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Genetic Dete`rminants of Clozapine-Induced Metabolic and Neurological Side Effects: A Comprehensive Investigation

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Introduction: Clozapine remains one of the most effective antipsychotic medications for treatment-resistant schizophrenia. However, its use is limited by significant metabolic and rare neurological side effects. The variability in patients' susceptibility to these adverse effects suggests an unidentified genetic predisposition, which is critical to personalizing treatment.
Objectives: This review aims to systematically investigate the genetic variants involved in the development of metabolic and neurological side effects in patients treated with clozapine. Specifically, it seeks to elucidate the pathways participating in the occurrence of these adverse reactions and identify genetic markers for personalized therapeutic approaches.
Methods: A literature search was conducted across multiple databases for studies published in recent years. Data were extracted from cohort studies and case-control studies based on predefined criteria, using keywords such as "clozapine", "metabolic side effects", "neurological side effects", "pharmacogenetics".
Results: Preliminary results identified that variants in the **FTO** gene, known for its role in adipogenesis and energy homeostasis, were linked to enhanced adiposity and altered leptin signaling, contributing to the metabolic syndrome. Similarly, **APOE** gene was strongly correlated with increased risk of severe weight gain, dyslipidemia, and insulin resistance due to association with impaired lipid transport and metabolism.
In the context of neurological side effects, SNPs within the **DRD2** Taq1A polymorphism, which affects dopamine receptor density and signaling, were associated with a higher incidence of extrapyramidal symptoms and tardive dyskinesia in patients on clozapine. The **COMT** Val158Met polymorphism, known to modulate prefrontal catecholamine degradation, was linked to cognitive impairments and clozapine-induced sedation.
Next-generation sequencing (NGS) enlightens rare SNPs, copy number variations (CNVs) and novel variants in genes related to drug metabolism, such as **CYP1A2** and **CYP2D6**, allowing for the identification of complex genetic interactions. Furthermore, patients with high **polygenic risk scores** (PRS) exhibited a markedly increased likelihood of developing severe metabolic and neurological side effects, underscoring the utility of PRS in stratifying patient risk.
Conclusions: In summary, our findings demonstrate that genetic factors are key contributors to the development of clozapine-induced metabolic and neurological side effects. Variations in genes related to drug metabolism, neurotransmitter regulation, and metabolic pathways significantly influence individual susceptibility to these adverse effects. A deeper understanding of pharmacogenetic approaches could offer the potential for more personalized and precise treatment strategies, reducing adverse effects and improving drug tolerance.

Disclosure of Interest: None Declared

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Individualised network connectivity-based targeting to improve outcomes of transcranial magnetic stimulation in difficult-to-treat depression

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Introduction: Transcranial magnetic stimulation (TMS) is an established treatment for difficult-to-treat depression (DTD), demonstrating moderate efficacy. In comparison to other non-invasive treatments in psychiatry, TMS can be relatively accurately directed at specific cortical subregions. TMS is typically targeted at the dorsolateral prefrontal cortex (DLPFC) based on scalp measurements. However, the DLPFC is a large and functionally heterogeneous region, with inter-individual variability in the localisation of target functions. The functional connectivity of the stimulation target with other brain areas has been shown to correlate with treatment outcomes. Nonetheless, the clinical benefits of connectivity-based individualised targeting remain to be demonstrated in randomised clinical trials, and the connections to be considered in such targeting are still inadequately understood.
Objectives: To test whether individualised network connectivity-based localisation improves outcomes, and to further investigate the relationship between clinical results and the stimulated connections
Methods: In this ongoing study, we acquire functional and structural MRIs from adult volunteers with DTD, referred to clinical TMS. We focus on brain regions associated with depression and emotion regulation to target the core affective symptoms of depression. We compute the individual connectivity distribution of these regions within the DLPFC. We then employ a realistic individual head conductor model to determine the coil position that aligns the distribution of TMS-induced electrical effects with the individual connectivity distribution. These coil positions, along with standard scalp-measure-based coil positions, are entered into the neuronavigation system, and patients are randomised 1:1 for the targeting used to receive intermittent theta burst stimulation over 20-25 sessions. Patients and outcome assessors remain blind to the targeting method, with the primary outcome being the change in the Montgomery-Åsberg Depression Rating Scale from before to after treatment.
Results: Interim analysis conducted by independent evaluators, based on results from the first 20 patients per group, suggested over 80% power to detect group differences at an alpha level of 0.048, with 40 patients in each group.
Conclusions: To our knowledge, these would be the first results from a randomised prospective trial indicating the superiority of functional targeting over standard scalp measure-based targeting. While these targeting methods require further refinement, clinical applications will depend on the balance between effectiveness and cost compared to standard targeting. Related studies exploring the relationship between targeted brain connections and clinical outcomes may illuminate the brain-level mechanisms underlying recovery from depression.