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Thirty Years of Clozapine Treatment: Successes, Challenges, and Future Directions

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Introduction

Clozapine is a unique antipsychotic medication, widely regarded as the most efficacious pharmacologic option available for the treatment of refractory positive symptoms in schizophrenia. Since its approval in 1989, a robust evidence base has characterized clozapine's superiority for its United States Food and Drug Administration (FDA)-approved indications in persons with schizophrenia or schizoaffective disorder: refractory psychosis and recurrent suicidal behavior. Despite the evidence supporting its use, clozapine remains vastly underutilized in the United States (Figure 1, Page 2). Moreover, recent evidence suggests its use should occur earlier in our treatment algorithms and be expanded to include patients with a partial response to other antipsychotic drugs. Here, we provide an overview of clozapine's role in our current treatment of psychotic disorders. We first focus on its interesting historical context prior to FDA approval, followed by a review of key evidence supporting its use. We then review the current state of, and challenges related to, clozapine utilization. Finally, we discuss future directions for clozapine's place within our treatment algorithms and novel research efforts to develop precision medicine approaches to optimize its use.

Continued on Page 2

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The Drug That Almost Never Happened: Clozapine Before FDA Approval

Clozapine was developed in the mid-1950s, shortly after chlorpromazine, by the Swiss pharmaceutical company Wander AG in their effort to synthesize a drug that would have dual antidepressant and antipsychotic properties (Figure 2). Clozapine demonstrated a similar pharmacologic profile to chlorpromazine in rodent trials but without signs of catalepsy, a key marker predictive of extrapyramidal symptoms (EPS) in humans and a mechanistic indicator of antipsychotic drug action. Several experimental trials were conducted to examine antipsychotic effects in humans over the next decade, and by 1966, 100 subjects had received clozapine. Evidence from these early trials suggested that clozapine unexpectedly possessed antipsychotic properties without a significant emergence of EPS, countering the belief that EPS was necessary for antipsychotic action. The international pharmaceutical giant, Sandoz, acquired Wander AG in 1967 and continued to conduct trials. By 1970, 2,200 patients had been administered clozapine in studies with overall positive results.[1]

While the cumulative results of these studies were intriguing, and despite Sandoz's marketing of clozapine in much of central Europe and Finland, it was not widely adopted into clinical practice. The lack of "neuroleptic" EPS symptoms, such as Parkinsonism or dystonia, led to skepticism amongst psychiatrists of the promise of this novel agent. Regardless, Sandoz started to work towards FDA approval in the United States, discovering there, in early clinical trials, that rapid titrations of clozapine were associated with severe orthostatic hypotension and even collapse. A slow titration schedule was adopted, and open label trials and the first double blind trial in the United States began.

Newly blossoming interest in clozapine turned to alarm in 1975, when the Finnish National Board of Health published concerning findings in *The Lancet*. Just four months after clozapine became commercially available in Finland, 18 patients developed severe blood disorders, nine of whom died. Eight of these patients, and 16 of the total 18, had developed agranulocytosis.[2] In a rebuttal to this finding, Sandoz showed that the incidence of agranulocytosis appeared to be 20 times higher in Finland than in any other country where clozapine had been prescribed or tested. A subsequent review suggested that, outside of Finland, the incidence of neutropenia was not significantly different from that associated with chlorpromazine. Nonetheless, clozapine was removed from the market in Finland and several other European countries. Sandoz began to explore blood monitoring guidelines to help monitor for neutropenia.

In the United States, while the FDA did not stop the use of clozapine, Sandoz further halted its development and only offered the medication for compassionate need. Meanwhile, clozapine gained traction amongst clinicians, who noted its unique properties. The reputation of clozapine grew in the United States, not only as an antipsychotic that did not cause EPS, but also as one that seemed to show superior results in populations who did not respond to other antipsychotic drugs, and in those who previously had developed severe disabling neuroleptic-associated movement disorders. At the same time, changes in the FDA regarding market exclusivity for new drugs spurred Sandoz to increase marketing. Efforts to complete a New Drug Application (NDA) to the FDA by Sandoz were hampered by a lack of completed trials in the United States. While the first NDA failed, the FDA asked Sandoz to resubmit an NDA but with research

