

Clozapine as a Long-Term Therapeutic Choice: Longitudinal Analysis of Schizophrenia Symptoms in a Naturalistic Setting

Rachel K. Scheinberg¹; Zhirui Fu^{2,✉}; Laura Scott³; Krista K. Baker⁴; Arlene Cuervo⁵; Lilian Zhong⁵; Chloe Bethany⁵; Malaka Harper⁵; Leslie G. Nucifora¹; Allison S. Brandt¹; Russell L. Margolis^{1,6}; Gayane Yenokyan^{1,2,✉}; Frederick C. Nucifora Jr^{1,*}

¹Schizoaffective Disorder Precision Medicine Center of Excellence, Division of Neurobiology, Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD 21287, United States; ²Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205, United States; ³Department of Anesthesiology and Critical Care, Johns Hopkins University School of Medicine, Baltimore, MD 21287, United States; ⁴Psychiatry and Behavioral Medicine, Banner University Medical Center South, University of Arizona, Tucson, AZ 85713, United States; ⁵Johns Hopkins Bayview Medical Center, Baltimore, MD 21224, United States; ⁶Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD 21224, United States

*To whom correspondence should be addressed: Frederick C. Nucifora Jr, Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, CMSC South, Level 5, Suite 5129, 600 N. Wolfe St, Baltimore, MD 21287, United States (nucifora@jhmi.edu).

Background and Hypothesis: Clozapine remains the gold standard for treatment-resistant schizophrenia (TRS), yet the time course of clinical response in naturalistic settings is not well characterized. We hypothesized that patients initiated on clozapine in an outpatient clinic would demonstrate measurable symptom reduction over time, including delayed response in a subset of patients. **Study Design:** We conducted a retrospective study of TRS patients ($N = 26$) newly initiated on clozapine at an outpatient clozapine clinic. Symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS) at baseline and follow-up visits. Linear spline regression modeled PANSS trajectories over time. Response was defined as achieving either a $\geq 20\%$ reduction in PANSS total score or a mild level of illness (PANSS score ≤ 58). **Study Results:** Patients demonstrated a mean 18.1-point reduction in PANSS total score during the first year of clozapine treatment, with significant improvements in positive and general psychopathology symptoms. Negative symptoms showed a modest, nonsignificant change. Overall, 20 patients (76.9%) achieved a $\geq 20\%$ PANSS reduction, and 15 (57.7%) reached a mild symptom level. Six patients (23.1%) met response criteria only after 12 months of treatment. **Conclusions:** In this naturalistic study, clozapine was associated with substantial symptom improvement, particularly within the first year. A subset of patients demonstrated delayed but clinically meaningful response, supporting the continued use of clozapine beyond 12 months. These findings underscore the value of sustained treatment in TRS.

Key words: treatment-resistant; ultra treatment-resistant; positive and negative syndrome scale.

Introduction

Schizophrenia, a severe and debilitating mental illness affecting approximately 1% of the population, is characterized by positive symptoms, negative symptoms, and cognitive impairment.¹⁻⁴ Symptoms, course, and response to treatment are highly heterogeneous. Unfortunately, approximately 30% of patients do not respond to standard antipsychotic medicines.⁵ After 2 failed antipsychotic trials, these individuals are considered to have treatment-resistant schizophrenia (TRS).⁶

Clozapine is the only medication with a US Food and Drug Administration (FDA) approval for TRS.^{7,8} Multiple studies have demonstrated clozapine's efficacy in reducing symptoms of TRS, though many of these investigations were of a short duration.^{7,9-12} Clozapine has additional benefits, including improved function and quality of life,¹³ and reduced risk of both suicide^{14,15} and tardive dyskinesia.¹⁶ Patients taking clozapine have a lower discontinuation rate, fewer hospitalizations, fewer adverse medical events, lower health care costs, and reduced mortality than comparable patients on other agents.¹⁷⁻²⁰

Despite its unique benefits to patients, the healthcare system, and society, clozapine is greatly underutilized. While 30% of individuals with schizophrenia might

benefit from clozapine, utilization may be as low as 4.4% in the United States.⁸ Even for patients who eventually receive treatment with clozapine, clozapine initiation is delayed by an average of 48 months after the second medication failure.²¹ Beyond the immediate consequences of untreated schizophrenia, delays in effective treatment are particularly concerning given the association of longer durations of untreated illness with worse prognosis.²²

