Evaluation of the Safety of Clozapine Use in Patients With Benign Neutropenia

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ABSTRACT

Objective: To determine if clozapine can be safely utilized in psychiatric patients with benign neutropenia.

Methods: A single-center, retrospective chart review study of records from 2001 to 2014 was conducted in an inpatient psychiatric hospital. Patients included had benign neutropenia prior to receiving clozapine and received clozapine using modified monitoring guidelines. All available laboratory values for absolute neutrophil count (ANC) before initiation and during treatment were evaluated. The primary endpoint was difference in ANC after initiation of clozapine from before clozapine.

Results: A total of 26 patients were reviewed. The mean age at clozapine initiation was 34 years. The majority were African-American (73% [n = 19]), with more men than women (73% [n = 19] vs 27% [n = 7]). The mean lowest ANC value was not significantly different after clozapine initiation compared to before (1.5×10^3 cells/mm^3 and 1.4×10^3 cells/mm^3, respectively; $P = .22$). The overall mean ANC was significantly higher after initiation than before (2.63×10^3 cells/mm^3 and 2.13×10^3 cells/mm^3, respectively; $P < .001$). There were no cases of severe neutropenia (ANC < 0.5×10^3 cells/mm^3), and no patient was discontinued for falling below modified guideline limits. There were fewer occurrences of mild neutropenia (ANC < 2.0×10^3 cells/mm^3) after clozapine initiation than before (16.0% and 31.4%, respectively; $P < .001$). There were also fewer occurrences of moderate neutropenia (ANC < 1.5×10^3 cells/mm^3), with 2.1% after clozapine and 13.3% before ($P < .001$).

Conclusions: Twenty-six patients with benign neutropenia were safely treated with clozapine. Pre-clozapine neutropenia did not predict increased risk for severe neutropenia with clozapine. Patients had significantly fewer episodes of mild and moderate neutropenia after receiving clozapine compared to before.

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It has been estimated that 35%–40% of all patients with schizophrenia should be considered for a trial of clozapine.[1] However, in the United States, only 4%–5% of patients with schizophrenia ever receive clozapine.[1] While the superior and unique efficacy of clozapine has been repeatedly supported by the literature, the frequency of clozapine use remains low.[2] Antipsychotic polypharmacy, which has virtually no support in the literature, is now used more frequently than clozapine.[3–5]

There are numerous reasons why clozapine is not more broadly used. Patient reluctance may be a factor, although education, motivation, and persuasion by the treating psychiatrist are skills that can and should be developed, and patients are actually more willing to take clozapine than physicians realize.[6,7] Reluctance by clinicians to prescribe clozapine may also play a role.[8,9] Some of this stems from the challenge of coordinating laboratory, pharmacy, and clinic visits and the extra time required to monitor laboratory results.[10] The fractured nature of community care amplifies these challenges. Clinician reluctance also stems from the medical risks of clozapine, especially severe neutropenia (formerly *agranulocytosis*).[8]

The estimated risk of severe neutropenia with clozapine treatment is less than 1%,[11] and US Food and Drug Administration (FDA)–mandated complete blood count (CBC) monitoring guidelines[12] have been effective in preventing agranulocytosis. In a recent study from Australia,[13] a review of national adverse events data revealed 141 cases of agranulocytosis due to clozapine during 1993–2011. Of these 141 cases, there were only 4 deaths. Because the death rate among those with agranulocytosis was so low, the authors concluded that early detection and clozapine withdrawal was unlikely to prevent many deaths due to clozapine-induced agranulocytosis. However, they estimated that without current monitoring, approximately 28 cases of agranulocytosis would occur per year.[13] Unfortunately, the apparent inflexibility of the pre-2015 FDA guidelines created a significant impediment to the broader use of clozapine in the United States, especially in patients of African and Middle Eastern descent, who may manifest benign ethnic neutropenia (BEN). This condition may be explained by a genetic polymorphism that affects the expression of the Duffy antigen on red blood cells. Homozygotes for this polymorphism do not express the Duffy antigen. Consequently, they are at lower risk of contracting malaria. For unclear reasons, homozygotes as a group also have an average absolute neutrophil count (ANC) that is roughly 1.5×10^3 cells/mm^3 less than that of groups of heterozygotes or noncarriers, with no evidence of immunocompromise.[3,14,15] By chance, a significant number of these individuals normally have circulating ANC values that fall into a "neutropenic" range as defined by norms created by study of European descent patients. In a large cross-sectional study of 25,222 participants, Hsieh et al[16] reported that 4.5% of African-American participants had an ANC of less than 1.5×10^3 cells/mm^3 versus only 0.79% of European Americans. This finding has been replicated in other studies