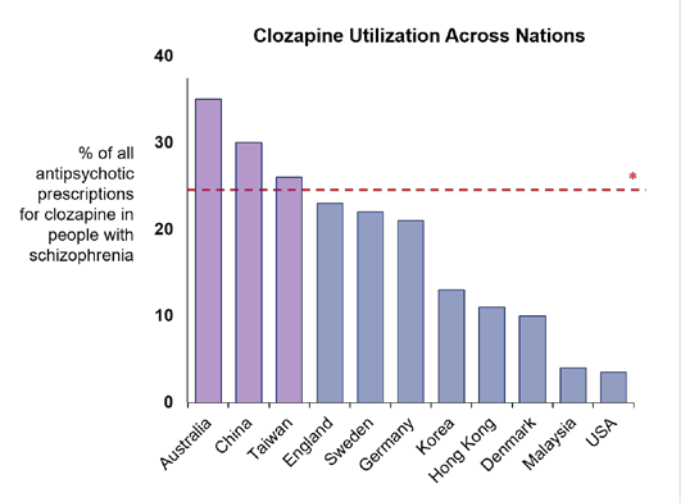

Figure 1. International Rates of Clozapine. Sampling of international utilization rates of clozapine out of all antipsychotic prescriptions for patients with schizophrenia.

*The theoretical minimum number of patients who may benefit from clozapine is approximately 25 percent, displayed with the dotted line. Data displayed in purple represent countries that exceed this minimum threshold.

findings supporting the following: that clozapine would be used only in people with schizophrenia who had failed other medication trials, and that clozapine worked better than other antipsychotic medications on the market.

Key Trials and Evidence Supporting Clozapine's Efficacy

Though early evidence demonstrated clozapine's superior efficacy over chlorpromazine in patients with refractory psychotic symptoms, no trials to date had definitively captured this phenomenon. In 1984, a multicenter, randomized controlled trial commenced (including patients at Mayview State Hospital in Pittsburgh), sponsored by Sandoz. In 1988, results of this work were published in *Kane et al.*, widely considered to be the landmark and pivotal clozapine trial supporting its benefit in treating refractory psychotic symptoms.[3] In this study, patients underwent a prospective trial of high dose haloperidol (60 mg/day) to confirm their lack of response and then were randomized to clozapine or chlorpromazine. The results demonstrated that 30 percent of treatment-resistant schizophrenia subjects randomized to clozapine had significant improvement in positive and negative symptoms compared to 4 percent of subjects randomized to chlorpromazine. These efficacy findings were so dramatic that they led to the FDA fully approving clozapine under the trade name Clozaril in 1989 (Figure 2), with blood monitoring

Timeline of Significant Events Related to Clozapine Development and Utilization

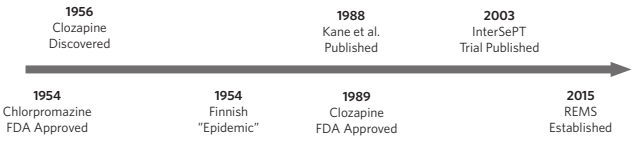

Figure 2. Timeline of significant events related to the history of clozapine.

parameters put in place, vis-a-vis agranulocytosis. This policy of filling clozapine prescriptions contingent on weekly blood draws to monitor absolute neutrophil counts, also known as "no blood, no drug," proved to be one of the barriers to wider use of clozapine in the U.S. market.

Since the publication of *Kane et al.,* clozapine has been developed as a gold standard treatment for refractory psychosis by a substantial evidence base consisting of additional trials and several meta-analyses. In relation to other first-generation antipsychotic drugs, trials conducted in the 1990s demonstrated clozapine's superior efficacy in reducing positive and, to a much lesser extent, negative symptoms of schizophrenia.[4] In a study of high-utilizers of hospital services followed for one year, *Rosenheck et al.* showed increased compliance, decreased hospitalizations, and fewer adverse effects relative to treatment with haloperidol.[5] Similar results were observed in a cohort of state hospital patients.[6]