Contributing factors to the underutilization of clozapine include concerns about the risks of life-threatening side effects, particularly agranulocytosis and myocarditis,²³ patient reluctance to undergo frequent blood draws,²⁴ and the burden historically associated with the mandated clozapine Risk Evaluation and Mitigation Strategy (REMS) program,²⁴ which required registration and monitoring by prescribers, pharmacies, and patients. Although the recent elimination of the REMS requirements by the FDA reduces some of the administrative complexity, significant clinical and logistical barriers to clozapine use remain. Nevertheless, for most patients with TRS, the benefits of clozapine use outweigh the risks.²⁵

While the value of clozapine for TRS has been well-established,¹³ the relationship between duration of clozapine treatment and clinical improvement has not been thoroughly investigated, particularly in naturalistic clinical settings. In particular, it is unclear (1) if the clinical benefits of clozapine plateau, or, as in the response of bipolar patients to lithium,²⁶ continue to accrue over time, and (2) if a subset of patients only respond to clozapine after a long duration of treatment. Establishing the pattern of response to clozapine may provide practical guidance for prescribers, and indirectly strengthen the case for clozapine utilization. The objective of the current study was therefore to assess the longitudinal symptom trajectories of patients on clozapine in a clinical setting, with the goal of determining the time course of symptom improvement after clozapine initiation, the extent of symptom improvement, and the particular symptom domains that improve. Importantly, we restricted the study to new starts, patients who were initiated on clozapine while under care in our clinic, ensuring that we had baseline PANSS scores on all participants and could follow them longitudinally from the start of treatment. This is not an acute treatment study, and the baseline PANSS scores do not reflect symptoms during an acute exacerbation, but rather represent the clinical status at the time of clozapine initiation in an outpatient setting.

Methods

Study Setting

The study protocol was approved by the Johns Hopkins Institutional Review Board. The study population consisted of patients with schizophrenia or schizoaffective disorder treated with clozapine at the Clozapine Clinic

of the Johns Hopkins Bayview Community Psychiatry Program. The Clozapine Clinic treats approximately 100 patients from the Baltimore Metropolitan area. Enrollment includes patients transferring care from the Johns Hopkins Bayview Adult Schizophrenia Clinic at the initiation of clozapine treatment, and referrals from outside hospitals and clinics. Each patient is assigned to a psychiatrist (typically the clinic director, FCN) and a therapist (all credentialed as Licensed Clinical Professional Counselors or Certified Social Workers-Clinical). All patients receive cognitive behavioral therapy and/or supportive therapy for schizophrenia during weekly to monthly appointments with their therapist. A senior therapist oversees clozapine REMS issues in conjunction with the director of the clinic. Patients can access phlebotomy services and receive medicines at Johns Hopkins Bayview, or they can choose a laboratory and pharmacy of their convenience.

Study Participants

Clinic patients were included in this study if they met DSM-5 criteria for schizophrenia or schizoaffective disorder, were prescribed clozapine, and had at least one Positive and Negative Syndrome Scale²⁷ (PANSS) rating during clozapine treatment. Demographic and clinical data were collected from interviews with patients and their families or from the medical records. Only patients who were newly initiated on clozapine while under care in our clinic were included in this study. Baseline PANSS ratings were obtained immediately prior to clozapine initiation, and patients were followed longitudinally with subsequent PANSS assessments over the course of treatment. Time on clozapine was calculated by determining a start date from the medical record. Subjects were administered the PANSS at visits with their clinic therapist or psychiatrist. Clinic therapists and psychiatrists underwent PANSS certification, and inter-rater reliability was maintained through annual standardization meetings. Half the patients ($N = 13$) were rated by the same clinician during a regular clinical visit throughout the course of their treatment, while the other half of the patients had more than one clinician perform PANSS ratings at different time points due to clinician turnover.

Data collection began in February 2014 and ended in May 2023. All patients ($N = 26$) had a baseline PANSS completed before beginning clozapine, with the exception of 1 patient whose first PANSS rating occurred within one month of clozapine initiation before a therapeutic dose was reached. All patients were classified as having TRS based on failure to respond to at least 2 antipsychotic trials, each lasting more than 6 weeks. Patients were at least moderately ill, defined by a PANSS score > 58 ,²⁸ except for 2 patients with PANSS scores of 58 or below, where the treating psychiatrist judged that clozapine treatment was warranted despite mild symptoms. A patient

with a PANSS score of 58 or below is considered to be mildly ill or have a mild level of symptoms, based on the study by Leucht et al.,²⁸ which used equipercentile linking between PANSS scores and Clinical Global Impression (CGI) scores to establish the clinical meaning of PANSS scores. Two outcome measures were used: (1) a PANSS total score declining to 58 or less, and (2) a PANSS total score decreasing by 20%, both for a minimum of one rating during the course of treatment. PANSS ratings were performed on average every 8.6 months while patients were enrolled in the clinic.