Clinical Points

- Despite its superior efficacy, clozapine is significantly underutilized in psychiatric illnesses, especially in patients with benign neutropenia.
- In this group of 26 psychiatric patients with benign neutropenia treated with clozapine using modified monitoring guidelines, there were no cases of severe neutropenia, and the incidence of mild and moderate neutropenia actually fell compared to pretreatment. Benign neutropenia did not predict negative hematologic consequences during treatment with clozapine.
- The US Food and Drug Administration's recent changes to the absolute neutrophil count monitoring guidelines during clozapine treatment should allow greater access to this potentially life-saving medication.

as well.[14,15] The incidence of BEN is estimated to be up to 25%–40% of those of African descent outside of the United States.[17,18] Despite having lower baseline white blood cell and neutrophil counts, these individuals appear to be at no greater risk of developing agranulocytosis or infection than those without BEN.[19–21] These data support the development of more flexible ANC monitoring guidelines for clozapine.

Numerous case reports in the literature describe the successful use of clozapine in patients with BEN.[22–24] Recognizing the inappropriateness of applying Caucasian-based CBC monitoring guidelines to patients of African descent, the United Kingdom has adopted modified monitoring guidelines for subjects with BEN.[25] At the time of this study, the FDA had not modified clozapine monitoring rules to adapt to the different needs of BEN patients. However, in October 2015, the FDA launched the new Risk Evaluation and Mitigation Strategy (REMS), which includes 1 central clozapine registry, and updated the clozapine monitoring guidelines to include algorithms for treatment in patients with BEN.[26,27] Prior to this change, in the Maryland public mental health inpatient setting, providers had the ability to request the use of individually modified clozapine monitoring parameters on a case-by-case basis. These individualized "waivers" were approved by the patient, treating physician, clinical pharmacist, and clinical director of the hospital and the State of Maryland Clozapine Authorization and Monitoring Program. The purpose of this study was to determine if clozapine can be safely utilized in a population of psychiatric patients with benign neutropenia prior to treatment with clozapine. To our knowledge, this is the first study to evaluate a larger group of patients and to incorporate statistical comparisons of blood counts before and after clozapine.

METHODS

The current report is a case series based on retrospective chart reviews conducted at a single hospital and research center. The study population consisted of patients with treatment-resistant psychotic disorders and benign neutropenia prior to receiving clozapine who received clozapine using modified monitoring guidelines. The modified monitoring guidelines were individualized on the basis of each patient's ANC history and gave a list of specified ANC values and corresponding actions required based on the value. Although most were developed before the UK and US guidelines were revised, they were similar to the UK guidelines where the thresholds for the green, amber, and red alerts were dropped by approximately 500 cells/mm^3. Patients with documented low baseline ANC without apparent African or Middle Eastern ancestry were also given individually modified guidelines. Although they may be of nonapparent descent, we will refer to these patients for the purposes of this article as having benign neutropenia and not BEN to account for them.