Spurred by clozapine's efficacy, additional second-generation drugs were developed to treat psychosis, but without the burden of EPS, starting with risperidone in 1993, and later olanzapine, quetiapine, ziprasidone, and others. The existence of these newer drugs led to comparisons with clozapine in several important trials. The Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS) found that clozapine treatment resulted in significant improvement in symptoms over the course of one year in patients who failed to respond to at least two other antipsychotic drugs.[7] In addition, findings from the second phase of the National Institute of Mental Health (NIMH)-funded multicentric Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study supported the use of clozapine over a switch to a different second-generation antipsychotic drug after an unsatisfactory therapeutic response.[8] Other trials have demonstrated increased efficacy of clozapine treatment over olanzapine.[9,10] A recent report from a NIMH study conducted in the 1990s by three early adopters of clozapine (University of Pittsburgh/UPMC, UCLA, and Hillside-Long Island Jewish Hospital) expanded the scope of clozapine's effectiveness beyond refractory illness, and compared its use against risperidone in moderately responsive patients.[11] Clozapine-treated participants were significantly less likely to discontinue for lack of efficacy (15 percent) than risperidone-treated participants (38 percent). These findings suggested that clozapine should not be restricted to the most treatment-refractory patients but instead could be expanded to include those who continue to experience troubling psychotic symptoms, even after a partial response to other antipsychotics.

In addition to studies focused on symptomatic improvement, clozapine has been evaluated across subpopulations of patients in relation to patient well-being. Findings from these reports show a clear benefit from clozapine on overall mortality over other antipsychotic agents on measures of lives saved and cost-per-life.[12] Overall mortality was further improved in a large population-based cohort in Finland,[13] and similar data are available in the United States.[14] In addition to mortality, clozapine treatment has demonstrated greater scores on measures of quality of life.[15]

Suicidality

Clozapine also is FDA-indicated for the treatment of individuals with schizophrenia or schizoaffective disorder with persistent or recurrent suicidal or self-injurious behavior.[14,16] In the seminal International Suicide Prevention Trial (InterSePT), individuals at high risk for suicidality were randomized to clozapine or olanzapine.[17] Those receiving clozapine were significantly less likely to engage in suicidal behavior, commit suicide, or require interventions to prevent suicide (including hospitalization). They also were less likely to require adjuvant treatment with antidepressants or anxiolytic medications.

Off-label Uses: Aggression and Others

The relationship between schizophrenia and violence is complex and influenced by numerous factors. Moreover, examining efficacy of medications for aggressive behavior secondary to psychotic illness poses ethical and methodologic challenges. Nonetheless, the risk of aggression and violence in patients with schizophrenia or related psychotic disorders may be mitigated by antipsychotic medications. The benefits of clozapine for aggression and violence has been reported in state hospitals and other institutional settings by noting its impact on the most restrictive of psychiatric interventions, namely restraints and seclusions.[18-20] In a 2001 trial by *Citrome et al.,* a group of patients with schizophrenia or schizoaffective disorder and suboptimal treatment response history were randomized to either risperidone, olanzapine, haloperidol, or clozapine.[21] Patients taking clozapine had significantly greater decreases on ratings of hostility than patients taking haloperidol or olanzapine, independent of other symptomatic improvements. Decreases in aggression also appear to be independent of cognition and sedation.[22] A 2012 systematic review of four case studies, four randomized controlled trials, 12 prospective noncontrolled studies, 22 retrospective studies, and six animal studies indicated that clozapine decreases aggression in schizophrenia, perhaps better than other antipsychotics and with potentially greater efficacy in treatment-resistant illness.[23] Taken together, clozapine likely has utility in treating aggression in patients with schizophrenia spectrum disorders, although the mechanism for this is not clear.

Other off-label uses for clozapine have been examined. Accumulating evidence, primarily from case studies, demonstrates clozapine's utility for the treatment of self-mutilation and aggression in borderline personality disorder,[24,25] amelioration of severe psychogenic polydipsia,[26,27] and severe treatment-resistant bipolar disorder.[28-30]