Statistical Analysis

PANSS scores were modeled as a function of duration on clozapine using a linear spline regression model, with fixed knots at 3 and 6 years. We pooled all visits together to explore population-level effects, aiming to understand how certain factors impact the overall group of patients, rather than focusing on individual differences. By examining the population as a whole, we sought to identify trends and patterns that are consistent across the group, which may not be visible when analyzing each patient separately. Combining data from all visits provided a larger dataset, which enhanced statistical power and increased the reliability of our findings. Additionally, the pooled approach allowed us to model time-dependent trends, such as long-term disease progression or treatment efficacy over time.

To further investigate treatment effects during the early phase of clozapine use, we specifically focused on the first 3 years of treatment. For this subset of data, we employed a linear spline regression model with fixed knots at 1 and 2 years to assess changes in PANSS Total, Positive, Negative, and General scores, using change scores relative to baseline values.

To assess the proportion of patients who improved on clozapine (defined as achieving mild symptom levels or a ≥ 20% reduction in symptoms), we tracked PANSS scores at baseline, 6 months, 12 months, and beyond 12 months. At each time point, patient response was analyzed using both an absolute and a relative measure of improvement: (1) PANSS ≥ 58 or < 58, and (2) < 20% or ≥ 20% improvement from baseline PANSS score.

Results

To explore the longitudinal benefit of clozapine, we examined PANSS data collected from patients at the Johns Hopkins Clozapine Clinic during their regular clinical care over a seven-and-a-half-year interval. The population included individuals with a baseline PANSS score who subsequently began clozapine while enrolled in the clinic.

Study Population

As depicted in Table 1, the male to female ratio was 2.25:1. Despite the historical underutilization of clozapine

Table 1. Patient Characteristics

	(N = 26)
Age at first PANSS (SD)	32.33 (16.3)
Sex M (%) / F (%)	18 (69.23) / 8 (30.77)
Race W (%) / B (%) / Other (%)	12 (46.15) / 11 (42.31) / 3 (11.54)
Duration on clozapine (months) at last PANSS (SD)	43.27 (28.24)
Clinic visits with PANSS ratings (SD)	6.69 (3.5)
Mean interval between PANSS assessments (SD)	8.59 (8.06)

among Black individuals,²⁹ there were close to an equal number of Black and White participants (Black: 42.3%; White: 46.2%).

Age at first clinic visit with a PANSS score ranged from 12.8 to 68.6 years, \bar{x} = 32.3 years (standard deviation [SD]: 16.3). Initial PANSS score \bar{x} = 79.8, with scores ranging from 55 to 106.

A mean of 6.7 PANSS assessments were completed per patient (range: 2–14, SD: 3.5), with \bar{x} = 8.6 months (SD: 8.1) between each assessment. The mean duration on clozapine at the last completed PANSS was \bar{x} = 43.3 months (range: 3.6–89.8; SD: 28.2).

Association of PANSS Scores With Duration of Clozapine Treatment

Data were modeled using a linear spline model to explore the relationship between clozapine duration and PANSS scores across all available data points (Figure 1). Each point represents an individual PANSS score, and patients contributed an average of 3.4 scores between baseline and 3 years of clozapine treatment. To visualize individual trajectories, we generated spaghetti plots showing each participant’s PANSS scores over time on clozapine (Supplementary Data Content 1), corresponding to the data shown in Figure 1. Nearly three quarters (72.5%) of the data were collected within the first 3 years of clozapine use. PANSS scores improved by 4.6 points per year for the first 3 years of treatment (confidence interval [CI]: –6.9 to –2.4; P < .001). PANSS scores were available for all 26 patients between years 0–3 of clozapine use. However, PANSS scores were available for only 17 patients at 3–6 years of clozapine use and 5 patients at 6–7.5 years of clozapine use, reflecting the staggered initiation times of patients, with fewer individuals reaching later timepoints. Due to the limited data, symptom changes after more than 3 years of clozapine use are difficult to interpret.

