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Treatment-resistant symptoms occur in about a third of patients with schizophrenia and are associated with a substantial reduction in their quality of life. The development of new treatment options for clozapine-resistant schizophrenia constitutes a crucial, unmet need in psychiatry. Additionally, an overview of past and possible future research avenues to optimise the early detection, diagnosis, and management of clozapine-resistant schizophrenia is unavailable. In this Health Policy, we discuss the ongoing challenges associated with clozapine-resistant schizophrenia faced by patients and health-care providers worldwide to improve the understanding of this condition. We then revisit several clozapine guidelines, the diagnostic tests and treatment options for clozapine-resistant schizophrenia, and currently applied research approaches in clozapine-resistant schizophrenia. We also suggest methodologies and targets for future research, divided into innovative nosology-oriented field trials (eg, examining dimensional symptom staging), translational approaches (eg, genetics), epidemiological research (eg, real-world studies), and interventional studies (eg, non-traditional trial designs incorporating lived experiences and caregivers' perspectives). Finally, we note that low-income and middle-income countries are under-represented in studies on clozapine-resistant schizophrenia and propose an agenda to guide multinational research on the cause and treatment of clozapine-resistant schizophrenia. We hope that this research agenda will empower better global representation of patients living with clozapine-resistant schizophrenia and ultimately improve their functional outcomes and quality of life.

Introduction

Improving the real-world functioning of people with schizophrenia is an important aim in the treatment of this disorder.[1] However, when treated with first-line antipsychotic treatments, at least a third of people with schizophrenia do not meet treatment response criteria (≥20% reduction in positive and negative syndrome scale scores).[2] Treatment-resistant schizophrenia is defined as the presence of substantial and persistent symptoms that have not responded to at least two antipsychotic trials with an adequate dose (medium to high—ie, >2·5 mg risperidone or equivalent), duration (at least 6 weeks per trial), and adherence (at least 80% antipsychotic intake).[3,4] Many patients with treatment-resistant schizophrenia have comorbid substance misuse, somatic conditions, suicidality, and functional deficits.[5]

Definitions of clozapine-resistant schizophrenia vary (appendix p 4) and are mainly based on positive symptoms, as the extension to negative, cognitive, or functional symptoms proposed by DSM-5 and ICD-11 has not been scientifically evaluated. In this Health Policy, we use the clozapine-resistant schizophrenia definition from the Treatment Response and Resistance in Psychosis (TRRIP) Working Group: the persistence of positive, negative, or cognitive symptoms with at least moderate severity, and less than 20% symptom reduction in patients with schizophrenia after an adequate clozapine trial.[3,6] An adequate trial of clozapine is in turn defined by plasma concentrations of more than 350 ng/mL, a minimum treatment duration of 8–12 weeks,[7,8] and the presence of at least moderate functional impairment before treatment (measured with a validated scale).[3] Although clozapine is effective for reducing the positive symptoms of schizophrenia,[9] hospitalisations,[10] and all-cause and specific-cause mortality,[11] up to 60% of patients with treatment-resistant schizophrenia eventually meet the criteria for clozapine-resistant schizophrenia.[12] Augmentation of clozapine with either electroconvulsive therapy[13] or other antipsychotics[14] might improve outcomes in some patients with clozapine-resistant schizophrenia, but this type of schizophrenia severely reduces patient quality of life and is associated with high health-care and societal costs.

To our knowledge, an overview of past and possible future research avenues to optimise the early detection, diagnosis, and management of clozapine-resistant schizophrenia is unavailable. To advance research in this area and thus improve treatment options for patients, our group of early-career, mid-career, and senior-career clinician–researchers from six continents joined forces with experienced experts. Our collaboration resulted in this Health Policy, in which we first revisit the existing methodological approaches that have been applied to further understanding of the cause (appendix p 5), diagnosis (appendix pp 6–8), and management of clozapine-resistant schizophrenia. We then propose an international agenda to guide research aimed at improving early detection, diagnosis, and management of patients with clozapine-resistant schizophrenia worldwide. Although similarities exist between treatment-resistant schizophrenia and clozapine-resistant schizophrenia, the focus of this Health Policy is on clozapine-resistant schizophrenia only.