Utilization of Clozapine

Despite the substantial evidence supporting the superior efficacy of clozapine over other antipsychotics in individuals with schizophrenia-spectrum illnesses and refractory psychotic symptoms, clozapine remains profoundly under-prescribed in the United States (Figure 1, Page 2). Given rates of treatment resistance, it is estimated that 25 to 40 percent of patients with schizophrenia would be candidates for clozapine. In published surveys of utilization across countries, Australia, China, and Taiwan show the highest rates of use (Figure 1, Page 2), with over a quarter of antipsychotic prescriptions written for clozapine. In Germany, approximately 21 percent of antipsychotic prescriptions for schizophrenia were for clozapine.[31] In several

countries in Asia, such as Korea and Singapore, rates of clozapine use have been increasing over the past decade. In China, clozapine use was once higher, comprising 40 percent of antipsychotic prescriptions in 2001. In recent years this number has dropped to 27 percent, which remains higher than numbers observed in western countries. The decrease in clozapine utilization in China has been thought to be due to an expansion of health insurance to cover other, nonclozapine second-generation antipsychotic medications, as well as to more stringent clozapine prescribing guidelines that mirror standard practice in most of the rest of the world.[32] Interestingly, in New Zealand, when clozapine use increased from 21 percent to 32.8 percent between 2000 and 2004, an increase was noted in numbers of patients with employment, coupled with overall decreased hospitalization rates.[33] The use of clozapine in the United States remains dismal, and over time has been worsening. While 11 percent of all antipsychotic prescriptions were accounted for by clozapine in 1999, only three percent went toward clozapine in 2008.[34] Clinicians may in fact be more likely to utilize polypharmacy, a practice not supported by evidence, than prescribe clozapine.[35] There is further evidence that clozapine may be even more dramatically under-prescribed in certain subpopulations, including in African Americans,[36] even with increasing recognition of benign ethnic neutropenia (BEN).

There are many known barriers to broader clozapine use in the United States. Patients and their families may be concerned about potential side effects, and the frequent blood draws set forth by the stringent requirements of the FDA-mandated Risk Evaluation and Mitigation Strategy (REMS) monitoring. These concerns might be shared by physicians who either lack, or perceive that they lack, knowledge and skills required to prescribe clozapine, particularly related to recognizing and treating side effects. While most clinicians monitor for the emergence of neutropenia, which occurs in up to three percent of cases,[37] vigilance for other rare but alarming side effects, like myocarditis and severe orthostasis, must also be maintained, particularly in the first few months of initiating treatment, given their demands for swift and effective clinical actions. The potential for other serious side effects such as severe constipation, seizures, and metabolic syndrome require additional screening questions and measures. More benign side effects, like sialorrhea and enuresis, may be troublesome for patients and a barrier to continued use, but the informed prescriber can help ameliorate these occurrences while continuing to target psychosis, suicidality, or aggression. A workgroup founded through the National Association of State Mental Health Program Directors (NASMHD) addressed these concerns and recommended improving education to resident trainees.[37] The Substance Abuse and Mental Health Services Administration (SAMHSA) also has developed training materials for individual prescribers and systems to better support clozapine use.[36] A focus on patient education and recovery likely will be helpful to empower patients to start clozapine.

Clozapine Treatment Monitoring

Many physicians work in environments without adequate administrative support to best support clozapine use. Clozapine prescribing requires coordinated resources to provide patient education and support, medical consultation, and medication and laboratory adherence tracking.[36] Adherence tracking is particularly crucial. Patients who miss more than 48 hours of clozapine must undergo a standard, slow retitration onto the medication that helps prevent orthostasis but can leave the patient vulnerable to psychotic relapse and cholinergic rebound. Patients also must obtain labs at standard intervals; not obtaining these labs risks not being dispensed clozapine per the REMS protocol (i.e., "no blood, no drug").

Starting on October 12, 2015, the FDA mandated the formulation of a new clozapine REMS program be implemented by the different manufacturers of clozapine, and that they would host a single registry of patients taking clozapine. This effort combined several disparate registries and so helped better ensure patient safety. After early challenges, this program further relaxed some of the rigorous monitoring guidelines for clozapine. White blood cell monitoring, aside from absolute neutrophil count (ANC), was no longer required, nor were repeating labs when ANC levels dropped significantly but were still within safe limits. Protocols for reinitiating labs after gaps in treatment also were greatly simplified such that monitoring could continue as previous if less than 30 days had elapsed, and monitoring would proceed as if for a new patient if the patient had not been treated for more than 30 days. The REMS also helped expand the potential use of clozapine in individuals with BEN, where neutrophil counts run lower than "normal" lab ranges but who remain healthy and not prone to infection. BEN may be found in up to 40 percent of African Americans, is thought to be relatively common in some Middle Eastern ethnic groups, and also may be noted in other non-European ancestral groups. While the REMS did thus allow for a broadening of who could receive clozapine, the reporting requirements for providers and pharmacists were increased such that pharmacists could not dispense clozapine without a Pre-Dispense Authorization (PDA), generated only when patients and prescribers were registered and an ANC within clinical guidelines was on file. Initially, the PDA was only to be given when patients had current labs on file, but the FDA has not yet been able to reliably enforce this measure; while this measure has increased administrative work for all who wish to responsibly prescribe and dispense clozapine, the patient safety assurances that were