Given the robust evidence of improvement in the first few years of clozapine treatment, we explored this time period in more detail.

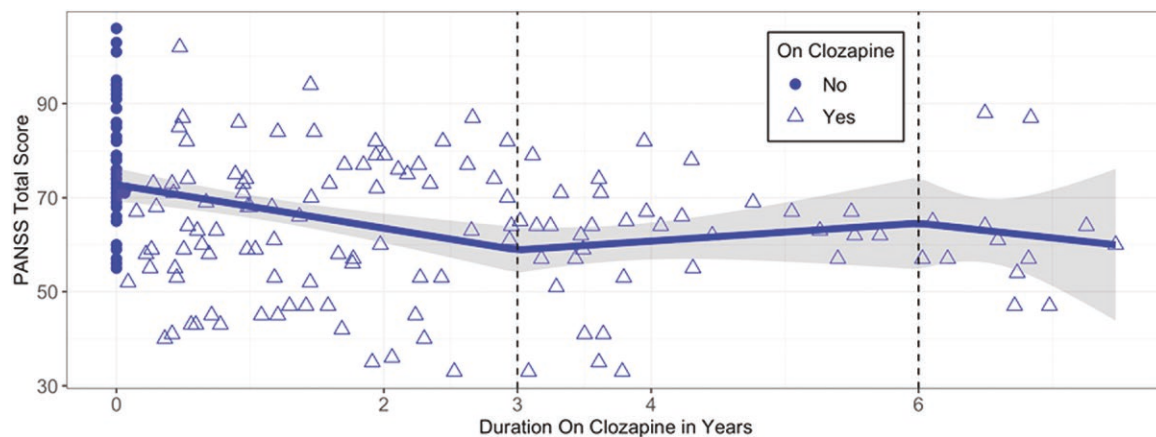


Figure 1. PANSS Total Score Improves During the First 3 Years of Treatment. Scatter Plot of All Visits and Fitted Line Between the Total PANSS Score and Duration on Clozapine (Unit: Years). The Line Represents the Linear Spline Regression Model With Knots at 3 and 6 Years. The Solid Circle Dots are PANSS Scores of Patients Before Starting Clozapine and the Hollow Triangles Show the Visits of Patients After Starting Clozapine. The Shaded Bands Around the Line are the 95% Confidence Intervals. The Model Shows a Significant Reduction in PANSS Scores Over the First 3 Years of Clozapine Treatment, Indicating Overall Symptom Improvement

Improvement During the First 3 Years of Clozapine Treatment

The linear spline regression model assessing changes in PANSS relative to baseline values shows that most PANSS score improvements occurred during the first year on clozapine, with significant reductions in the total score as well as the positive and general psychopathology subscales (Figure 2, Table 2). Negative symptoms decreased modestly but non-significantly (Figure 2). After 1 year on clozapine, a slight increase in PANSS score was observed for all subdomains; however, PANSS total, positive, and general scores remained improved compared to baseline, whereas scores for the negative subdomain showed a gradual return toward baseline (see Discussion).

Progression Toward Clinical Improvement: Time to Mild Symptoms or $\geq 20\%$ PANSS Reduction

After 6 months on clozapine, 10 patients (38.5%) achieved a $\geq 20\%$ improvement in PANSS scores, with 6 (23.1%) of these patients reaching a mild level of symptoms (PANSS ≤ 58) (Table 3). By 12 months, an additional 4 patients (15.4%) met the $\geq 20\%$ improvement threshold, with PANSS scores of 1 patient (3.8%) declining to the mild category. Following 12 months of treatment, 6 more patients (23.1%) experienced a $\geq 20\%$ improvement, all of whom also reached a mild level of symptoms. In total, 20 patients (76.9%) achieved a $\geq 20\%$ improvement during treatment, and 15 patients (57.7%) reached a mild symptom level.

Discussion

In this naturalistic study, we examined the course of symptoms in patients who began clozapine at the Johns

Hopkins Bayview Community Psychiatry Clozapine Clinic after a baseline PANSS score was obtained. Most patients demonstrated significant and meaningful symptom improvement during the course of clozapine treatment. In total, 58% of patients improved to a mild level of symptoms (PANSS ≤ 58), 77% of patients improved by 20% or more, and 81% of patients met at least 1 of these criteria. Most of the improvement occurred in the first year of treatment, with significant reductions in both positive and general symptoms, while negative symptoms did not significantly change.