The primary outcome was the difference in ANC values after initiation of clozapine compared to those values before clozapine initiation. Secondary outcomes included within-participant fluctuations in ANC and patient outcomes on clozapine. In this study, the definition of mild neutropenia was ANC $< 2.0 \times 10^3$ cells/mm^3, and the definition of moderate neutropenia was ANC $< 1.5 \times 10^3$ cells/mm^3. The new FDA clozapine guidelines are now defined differently, with mild neutropenia as $< 1.5 \times 10^3$ cells/mm^3 and moderate neutropenia as $< 1.0 \times 10^3$ cells/mm^3. Severe neutropenia (formerly referred to as *agranulocytosis*) was defined as $< 0.5 \times 10^3$ cells/mm^3 in this study.

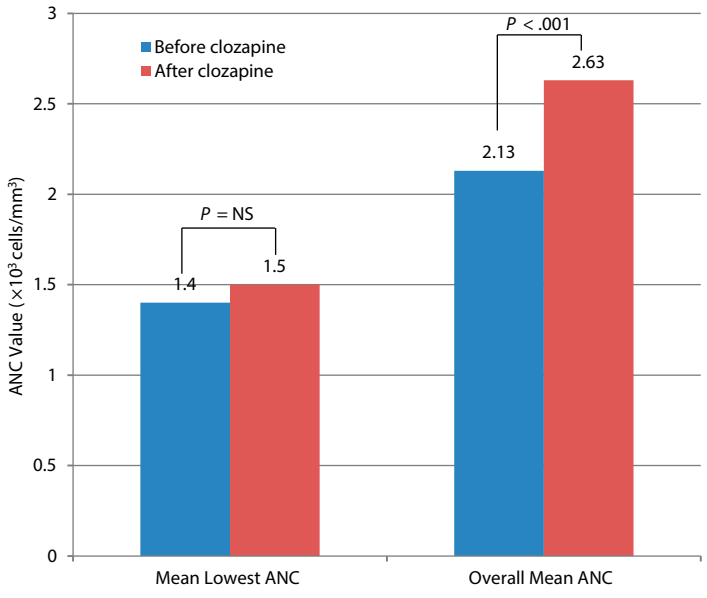
Data collected on each patient included age at clozapine initiation, sex, race/ethnicity, stabilized clozapine dose, ANC values, and patient outcome at the time of data collection. All ANC values available from hospital records before or after initiation of clozapine were used to compute within-patient summary statistics (mean, SD, minimum, etc), with the exception that any ANC values obtained while the patient was receiving concomitant lithium treatment were excluded due to the potential elevation in ANC values. Data were collected retrospectively from clinical hospital records between July 2014 and December 2014, with all patients having their period of treatment between 2001 and 2014. Data were analyzed with Microsoft Excel and SAS. Analyses included descriptive statistics, paired Student *t* test for pre/post clozapine average within-patient mean ANC values, and sign test for before/after changes in within-patient ANC standard deviations.

This data collection examining clozapine use was institutional review board–approved as a retrospective review of existing records with a waiver of informed consent from both the University of Maryland and the Maryland Department of Health and Mental Hygiene Institutional Review Boards.

RESULTS

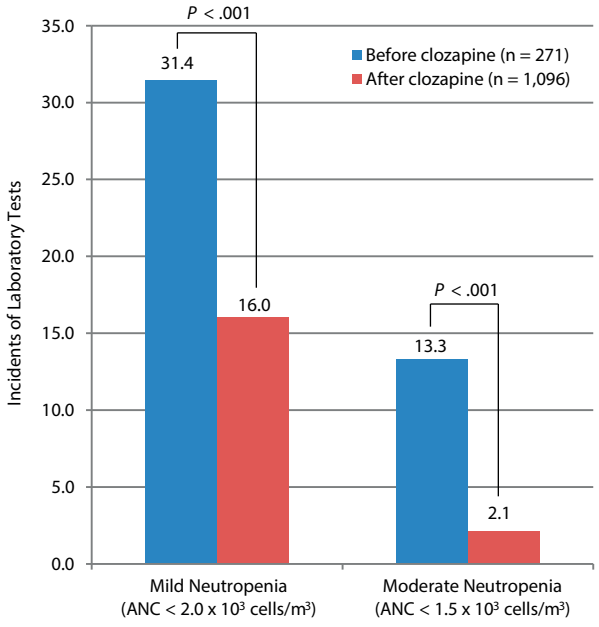
Records were reviewed for 26 patients with a mean age of 34 years at clozapine initiation (range, 20–56 years), including 19 men (73%) and 7 women (27%). Nineteen (73%) patients identified as African-American, while 7 identified as Caucasian (27%).