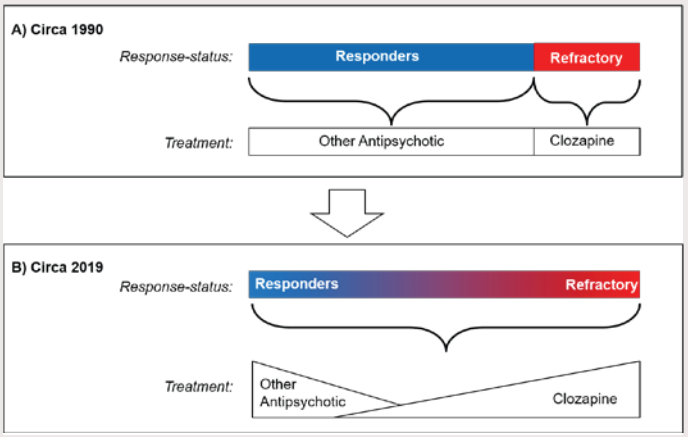

Figure 3. Changing Position of Clozapine Within the Antipsychotic Treatment Algorithm. This is a depiction of the evolving evidence for clozapine use over the past three decades. Following FDA approval, clozapine was restricted to patients who were refractory to other antipsychotic treatments (**A**). Over time, evidence has supported use of clozapine earlier in treatments, and for partial responders to other antipsychotic drugs (**B**).

promoted with the REMS have not come to full fruition. The REMS also has been thought to strain interdisciplinary collaboration and complicate transitions of care.[36]

To help address barriers to patient access and psychiatrist prescribing of clozapine, workgroups have continued to recommend improvement to the REMS in collaboration with key stakeholders. Support for dissemination and implementation of widespread "clozapine clinics" or similar multidisciplinary collaborations to facilitate clozapine prescribing continues to be a challenge.[38]

Clozapine's Future Place in the Schizophrenia Treatment Algorithm

While the availability of clozapine combined with the vast evidence-base supporting its superior efficacy in treatment-resistant patients has revolutionized the treatment of psychosis, clozapine's potential impact has not been fully realized. In addition, our understanding of the mechanism of action underlying its uniqueness from a scientific perspective remains unknown, hindering the development of individualized treatments for patients with schizophrenia. Meanwhile, treatment-refractory psychosis continues to account for a large majority of total health resource utilization associated with chronic psychotic disorders.[39] This includes up to a 10-fold increase in health care utilization relative to patients who demonstrate a response to nonclozapine antipsychotics, amounting for more than $34 billion in medical costs in the United States per year.

Evidence from work in the 1990s showed that clozapine is efficacious even in moderately responsive cases of psychosis, suggesting that its use could be expanded beyond its place as a third-line agent for cases deemed refractory.[11] Modern conceptualizations of clozapine's place in schizophrenia treatment echo an evolving literature that advocates for clozapine use earlier in our treatment algorithms, perhaps even as a second-line agent. Recent attention has been given to first-episode schizophrenia. It is estimated that up to 75 percent of these patients will respond to an initial antipsychotic trial. For the remaining 25 percent of patients who do not respond to initial treatment, the question becomes: What to do next? Most algorithms suggest switching to another antipsychotic agent prior to consideration of clozapine, which is often not recommended until after at least six months of illness. However, a considerably low response rate occurs with this switch to a second antipsychotic following treatment failure,[40,41] ranging from four percent to 16 percent for most drugs and a slightly higher chance for success with olanzapine treatment at around 25 percent.[40,42]