Current evidence and recommendations for clinical practice

Clozapine use has increased globally in the past 10 to 15 years, however this treatment is still underused in many countries, with figures ranging from 0·6 cases of clozapine use per 100 000 people with schizophrenia in Japan (probably due to the 2009 approval of clozapine and the treatment's required inpatient initiation) to 116·3 cases per 100 000 people in New Zealand, and 189·2 cases per 100 000 people in Finland.[15] Patient, clinician, and administration-related factors might contribute to underprescription rates worldwide.[16]

The first 3 years after a diagnosis of schizophrenia constitute a crucial window for a trial of clozapine, with substantial decreases in response rates thereafter.[17] Each antipsychotic trialled before the initiation of clozapine treatment was found to be associated with an approximate 10% reduction in clozapine response rate.[18] Despite this evidence, clozapine initiation in patients with treatment-resistant schizophrenia is typically delayed by an average of 48 months.[18]

Although meta-analyses have reported only low-quality evidence for antipsychotic-addition strategies in people with clozapine-resistant schizophrenia,[6–19] concomitant use of aripiprazole, fluoxetine, and sodium valproate with clozapine might be beneficial in treating total symptoms, whereas use of memantine might help counter negative symptoms in these patients.[16] A real-world study suggested that the risk of rehospitalisation is lower for the combination of clozapine and aripiprazole than for any other antipsychotic monotherapy and antipsychotic polypharmacy combinations.[14] In line with such evidence, the TRRIP Working Group recommends amisulpride, aripiprazole, and electroconvulsive therapy (ECT) addition for clozapine-resistant positive symptoms; antidepressant augmentation for clozapine-resistant negative symptoms; and mood-stabiliser or antipsychotic addition for clozapine-resistant aggression.[6] Despite some promising small studies on the effect of adjuvant *N*-acetyl cysteine in people with clozapine-resistant schizophrenia, a 52-week placebo-controlled randomised controlled trial (RCT) found no improvement in negative symptoms, overall cognition, or quality of life.[20]

A Cochrane review found that, when compared with standard treatment, ECT augmentation has a positive effect on clinical response in the medium term (ie, in the first 3–6 months after treatment has been suspended) for people with treatment-resistant schizophrenia.[21] A meta-analysis including 18 clinical trials of clozapine combined with ECT showed that this combination is superior to clozapine alone in achieving symptomatic improvement.[13] None of the RCTs included in this meta-analysis[13] used sham ECT (anesthaesia without induced seizure), and only one RCT[22] reported masking methods for raters in the quality assessment. A single-blinded sham-controlled trial in patients with clozapine-resistant schizophrenia did not show superiority of ECT over sham ECT,[23] although a secondary analysis showed that hallucinatory behaviour and negative symptoms were worse in the sham group.[24] Evidence from 2022 indicates that in some patients with inadequate response to two adequate antipsychotic trials, ECT could be superior to clozapine in terms of efficacy and safety,[25] especially in patients with severe clozapine-resistant schizophrenia treated at high clozapine blood concentrations.[22]

Brain stimulation techniques, such as repetitive transcranial magnetic stimulation (rTMS), have also been studied for their therapeutic potential in clozapine-resistant schizophrenia. Active rTMS applied to the left dorsolateral prefrontal cortex was not superior to sham rTMS in patients on clozapine with burdensome negative symptoms.[26] A small meta-analysis showed subtle effects of rTMS for this indication,[27] but a larger, individual patient-level meta-analysis did not confirm this effect.[28] Persistent auditory hallucinations in patients treated with clozapine could be another target for rTMS. One sham-controlled RCT of low-frequency rTMS over the left temporoparietal cortex showed no difference between active and sham rTMS in patients with clozapine-resistant schizophrenia.[29] Another sham-controlled RCT showed statistically significant effects for general psychopathology but not for auditory hallucinations for low-frequency rTMS over the left temporoparietal cortex in patients with clozapine-resistant schizophrenia.[30] Regarding transcranial direct stimulation, no evidence is available to support its effectiveness in patients with clozapine-resistant schizophrenia. A case series using θ-rhythm transcranial alternating current stimulation (4·5 Hz-tACS) indicates a possible effect on clozapine-resistant negative symptoms,[31] but these findings await replication.

Of the psychotherapeutic options used to treat clozapine-resistant schizophrenia, cognitive-behavioural therapy (CBT) has been the best (and most extensively) studied. Although meta-analyses point to small benefits of CBT in ameloriating clozapine-resistant positive symptoms,[32] the largest RCT of CBT augmentation to clozapine was negative.[33]

We have summarised the current diagnostic and treatment guidelines in clozapine-resistant schizophrenia (appendix p 8).