Figure 1. Mean of the Lowest and Overall Average Within-Patient ANC Values



Abbreviation: ANC = absolute neutrophil count.

Figure 2. Percentage of Laboratory Tests Below Pre-2015 FDA Monitoring Thresholds



Abbreviation: FDA = US Food and Drug Administration.

Clozapine Characteristics

The mean stabilized dose of clozapine was 456 mg (range, 50–900 mg). Patient laboratory values were reviewed before the start of clozapine treatment for a median of 230 days (range, 33–5,259 days) and followed after the initiation of clozapine for a median of 364 days (range, 28–399 days). There was a nonsignificant trend toward greater variability in ANC values after initiation of clozapine, with a median within-patient standard deviation of 0.75×10^3 cells/mm^3 compared to 0.54×10^3 cells/mm^3 pre-clozapine ($P = .052$). The mean of the lowest within-patient ANC values was not significantly different after clozapine initiation ($1.5 \pm 0.37 \times 10^3$ cells/mm^3) compared to the pre-clozapine period ($1.4 \pm 0.33 \times 10^3$ cells/mm^3) ($P = .224$) (Figure 1). The mean of within-patient ANC values was significantly higher after clozapine initiation ($2.63 \pm 0.50 \times 10^3$ cells/mm^3) compared to before ($2.13 \pm 0.51 \times 10^3$ cells/mm^3) ($P < .001$). There were no cases of severe neutropenia (ANC $< 0.5 \times 10^3$ cells/mm^3), and no patients were discontinued for falling below their waiver parameters.

Incidents of Laboratory Values Below Monitoring Thresholds

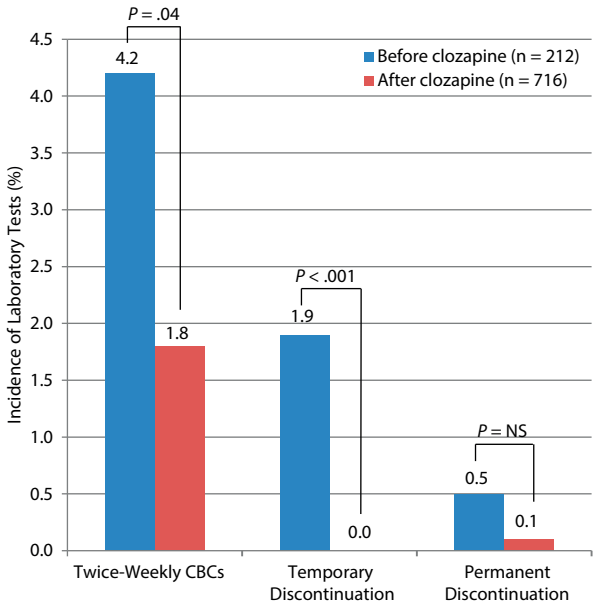
According to the thresholds specified in pre-2015 FDA guidelines,[12] there were approximately half as many incidents of mild neutropenia (ANC $< 2.0 \times 10^3$ cells/mm^3) after clozapine initiation than before ($P < .001$), as well as less than one-sixth as many incidents of moderate neutropenia (ANC $< 1.5 \times 10^3$ cells/mm^3) after clozapine initiation ($P < .001$) (Figure 2). The percentage of blood tests with ANC $< 1.0 \times 10^3$ cells/mm^3 did not differ after clozapine (0.3%) compared to pre-clozapine (0.4%) ($P = .795$), and there were no cases meeting FDA guidelines for "agranulocytosis" (ANC $< 0.5 \times 10^3$ cells/mm^3).