A recent report from a large trial with 27 sites in 14 countries (Europe and Israel) systematically addressed this question by examining the utility of switching an antipsychotic drug in patients with first-episode schizophrenia who do not respond to an initial treatment choice.[43] A total of 446 patients were examined with amisulpride as a first-line agent for four weeks in the first phase of the study. Those who did not respond were randomly assigned to either olanzapine or continued amisulpride treatment for six weeks during a second phase. Patients who continued to show nonresponse after this phase were then given clozapine for an additional 12 weeks in a third study phase. Results showed a 56 percent response in the first phase of the study with amisulpride, followed by no notable difference in response rates between olanzapine and continued amisulpride treatment in phase two of the trial. In the patients who remained nonresponsive after both study phases, fully an additional 28 percent achieved remission with clozapine. These findings indicated that switching to olanzapine did not improve outcome and that a second-line switch to clozapine after nonresponse to an initial trial may be a simple and efficient algorithm to adopt. A recent meta-analysis supports this work across other trials and concludes that clozapine may be useful as a second-line drug.[44] In a survey of a first-episode clinic in Australia with a high rate of clozapine use, high response rates and low rates of discontinuation were observed in patients demonstrating early refractory illness.[45] Early use is argued to outweigh typical delays in receiving the clozapine later in treatment, often years after diagnosis of a schizophrenia-spectrum illness.

Treatment Biomarkers

Evidence supporting the expansion of clozapine use coincides with efforts to objectively determine who may be exclusive responders to clozapine, ushering in a precision medicine approach to the treatment of psychotic disorders. Objective biomarkers also may allow us to stratify patient populations and identify those more likely to benefit from clozapine, preventing unnecessary medication trials with ineffective agents.

Work from pharmacogenetic studies aim to examine whether inherent genetic variants could provide clinicians with objective measures to guide clozapine utilization in a more personalized treatment model. Pharmacogenetic assays have the potential to help predict which patients have a lower chance of developing an adverse effect from clozapine treatment or have a greater chance for response. Arguably the most promising finding in this effort, thus far, is the association between polymorphisms in the human leukocyte antigen genes HLA-DQB1 and HLA-B that have reached genome-wide significance with clozapine-induced agranulocytosis.[46,47] While this finding has been replicated independently by several studies, and clozapine treatment guided by HLA-DQB1/HLA-B testing has been demonstrated to be cost effective in simulated data,[48] the assay has not yet demonstrated sensitivity and specificity necessary for routine clinical use.

Few neuroimaging studies have examined neural markers of treatment-refractory illness and clozapine efficacy. Structural neuroimaging has shown that greater prefrontal grey matter volumes may be associated with response to clozapine.[49] Moreover, recent work using magnetic resonance spectroscopy has shown that elevated prefrontal glutamate levels are associated with treatment-refractory illness,[50] which may be related to pathologic differences underlying patients who may be clozapine responsive. While these neuroimaging efforts shed light on possible prefrontal systems potentially related to glutamatergic dysfunction, our understanding of clozapine's unique mechanism of action remains largely unknown. Ongoing studies, including at the University of Pittsburgh, aim to use methods from functional neuroimaging to characterize response to clozapine treatment and develop prognostic biomarkers of outcome based on brain connectivity measures (ClinicalTrials.gov ID: NCT03076346). Efforts from this work may optimize our treatment with clozapine by allowing for the identification of patients who may benefit from clozapine earlier in their illness over other treatments and resulting in quicker remission of psychosis and improved overall outcomes.

Conclusion

Clozapine's place within the treatment algorithm for schizophrenia-spectrum illnesses is backed by one of the most formidable evidence-bases in psychiatry. However 30 years after its FDA approval, clozapine has not yet come close to reaching its full potential for reducing the morbidity that results from untreated psychotic illness. Refractory psychosis continues to account for a large portion of morbidity in schizophrenia and resultant economic burden on health care systems, while clozapine remains grossly underutilized, particularly in the United States. Future challenges for clozapine treatment include efforts to increase utilization, a transition to clozapine use as a second-line agent, and stratification of patients based on risk of adverse effects. Efforts to understand the mechanism of clozapine's unique action also are underway, potentially shedding light on neurobiological markers that may differentiate patients who are clozapine-responsive, while also predicting response.

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