechanisms could inform strategies to reduce the high mortality associated with clozapine-induced ileus and pneumonia. Targeted modulation of the microbiota may offer a promising preventive approach to mitigating these severe adverse effects.

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First received 27 Oct 2024, revised 29 Oct 2024, accepted 30 Oct 2024

Data availability

Data availability is not applicable to this article as no new data were created or analyzed in this study.

Author contribution

K.H. is the sole author who conceived, drafted and approved the final version of this work.

Funding

None.

Declaration of interest

The author has no conflicts of interest to disclose related to this study.

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https://doi.org/10.1192/bjp.2024.255 Published online by Cambridge University Press

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https://doi.org/10.1192/bjp.2024.255 Published online by Cambridge University Press