A call for action: new research to advance the understanding and treatment of clozapine-resistant schizophrenia

Despite the prevalence and substantial individual and societal impact of clozapine-resistant schizophrenia, the cause of this condition is probably heterogeneous, and is currently unclear and understudied.[34] There are multiple unmet needs when considering the diagnostic investigations of clozapine-resistant schizophrenia (eg, what diagnostic tests are helpful to improve outcomes?), its underlying basis (eg, what environmental and genetic factors contribute most to its cause?), and its management

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(eg, what treatments and combinations could be helpful for patients?). To facilitate the development of guidelines for diagnostic tests, innovative treatments, and evidence-based treatment algorithms for clozapine-resistant schizophrenia, we argue that research in clozapine-resistant schizophrenia should not focus on a single avenue or a single geographical region, but instead capitalise on diverse methodological approaches—ie, nosological, translational, epidemiological, and interventional studies (figure). Given the scarcity of clozapine-resistant schizophrenia research in low-income and middle-income countries (LMICs), we advocate the development of international collaborations to increase the generalisability of findings to diverse clinical practice settings, not only in wealthy countries, but also in LMICs where most patients with clozapine-resistant schizophrenia live.

Nosological research

Although little research has been done on the validity of treatment-resistant and clozapine-resistant schizophrenia, both concepts are helpful in clinical practice for diagnostic and therapeutic reasons. International field trials could assess the validity of treatment-resistant schizophrenia and clozapine-resistant schizophrenia across nations and cultures.[35] Dimensional approaches to persistent symptoms, functional outcomes, and quality of life could improve the classification of patients according to treatment-resistant or clozapine-resistant schizophrenia severity, and advance personalised medicine for patients with clozapine-resistant schizophrenia. Given the often observed development of treatment resistance in early stages of treatment,[2] differentiating early-onset (within 1 year of treatment onset), medium-term onset (within 1–5 years of treatment onset), and late-onset (after 5 or more years from treatment onset) treatment resistance[3] might help to determine the neurobiological underpinnings of clozapine-resistant schizophrenia (including possible subtypes) and empower personalised intervention studies.

Translational research

On the basis of preliminary evidence, these factors have been suggested as possible biomarkers for clozapine-resistant schizophrenia: neurotransmitters and their metabolites in both plasma and cerebrospinal fluid, inflammatory markers, findings from structural and functional neuroimaging, and from electro-encephalography (EEG), epigenetic markers, and common and rare genetic polymorphisms. Ideally, study