According to the individually modified monitoring guidelines that were used for each patient, there were significantly fewer incidents of ANC values requiring twice-weekly monitoring after clozapine (1.8%) compared to before clozapine (4.2%) ($P = .04$) (Figure 3). There were also significantly fewer incidents of ANC values requiring temporary discontinuation, with 0.0% after clozapine and 1.9% before clozapine ($P < .001$).

Patient Outcomes on Clozapine Treatment

At the time of the data collection in this report, 14 of the 26 patients were successfully discharged on clozapine treatment (Figure 4). Eight patients remained hospitalized and continued to receive clozapine. Of the remainder, 1 patient eloped from a general hospital during clozapine treatment, 1 was discontinued due to refusal of laboratory work, and 2 patients were discontinued due to thrombocytopenia. Of these 2 patients, the first was thrombocytopenic pre-clozapine and no change in platelets was seen with the addition of clozapine, but the medication was discontinued per physician decision. The second patient had normal platelet values pre-clozapine. With the addition of clozapine, this patient had a steady decline in platelets to a minimum of 93×10^3 cells/μL. After

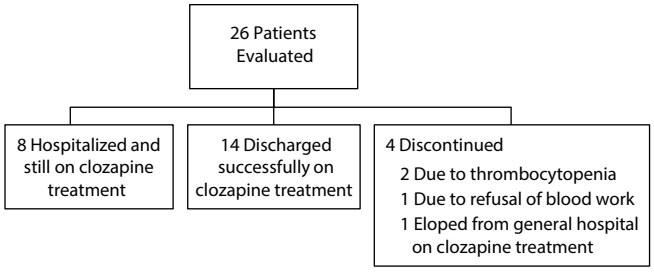
Figure 3. Percentage of Laboratory Tests Below Individualized Modified Monitoring Guidelines[a]



[a]Modified monitoring guidelines were individualized based on each patient's ANC history and gave a list of specified ANC values and corresponding actions required based on the value. All patients were monitored on a weekly basis, with a certain ANC value requiring twice weekly CBCs until ANC recovered to the specified value. There were further ANC values requiring temporary discontinuation and monitoring. These patients were able to be restarted on clozapine once the ANC increased to a predetermined value. Another specified ANC value required permanent discontinuation of clozapine without the chance for rechallenge

Abbreviations: ANC = absolute neutrophil count, CBC = complete blood count, NS = nonsignificant.

Figure 4. Patient Outcome on Clozapine Treatment



clozapine was discontinued, the patient's platelet count improved, but did not recover to baseline when he was discharged 4 months after clozapine discontinuation. It is unknown if the patient had any medical consequences due to the thrombocytopenia or if other causes were identified. Of note, 7 patients (26.9%) of the 26 evaluated had their individually modified monitoring guidelines discontinued and successfully remain to date on clozapine treatment using pre-2015 manufacturer monitoring guidelines.

DISCUSSION

In this study of psychiatric patients with benign neutropenia and mostly benign ethnic neutropenia pre-clozapine, treatment with clozapine did not increase the risk of severe neutropenia. There were significantly fewer incidents of mild and moderate neutropenia after addition of clozapine compared to laboratory values before clozapine initiation. Compared to pre-clozapine ANC values, patients had significantly fewer incidents of ANC values requiring twice-weekly CBCs and temporary discontinuation as outlined in the patients' individually modified monitoring parameters after clozapine treatment. Furthermore, the average of within-patient mean ANC values increased significantly after clozapine initiation, with no difference in the average of within patient minimum ANC values. Based on this small population, clozapine appears to be a safe treatment option in these patients. This is supported by the existing literature, which contains a few case reports of patients with benign ethnic neutropenia. Blackman[23] described a case of a 19-year old man with a robust response to clozapine therapy. However, his frequently fluctuating ANC values necessitated once- to twice-weekly blood draws. Others have described cases of patients who responded well to clozapine, but the medication was discontinued due to low white blood cell count (WBC) and ANC values. These patients were started on medications (lithium[28,29] and granulocyte colony stimulating factor[22]) in order to augment their WBC and ANC values, which allowed for continued use of clozapine. It is unfortunate that these patients and possibly others like them have been exposed to unnecessary, potentially harmful medications in order to meet guidelines for use of clozapine.

