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# Indicators of response to clozapine treatment

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## Abstract

Since its initial landmark trial against chlorpromazine in 1988, clozapine has been the drug of choice for the treatment of refractory schizophrenia. However, variability in clinical response to clozapine treatment is unequivocal. In an effort to preselect patients who are most likely to benefit from clozapine, a number of patient and disease variables and select genetic differences have been studied for their association with positive treatment response to clozapine. Because of small trial sizes and the heterogeneity of study design, findings have resulted in no generalizable conclusion. Future pharmacogenetic studies hold the promise of antipsychotic treatment personalization.

**Keywords:** treatment resistant schizophrenia, clozapine, response, indicator

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## Introduction

Schizophrenia is a severe psychiatric disorder that has a multidimensional impact on a person's psychosocial functioning. Its etiology indicates that its origin encompasses environmental and genetic factors.[1] Although antipsychotic pharmacotherapy is the main treatment option for the management of schizophrenia, there is a significant proportion of patients (20%-30%) who will continue to have symptoms and a degree of psychosocial dysfunction despite adequate antipsychotic treatment.[2] The rate of nonresponse to antipsychotics for chronic schizophrenia is closer to 50%. These patients have been referred to as *treatment resistant*.[3] The economic burden of treatment-resistant schizophrenia is disproportionate across the globe.[1,4] Because of its superior efficacy in patients who fail on other antipsychotic therapies, clozapine remains the treatment of choice for treatment-resistant schizophrenia.[5] Clozapine has been compared with first- and second-generation antipsychotics and has a proven superiority in reducing symptoms.[6-8] Major guidelines recommend the use of clozapine for patients who do not receive adequate benefit from other antipsychotics.[9-11]

Residual symptoms that do not respond adequately to clozapine are categorized as *clozapine nonresponse*. This phenomenon is not surprising, because nonresponse to all other antipsychotics has been reported previously.[12,13] For those patients who agree to go on clozapine treatment, more than 50% of patients may exhibit poor response to clozapine.[5,14] In order to maximize the cost-effectiveness of clozapine treatment, as well as to limit exposing patients to the risk of severe neutropenia, it is reasonable to identify subgroups that are most likely to show improvement.[15,16]

## Methods

A literature search was conducted of Pubmed and ScienceDirect for clinical trials (randomized, nonrandomized, controlled, and noncontrolled), case control studies, and systematic reviews evaluating predictive factors for positive response to clozapine. The following terms were used: *clozapine*, *treatment resistant schizophrenia*, *predictive*, *clinical*, *pharmacogen**, and *outcome*. Studies that linked specific patient characteristics (eg, female, younger onset of disease), disease manifestations (eg, paranoid,

aggression), and other physiologic signs of early treatment (eg, rise in serum triglyceride) are discussed below. Pharmacogenetic studies that assessed polymorphism at cytochrome 1A2 and variations of dopaminergic and serotonergic receptors are also addressed.

## Results

### Clinical Predictors

Studies have suggested that clozapine may be more effective in patients with more severe baseline psychiatric symptoms.[17,18] The study by Stern et al[17] was a prospective, randomized study that included 40 patients with treatment-refractory schizophrenia. The authors concluded that greater severity of symptoms at baseline suggested favorable response to clozapine, with 75% predictability. However, the follow-up was terminated at the end of week 1, and it is possible that patients who exhibited delayed response might have been excluded from the result.[19] The study by Rosenheck et al[18] assessed several baseline characteristics for clozapine response. Unlike previous studies, this study was carried out with a haloperidol control group. At 12 months, the strongest correlation with positive response to clozapine treatment was seen in those with high baseline symptoms. There was a significantly greater decrease in the Brief Psychiatric Rating Scale and a significantly greater increase in quality of life.

Female gender and early onset of disease may predict poorer response to clozapine, whereas prior extrapyramidal side effects from antipsychotics suggest good response to treatment with clozapine.[20] Younger age at onset most likely reflects a more severe form of the disease. Kelly et al[14] conducted an open-label trial and, using Cannon-Spoor Premorbid Adjustment Scale to assess social functioning and scholastic performance in childhood, early adolescence, late adolescence, and adulthood, reported a trend between poorer premorbid functioning and poorer response to clozapine.[21] These findings suggest that aggressive intervention with clozapine may benefit patients who manifest early symptoms, including early premorbid dysfunction.

Some factors are not trait dependent but can potentially develop in the course of the disease or as a consequence of the treatment.[22] One example would be the association of increase in triglyceride concentrations with clinical response to clozapine treatment.[23] In 49 patients with treatment-resistant schizophrenia, increase in triglyceride concentrations was significantly predictive of improvement in the Positive And Negative Syndrome Scale. The authors hypothesize that clozapine might possibly redistribute to the very low-density lipoprotein fraction as triglyceride concentrations increase, allowing for a more sustained drug release.