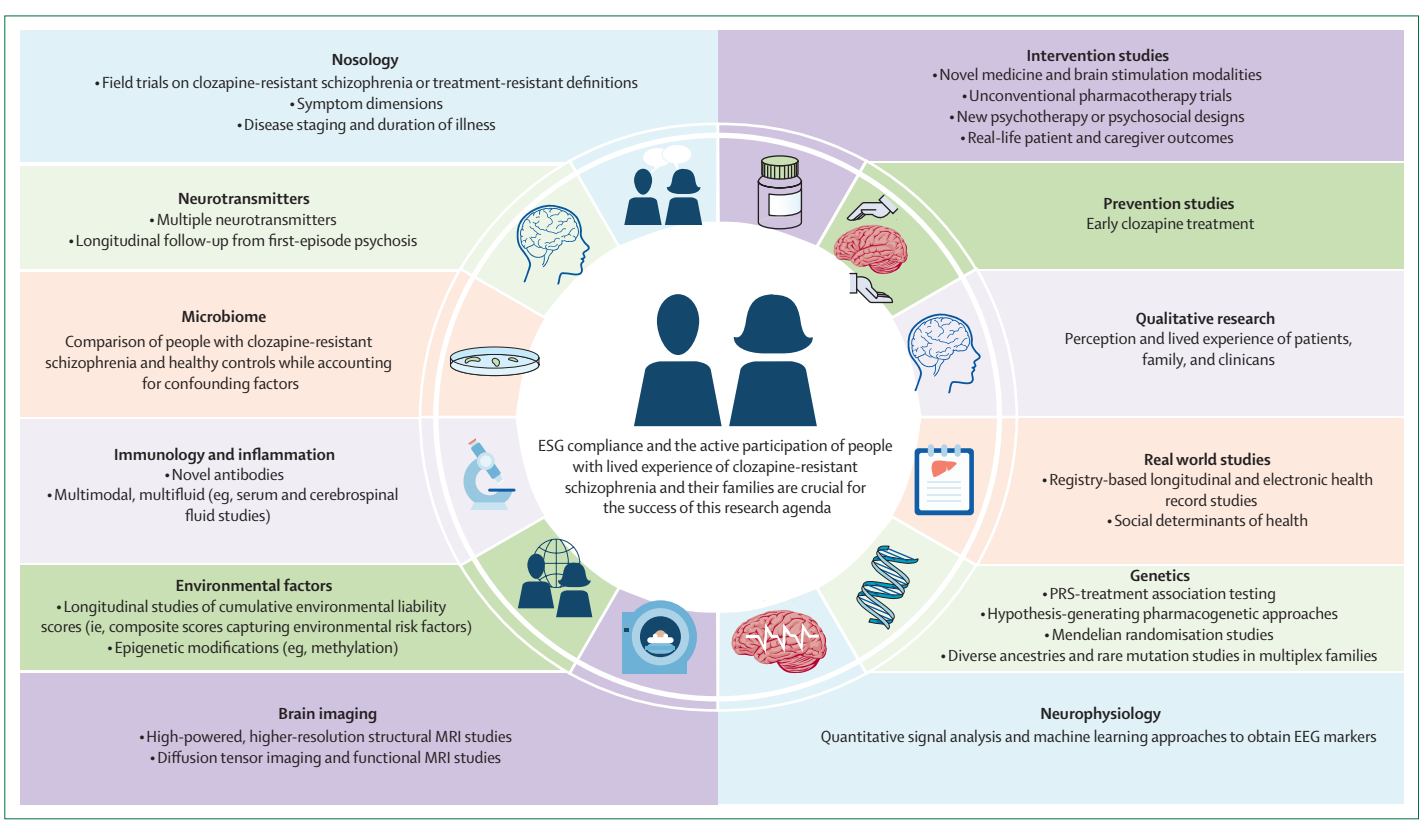

Figure: **Our proposed international research agenda**
The agenda we propose leverages a range of approaches that will benefit from the active participation of people with lived experience of clozapine-resistant schizophrenia and their families. Each of these research approaches and their possible benefits for people with clozapine-resistant schizophrenia are discussed in detail in the main text. EEG=electroencephalography. PRS=polygenic risk score. ESG=environmental, social, and governance.

designs should be prospective, starting with first-episode psychosis or individuals at clinical high risk for psychosis,[36] and should include healthy control individuals to understand case-control differences over time. In the following sections, we propose pathways to elucidate the causes of clozapine-resistant schizophrenia and to aid in the diagnostic investigations of clozapine-resistant schizophrenia.

Neurotransmitters

Longitudinal studies that are not restricted to single neurotransmitter measurements are needed to explore whether (glutamate) biomarkers reflect trait or state, and whether they change over time in ways that are relevant to patient outcomes, such as recovery. For example, hypothesis-generating proteomic and metabolomic studies, including plasma and cerebrospinal fluid measurements of several neurotransmitters and their metabolites,[37,38] could help assess the neurotransmitters' associations with the occurrence of clozapine-resistant schizophrenia and with functional remission status.

The microbiome

Evidence from 2022 hints at relationships between antipsychotic treatment response and specific bacterial groups (eg, *Lactobacillus* spp and *Bacteroides* spp).[39] The gut microbiome might also have a role in mediating adverse drug reactions associated with antipsychotics, including clozapine.[39] Studies exploring the role of the microbiome among people with clozapine-resistant schizophrenia require groups matched to age, sex, and weight comparing healthy control individuals with patients with antipsychotic-responsive, clozapine-responsive, and clozapine-resistant schizophrenia.

Immunological or inflammatory processes

Immunological or inflammatory processes have become increasingly important in understanding treatment-resistant or clozapine-resistant schizophrenia. Studies have described increased permeability of the blood–brain barrier and changes in peripheral and central inflammatory biomarkers in schizophrenia. Of immediate relevance to patients, cases of treatment-resistant and clozapine-resistant schizophrenia with underlying autoimmune psychosis are rare. To date, mostly unimodal studies have characterised such patients, by use of either immunological blood or cerebrospinal parameters or neuroimaging markers. A multimodal diagnostic investigation, including blood, EEG, MRI, and cerebrospinal fluid analysis, might help elucidate the neurobiologial processes influencing the course and prognosis of autoimmune psychosis.[40] In addition, fluorodeoxyglucose-PET can be useful for the detection of autoimmune inflammatory processes and 18 kDa translocator protein-PET for the detection of microglia activation. Cerebrospinal fluid analysis provides the opportunity to investigate new CNS immunological biomarkers.[41] Although a first comparison study did not suggest increased seropositivity of N-methyl-D-aspartate receptor antibodies in clozapine-resistant schizophrenia,[42] examining the role of novel CNS antibodies and of associated antigens in clozapine-resistant schizophrenia might help elucidate whether some cases of clozapine-resistant schizophrenia could benefit from immunotherapy.[41] T-cell-mediated inflammatory processes should also be examined in clozapine-resistant schizophrenia. Future multimodal, high-quality, large-scale studies might show whether immunological or inflammatory signatures occur consistently in subgroups of treatment-resistant or clozapine-resistant schizophrenia[43] and whether any of these patients can be diagnosed with an autoimmune psychosis subtype.[40]