The findings are consistent, but expand upon the limited data on the value of long-term clozapine use for treating symptoms. A meta-analysis comparing clozapine to first-generation antipsychotics found clozapine superior, typically after a relatively short duration of use (6 weeks to 1 year).³⁰ A second meta-analysis of randomized control trials of clozapine for TRS divided studies into short term (< 3 months of clozapine treatment), and long term (≥ 3 months of clozapine treatment). This analysis concluded that clozapine was superior to other antipsychotics in both the short and long term, but recommended changing to a different antipsychotic if there was no response to clozapine by 6 months.³¹ The Clinical Antipsychotic Trials of Intervention Effectiveness phase 2 study¹⁰ also demonstrated that clozapine was superior, based on length of time to clozapine discontinuation, compared to other second-generation antipsychotics.¹⁰ Here we demonstrate that for a subset of patients, there is potential for improvement after 12 months of clozapine, even if there had not been a significant response by 12 months. Further, patients in our clinic have successfully continued clozapine for years without discontinuation.

Our results are consistent with 2 long-term clozapine outcome studies. A retrospective 10-year study³² of

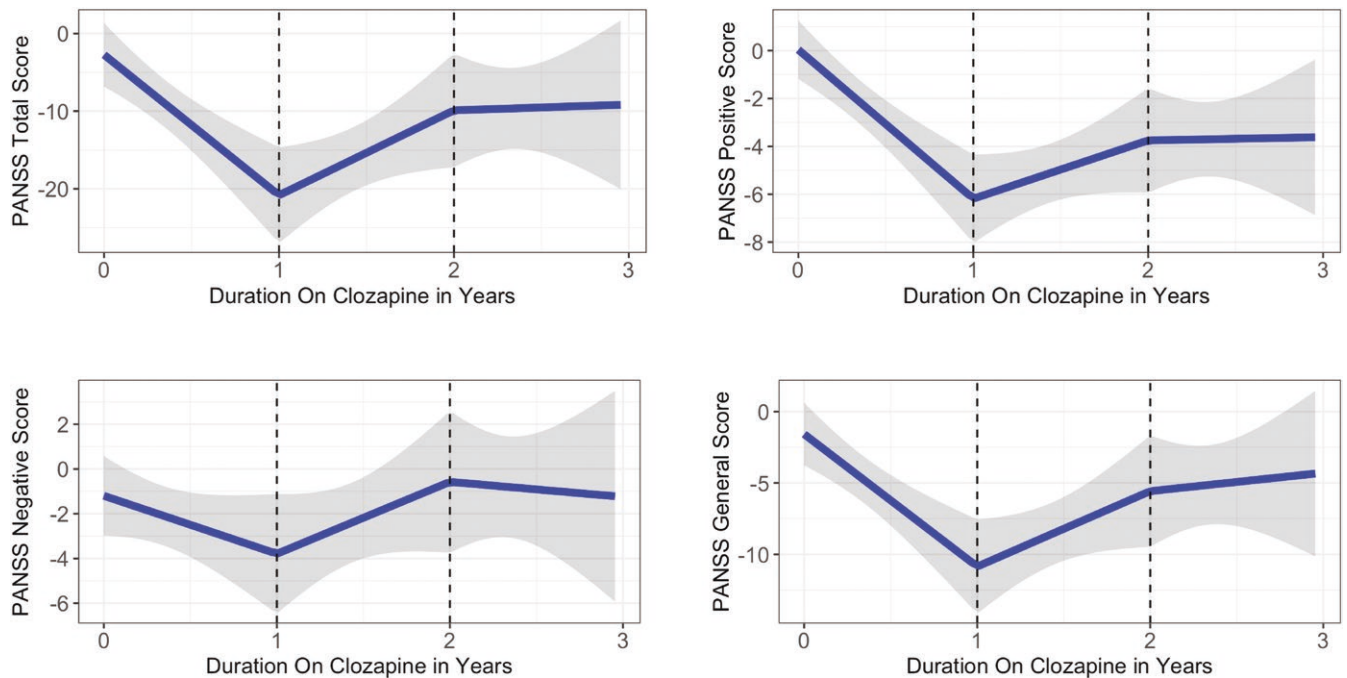


Figure 2. PANSS Scores Improve During the First Year of Treatment With Clozapine. The Fitted Lines Between the Total PANSS Score, Positive PANSS Score, Negative PANSS Score, General PANSS Score, and Duration on Clozapine (Unit: Years) for the New Start Cohort With Duration Between 0–3 years. The Lines Represent the Linear Spline Regression Model With Knots at 0, 1, and 2 Years. The Shaded Bands Around the Line are the 95% Confidence Intervals of the Fitted Lines. Statistically Significant Reductions Were Observed in Total, Positive, and General Scores During the First Year. Negative Symptoms Showed a Modest, Nonsignificant Improvement