A number of studies have been done to evaluate the association between specific manifestations of schizophrenia and the clinical response to clozapine treatment. In two studies, paranoid subtype was associated with greater response to clozapine treatment.[20,24] However, in a 16-week open study with 96 Turkish patients with schizophrenia, paranoid subtype was not associated with response to clozapine. Instead, evident negative symptoms were associated with greater response to clozapine treatment.[25] A naturalistic study done by Ciapparelli and colleagues[26] included bipolar disorder with psychotic features along with schizoaffective disorder and schizophrenia. In their study, bipolar disorder was significantly related to clinical outcome, defined a priori as a 50% reduction in the Brief Psychiatric Rating Scale.

### Genetic Predictors

Traditionally, pharmacogenetic factors based on genetic variation in enzymes that metabolize a drug account for much of the variability in the response profile of that drug.[27] Drug metabolism at cytochrome 450 subtype 1A2 has consistently been shown to be responsible for metabolizing clozapine.[28,29] However, one study confirmed that polymorphism is absent at cytochrome 450 subtype 1A2, and it is unlikely that response to clozapine can be predicted using only this traditional paradigm of genetic variability in drug-metabolizing enzymes.[30]

Because clozapine has affinity for the receptors of many different neurotransmitters, there has been considerable effort in studying the effect of polymorphisms at different neurotransmitter receptors. These include dopamine receptors $D_1$ to $D_5$; serotonergic receptors $5HT_{1A}$, $5HT_{2A}$, $5HT_{2C}$, $5HT_3$, $5HT_6$, and $5HT_7$; and alpha1-adrenergic, muscarinic cholinergic $M_1$ to $M_5$, and histaminergic $H_1$ and $H_3$ receptors.[31] Clozapine's affinity to $D_1$ receptors is much less significant than its affinity to $D_2$-like receptors, and therefore investigations of polymorphisms at $D_1$ receptors have not been a major research focus.[32] $D_2$-like receptors, such as $D_2$, $D_3$, and $D_4$, have yet to show evidence to support the involvement of the polymorphisms in treatment response.[32] As an atypical antipsychotic, clozapine exhibits high affinity to 5HT receptors. Masellis et al[33,34] found an association between $5HT_{2A}$ receptor polymorphism, but another study had a negative finding. The meta-analysis by Arranz et al[35] included 6 trials that investigated polymorphisms at 5HT receptors (including the authors' own studies). The two polymorphisms in the $5HT_{2A}$ receptor gene, a silent 102-T/C change, and a His452Tyr substitution were associated with poorer response to clozapine in a pooled statistical analysis. There is no evidence to support that adrenergic receptor

polymorphisms contribute to clinical response to clozapine therapy.[36] Histamine receptor promoter gene polymorphism was found with no evidence of association toward clozapine treatment outcome.[32]

## Discussion

Many pharmacogenetic studies are criticized for having studies that have inconsistent findings with other studies or that have findings that subsequently fail. The heterogeneous nature of these studies, with their differing treatment durations, response assessment methods, and baseline patient characteristics, makes it extremely difficult to replicate the findings.[31] Pharmacogenetic studies seem to suggest that dopamine and serotonin systems (and possibly other neurotransmitter systems) contribute to antipsychotic efficacy. However, there is no clear picture of their influence on final clinical response.[1] Genetic factors affecting pharmacokinetics of clozapine, specifically the serum concentration, seem more applicable in determining adverse effect risks. This discussion is beyond the scope of this review.

## Conclusion

Thus far, studies evaluating clinical and genetic factors that are associated with positive response to clozapine treatment have been pursued rigorously but with no meaningful clinical applicability. These studies have had small sample sizes and do not carry adequate power to detect the difference. Also, the heterogeneity of the study designs makes it extremely difficult to generalize findings. For example, one study may define response to clozapine as a reduction in the Brief Psychiatric Rating Scale by greater than 20%.[33] However, other studies may consider this to be a lenient assessment.[15] Related studies look at the numeric reduction of the Brief Psychiatric Rating Scale, yet forego the categoric assessment of the response (eg, positive response versus negative response).[31] Other areas of this heterogeneity and suggestions for authors are discussed elsewhere.[31] Furthermore, the complex nature of the phenotype of clozapine response, as well as the pathophysiology of schizophrenia, further complicates the picture. Because of clozapine's seriously adverse hematologic effect, it is ideal to target a defined group of people who exhibit the greatest potential for positive outcome. More studies are needed to delineate the specific clinical and genetic factors that are associated with positive outcome to clozapine treatment. It is further hoped that ongoing pharmacogenetic studies will lead to personalization of antipsychotic treatment.

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