DNA methylation

To understand the relationship between environmental factors and neurobiological mechanisms, DNA methylation studies might be helpful as they can further the understanding of pathophysiological mechanisms—eg, by leveraging the use of epigenetic clocks that capture biological ageing. DNA methylation comparisons between patients with clozapine-resistant schizophrenia and healthy control individuals have, to our knowledge, not been explored. Nonetheless, a landmark study identified DNA methylation patterns that might be specifically related to clozapine use,[44] which would be consistent with a distinct neurobiological profile of treatment-resistant schizophrenia. A smaller study reported a correlation between epigenetic clock acceleration and psychosis severity.[45] These findings suggest that studying DNA methylation in peripheral blood cells might be an effective strategy to investigate the neurobiological characteristics and risk factors of clozapine-resistant schizophrenia.

Brain imaging studies

Several studies have examined the association between neuroimaging findings and response to clozapine (appendix p 9). Better powered, higher resolution studies with larger sample sizes are needed to determine morphology patterns in patients with clozapine-resistant schizophrenia and their associations with clozapine response. Additionally, neuroimaging research with diffusion tensor imaging and functional MRI might help elucidate the neurobiology of clozapine-resistant schizophrenia.

Neurophysiology

EEG patterns might help predict treatment outcomes for clozapine-resistant schizophrenia. EEG is cheap and fairly readily available worldwide. Advances in quantitative signal analysis and machine learning approaches have identified several EEG markers with high test or retest reliability.[46] Better powered studies of

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See **Online** for appendix

the predictability of clozapine response based on EEG patterns are therefore warranted.[47]

Genetics

Polygenic risk scores (PRSs) calculated from genome-wide association studies might help us understand whether loading of risk polymorphisms can predict treatment outcomes. Initial research into the potential diagnostic value shows that patients on clozapine have higher schizophrenia-PRSs than patients on other antipsychotic drugs during follow-up.[48] If this finding is confirmed in additional cohorts, PRSs could help identify individuals who might benefit from clozapine and thus ensure that clozapine treatment is started at the appropriate time. Given evidence of the increased likelihood of remission following ECT and clozapine treatments in patients with high schizophrenia PRSs,[49,50] future studies of clozapine-resistant schizophrenia might uncover associations between PRSs and specific symptom domain improvements following augmentation strategies.

Genetic studies of *CYP1A2*, *CYP2D6*, and liver transporter systems have shown associations with clozapine efficacy, pharmacokinetics, and agranulocytosis.[51] With regard to agranulocytosis, ancestry-dependent negative predictive values for wild-type alleles are greater than 90%, giving rise to actionable targeted genetic tests that should be subjected to further research across multiple ancestries.[52]

Mendelian randomisation uses genetic instruments and outcomes, and is not affected by reverse causation and the influences of confounding factors. Investigation of the possible environmental factors influencing the risk of clozapine-resistant schizophrenia with Mendelian randomisation would be of interest.

Further exploration of the genetics of families with high incidences of schizophrenia might also prove beneficial.[53] In these multiplex families, whole genome sequencing could help identify putative rare mutations associated with schizophrenia within the family, and these mutations could then be studied with precise phenotyping of the affected individuals, particularly in terms of pharmacological treatment response and outcome.

Finally, multi-ancestry common variant analysis could clarify which genetic variants in which populations might predict the emergence of clozapine-resistant schizophrenia and severe clozapine-related adverse effects. Attaining sufficient power by recruiting representative study populations worldwide should be a first priority for meeting this goal.

Real-world studies and other epidemiological approaches

As only 20% of people with schizophrenia are eligible for RCTs, more real-world studies of people with clozapine-resistant schizophrenia are needed to reflect and inform clinical practice.[54] Although real-world studies require solid clinical and data infrastructure, these studies might be less laborious and expensive than RCTs and also allow for longer follow-up and the inclusion of larger sample sizes.