Table 2. First Year on Clozapine

PANSS subdomain	Slope (95% Conf. interval)	T-statistic	Effect size	P-value
Total score	-18.1 (-26.2, -10.0)	-4.41	-1.09	.000
Positive score	-6.2 (-8.7, -3.8)	-5.08	-1.21	.000
Negative score	-2.6 (-6.1, 0.9)	-1.46	-0.39	.147
General score	-9.3 (-13.6, -4.9)	-4.24	-1.06	.000

Table 3. Continued Improvement Over Time

Time point	Patients with mild symptoms (PANSS ≤ 58)	Percentage of total patients (N = 26)	Patients achieving 20% improvement	Percentage of total patients (N = 26)
By baseline	2	7.70%	N/A	N/A
By 6 months	6	23.10%	10	38.50%
By 12 months	1	3.80%	4	15.40%
After 12 months	6	23.10%	6	23.10%
Total	15	57.70%	20	76.90%

TRS showed a greater improvement in symptoms with clozapine treatment compared to other antipsychotic medications. A prospective 14-year study¹¹ showed significant symptomatic improvements from baseline or 6 months to study end as assessed with the Brief Psychiatric Rating Scale.³³ Our data is consistent with these studies, but included more frequent PANSS ratings that enabled us to identify patients who responded to the extent that symptoms could be classified as mild.

There are several limitations to this study. The sample size is small, especially after 12 months. While the goal was to obtain PANSS scores for all patients every six months, the average interval between assessments was longer, and varied among patients, with some time points missing. This reflects the naturalistic setting of the study. Further, the successful use of the data, even though limited, demonstrates the feasibility and utility of obtaining objective data in the

clinical setting of this patient population to help guide clinical treatment. Patients were classified as reaching a mild level of symptoms if their PANSS score was ≤ 58 at any assessment point, rather than classifying an adequate response solely on the final PANSS assessment. While not typical of most clinical trials, this approach enabled us to identify if a patient could ever respond to clozapine, and if so, how soon after clozapine initiation. Determining outcomes based on only the final symptom assessment risks underestimating the clozapine response.

The lack of continued improvement after the first year of clozapine treatment may reflect a plateau in treatment response or a limitation in the available data. Given the observational nature of the data and the absence of a comparison group, the extent to which clozapine contributed to the observed long-term outcomes cannot be determined with certainty. It is also possible that as patients stabilize and begin to reengage with life demands (work, relationships, independent living, etc.), emergent psychosocial stress could contribute to fluctuations in symptom severity or increased variability, reflected in PANSS scores.

We also note that while group-level PANSS scores plateaued after 12 months, nearly 1-quarter of patients achieved clinical response only after the first year. This suggests considerable heterogeneity in response trajectories, with some patients demonstrating delayed but meaningful improvements that may be obscured in group averages. More fundamentally, it is difficult to discern the extent to which improvement observed 12 months after the first PANSS assessment was a consequence of clozapine, or if therapy, access to psychosocial rehabilitation, other external factors, or variations in the intrinsic course of the illness, influenced clinical improvement. Finally, this study focused on symptom improvement as measured by the PANSS; the long-term impact of clozapine on functional, social, cognitive, or quality of life measures remains to be determined.

Overall, the data from this naturalistic study support the use of clozapine in TRS. A substantial portion of patients who did not improve after 12 months of clozapine treatment eventually improved with continued clozapine treatment, suggesting that in the absence of alternatives or major side effects, continuing clozapine past 12 months is clinically warranted even in patients not yet improving. Further, this study demonstrates the feasibility of initiating and maintaining clozapine for years in an outpatient setting, and the value of routine but rigorous use of rating scales during treatment.

Supplementary Material

Supplementary material is available at Schizophrenia Bulletin Open online.

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