A longitudinal perspective, which is possible in most registries, should prioritise assessments of long-term treatment response, relapse prevention, and treatment-emergent and adverse effects. Severe but rare outcomes are difficult to study in RCTs; registry studies can overcome this barrier by including tens of thousands of patients with years of follow-up.

Real-world studies have shown that clozapine use is associated with the lowest risk of severe relapse when compared with other oral antipsychotic medications.[10,55,56] Future real-world studies could help identify demographic and other characteristics (eg, comorbidities) that put newly diagnosed patients with schizophrenia at risk of developing clozapine-resistant schizophrenia, potentially adding an element of personalisation to early intervention programmes. Additionally, real-world studies could compare augmentation strategies in clozapine users with high relapse rates (as a proxy for clozapine-resistant schizophrenia), and these studies could identify long-term outcomes associated with ECT augmentation.

Electronic health record studies can provide valuable information on the associations between course of illness and variables of interest, such as clinical characteristics, psychosocial factors, comorbidities, and prescription patterns. Future electronic health record studies using machine-learning methods could help elucidate the best treatment options for patients with clozapine-resistant schizophrenia grouped by variables of interest.

Epidemiological approaches should address the environmental aspects of clozapine-resistant schizophrenia. A cumulative environmental liability (exposome score) for schizophrenia might prove to be a clinically useful tool to predict clozapine-resistant schizophrenia.[57,58] Furthermore, some environmental conditions (eg, low-income neighbourhoods and racism) might increase the likelihood of clozapine-resistant schizophrenia. Finally, sex differences are understudied in clozapine-resistant schizophrenia. Thus, studies could focus on potential sex differences in the epidemiology, course, and outcomes of clozapine-resistant schizophrenia.

Qualitative research

Due to the heterogenous response to and adverse effect burden of clozapine, it is often not perceived by patients and clinicians as a silver bullet solution to the severe positive and negative symptoms and impaired daily functioning associated with schizophrenia. Clinicians could promote treatment adherence by discussing uncertainties in treatment outcomes with patients and their families or carers. Approaches to manage expectations could be investigated using combined

quantitative–qualitative research designs, with the aim of ascertaining how communication and the educational skills of families and clinicians might boost patient empowerment.

Prevention studies

There is little evidence to suggest that prevention of clozapine-resistant schizophrenia is possible. However, RCTs investigating ways of reducing delays in clozapine prescription and trials evaluating clozapine as a second-line treatment option, particularly when no improvement is seen after a single antipsychotic trial, could help determine whether early and personalised clozapine use reduces the chances of patients developing clozapine-resistant schizophrenia.

Intervention studies

Intervention studies are key to obtaining more definite information about optimal treatment options for clozapine-resistant schizophrenia. These interventions can be divided into subgroups, such as pharmacological, neurostimulation, brain stimulation, psychotherapy, and psychosocial interventions.

Concerning medications, we observe a need to diversify both the agents under examination and the study designs. Promising results for innovative agents in schizophrenia have been presented in the past 5 years. For instance, ulotaront, an oral compound with agonist activity at trace amine-associated receptor 1 and 5-hydroxytryptamine type 1A receptors, significantly reduced core symptoms in patients with schizophrenia in a short-term follow-up, placebo-controlled setting.[59] Similarly, combining the muscarinic receptor M1/M4 agonist xanomeline with the peripherally restricted muscarinic receptor antagonist trospium resulted in symptom relief in patients with schizophrenia.[60] To our knowledge, although agents that do not work via postsynaptic dopamine receptors have not been studied in clozapine-resistant schizophrenia, we anticipate that some patients with clozapine-resistant schizophrenia could benefit from a multifaceted approach whereby classic D2-antagonists or clozapine are combined with non-postsynaptic D2 agents. Thus, placebo-controlled augmentation RCTs of clozapine with non-postsynaptic D2 agents could be worthwhile in patients with clozapine-resistant schizophrenia.

With regards to RCT designs, innovative trial approaches could be leveraged to elucidate which treatment options are most viable for patients with clozapine-resistant schizophrenia, eg, n-of-1 trials (involving prospective crossover exposure to different treatment conditions in a single patient). Master protocols, enrichment, and adaptive designs[61] could also be used.

ECT is a possible effective augmentation strategy in clozapine-resistant schizophrenia,[13] but further sham-controlled trials are needed. High relapse rates of roughly 60% at 1 year after acute ECT treatment are a concern.[62] Maintenance strategies that are most effective for relapse prevention are needed. Non-invasive stimulation therapies (rTMS and transcranial direct stimulation) are safe but their efficacy remains uncertain for patients with treatment-resistant or clozapine-resistant schizophrenia,[63] so more effective stimulus parameters and predictive markers should be investigated.

Pharmacotherapeutic knowledge must be paralleled by insights from psychotherapy and psychosocial intervention projects. There is space for more assessor-masked, well-powered trials examining the benefits of CBT and other psychotherapies in clozapine-resistant schizophrenia. For example, acceptance and commitment therapy (ACT) has shown preliminary evidence of positive effects in schizophrenia,[64] but has not been studied specifically for use in clozapine-resistant schizophrenia. ACT could be of particular interest for clozapine-resistant schizophrenia given its focus on resilience as opposed to symptom reduction, because patients with clozapine-resistant schizophrenia often do not reach full remission in their lifetimes, despite trials of augmentation treatments. In addition, future psychotherapy trials could address possible placebo and nocebo effects more efficiently with preference-guided alternative treatment arms and cluster RCTs wherein participants are randomly assigned in groups. Furthermore, psychosocial intervention and psycho-education programmes have, to our knowledge, not been studied in patients with clozapine-resistant schizophrenia. Examining such interventions and trauma-focused therapies for clozapine-resistant schizophrenia could be a relevant research avenue to improve quality of life for patients with clozapine-resistant schizophrenia. Finally, knowledge from network science and complexity science might aid research in and clinical approaches to patients with clozapine-resistant schizophrenia. For example, recovery might be best achieved by simultaneously intervening on key nodes in networks of impairing factors.[65]

Research coproduced with carers and experts from experience

The voices of people with lived experience of clozapine-resistant schizophrenia and their support networks should by heard by those conceiving clozapine-resistant schizophrenia research. Addressing caregivers' perspectives and deepening the understanding of recovery in clozapine-resistant schizophrenia is essential.[66] Intervention studies leveraging lived experiences are needed to decipher how this approach might help empower patients with clozapine-resistant schizophrenia. The James Lind Alliance, a non-profit initiative that brings patients, carers, and clinicians together to prioritise research topics, listed improving treatment for those unresponsive to regular treatment as the number one priority in schizophrenia research.[67]

Probably the greatest cost faced by people with clozapine-resistant schizophrenia, as identified in a qualitative metasynthesis of lived experiences of schizophrenia, is the depletion of social relationships.[68] Marginalisation, stigmatisation, loneliness, isolation, and self-stigmatisation are common but under-researched patient experiences that should be included as treatment targets in future clozapine-resistant schizophrenia studies. A multinational study found that people with schizophrenia consistently experienced high rates of discrimination across the 27 countries studied.[69] Although the past decade has seen progress in broader public mental health literacy, attitudes to people with schizophrenia have not improved, and by some metrics have deteriorated,[70] with higher stigma-related burdens reported for people with treatment-resistant illness.[71]

Conclusions

We revisited causal hypotheses, risk factors, diagnostic investigations and treatment steps, guideline recommendations, and the current state of the evidence for research being done in clozapine-resistant schizophrenia. We have suggested possible avenues for future research that might overcome some of the current gaps and challenges in clozapine-resistant schizophrenia research (figure), and thus reach the following conclusions.

First, understudied aspects of clozapine-resistant schizophrenia research relate to nosology, neurobiology, epidemiology, and qualitative, prevention, and intervention studies. We have provided clinicians and researchers working in this field with avenues to deepen the understanding of clozapine-resistant schizophrenia and improve management options.

Second, we noted that most national schizophrenia guidelines either devote only a small section to clozapine-resistant or treatment-resistant schizophrenia, or do not specifically discuss diagnostics and treatments for patients with treatment-resistant symptoms. We therefore recommend that clinicians complement the use of national guidelines with a prescribing checklist that can be used before and during clozapine treatment.[72]

Finally, in clozapine-resistant schizophrenia research, patients, carers, and researchers from LMICs are underrepresented, few efforts have been made to capitalise on lived experience, and (ecological) sustainability has not been adopted as a key criterion. As the vast majority of treatment-resistant or clozapine-resistant schizophrenia patients live in LMICs, and as culture, economic abilities, and health-care systems probably moderate the outcomes of people with clozapine-resistant schizophrenia, this shortfall constitutes an unmet need in clozapine-resistant schizophrenia research. A first step in meeting this need might be to draw inspiration from companies that have enshrined environmental, social, and governance measures in their policy making. This approach would also allow clozapine-resistant schizophrenia researchers to consider the planet and all humans living on it when developing their research—a consideration that is crucial for LMICs given the hazards of climate change in regions such as sub-Saharan Africa. Setting up more inclusive, international consortia composed of clinicians, researchers, caregivers, and people with lived experience of clozapine-resistant schizophrenia is pivotal to better represent the broad range of patients with clozapine-resistant schizophrenia living in LMICs and to inform research and real-world practice.

Search strategy and selection criteria

Between June and October, 2022, we searched PubMed and the available guidelines in the countries where we work (see affiliations) for relevant articles combining the search term "clozapine-resistant" with one of the following for each of the research sections: "treatment", "therapy", "psychotherapy", "risk factor", "genetic", "imaging", "epidemiological", "methylation", "epigenetic", "neurotransmitter", "microbiome", "immunological", "inflammation", "prevention", and "expert by experience". Our goal was not to write a systematic review about research findings for clozapine-resistant schizophrenia, but instead to conceive a consensus Health Policy outlining possible research avenues to improve the diagnostic tests, understanding, and treatment of clozapine-resistant symptoms. As such, we have included what we believe to be the relevant papers on this topic published before October, 2022. Although this process is inherently subjective, our approach was rigorous in that we agreed on our approach and the scope of our work in the spring of 2022 after virtual correspondence. We then met on June 14, June 28, and Oct 20, 2022, to settle on the most important literature and guideline content to include in this Health Policy and the specific sections of the international research agenda we would propose.

Contributors

JJL, CUC, AH, DSi, DE, JM, and JT conceived this Health Policy. JJL and JMG-D wrote the first draft. CUC, AH, DSi, DE, JM, and JT supervised the project. All authors provided critical feedback and helped shape this Health Policy. All authors reviewed and approved the final version of the manuscript.

Declaration of interests

JL has received honoraria from Otsuka, Janssen, Lundbeck, and Sumitomo Pharmaceuticals. CUC has been a consultant or advisor to, or has received honoraria from AbbVie, Acadia, Alkermes, Allergan, Angelini, Aristo, Boehringer Ingelheim, Cardio Diagnostics, Cerevel, CNX Therapeutics, Compass Pathways, Darnitsa, Gedeon Richter, Hikma, Holmusk, IntraCellular Therapies, Janssen (Johnson & Johnson), Karuna, LB Pharma, Lundbeck, MedAvante-ProPhase, MedInCell, Merck, Mindpax, Mitsubishi Tanabe Pharma, Mylan, Neurocrine, Newron, Noven, Otsuka, Pharmabrain, PPD Biotech, Recordati, Relmada, Reviva, Rovi, Seqirus, SK Life Science, Sunovion, Sun Pharma, Supernus, Takeda, Teva, and Viatris. He has provided expert testimony for Janssen and Otsuka. He has served on a data safety monitoring board for Lundbeck, Relmada, Reviva, Rovi, Supernus, and Teva. He has received grant support from Janssen and Takeda. He has received royalties from UpToDate and is also a stock option holder of Cardio Diagnostics, Mindpax, LB Pharma, and Quantic. ROC has received research funding

(awarded to his institution) from Roche and Alkermes, is a consultant to Saladax Biomedical, and is a speaker for Clinical Care Options. ST has received speaker honoraria from Otsuka, Mochida, Takeda, Meiji, Eisai, Sumitomo, Viatris, and Teijin. JT has participated in research projects funded by grants from Janssen-Cilag and Eli Lilly awarded to his institution. He also reports personal fees from Eli Lilly, Evidera, Janssen-Cilag, Lundbeck, Mediuutiset, Otsuka, Sidera, and Suvovion; and he is a consultant to HLS Therapeutics, Orion, and WebMed Global. AH is co-editor of the German Association for Psychiatry, Psychotherapy and Psychosomatics schizophrenia treatment guidelines and first author of the World Federation of Societies of Biological Psychiatry schizophrenia treatment guidelines. He has been on the advisory boards and has received speaker fees from Janssen, Lundbeck, and Otsuka. EW has been on the advisory boards of Recordati. JMG-D is funded by a grant from Ministerio de Ciencia y Tecnología (Colombia), and has been a consultant for, received honoraria from, or been on the speakers or advisory boards of Janssen, Eurofarma, Servier, Sanofi, Lilly, and Pfizer. DSh is an expert advisor to the National Institute for Health and Care Excellence (NICE) centre for guidelines; the views expressed in this Health Policy are the authors' and not those of NICE. All other authors declare no competing interests.

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