In our study, 2 patients (7.7%) discontinued clozapine due to thrombocytopenia. Although 1 of these patients had low platelet count pre-clozapine, the other can potentially be attributed to the addition of clozapine. The literature contains a few case reports and studies reporting the incidence of thrombocytopenia associated with clozapine up to a maximum of 17.8% of cases.[30–32] The pre-2015 US clozapine labeling lists the incidence of thrombocytopenia as less than 1%, although Canadian labeling recommends discontinuation if platelets fall below 50,000/mm^3.[33] Based on our findings, we recommend that clinicians include platelet count with regular CBC monitoring in patients with benign neutropenia.

The first patient in this study was treated in 2001, well before the phenomenon of BEN was described. Nineteen of the 26 patients in this study were self-identified African Americans, and it is reasonable to hypothesize that the majority of these patients have benign ethnic neutropenia. However, it is notable that 7 of the patients identified as Caucasian, with no evidence of African or Middle Eastern heritage. It is possible that they were of Yemenite Jewish descent as BEN among this Jewish group may be attributable to the same gene and is present in about 58% of this population.[34] It is also possible that there are other genetic or acquired

Table 1. New FDA Guidelines for ANC Monitoring in BEN Patients

ANC Level	Treatment Recommendation	ANC Monitoring
Normal range for a new patient BEN population ANC ≥ 1.5×10^3 cells/mm^3 Obtain at least 2 baseline ANC levels before initiating treatment	Initiate treatment If treatment interrupted: < 30 days, continue monitoring as before ≥ 30 days, monitor as if new patient	Weekly from initiation to 6 mo Every 2 weeks from 6 to 12 mo Monthly after 12 mo
Mild neutropenia ($1.0–1.499 \times 10^3$ cells/mm^3)[a]	Mild neutropenia is normal range for BEN population, continue treatment Obtain at least 2 baseline ANC levels before initiating treatment If treatment interrupted: < 30 days, continue monitoring as before ≥ 30 days, monitor as if new patient	Weekly from initiation to 6 mo Every 2 weeks from 6 to 12 mo Monthly after 12 mo
Moderate neutropenia ($0.5–0.999 \times 10^3$ cells/mm^3)[a]	Recommend hematology consultation Continue treatment	Three times weekly until ANC ≥ 1.0×10^3 cells/mm^3 or ≥ patient's known baseline Once ANC ≥ 1.0×10^3 cells/mm^3 or patient's known baseline, then check ANC weekly for 4 weeks, then return to patient's last "normal BEN range" ANC monitoring interval[b]
Severe neutropenia (less than 0.5×10^3 cells/mm^3)[a]	Recommend hematology consultation Interrupt treatment for suspected clozapine induced neutropenia Do not rechallenge unless prescriber determines benefits outweigh risks	Daily until ANC ≥ 0.5×10^3 cells/mm^3 Three times weekly until ANC ≥ patient's established baseline If patient rechallenged, resume treatment as a new patient under "normal range" monitoring once ANC ≥ 1.0×10^3 cells/mm^3 or at patient's baseline

[a]Confirm all *initial* reports of ANC less than 1.0×10^3 cells/mm^3 for BEN patients with a repeat ANC measurement within 24 hours.
[b]If clinically appropriate.
Abbreviations: ANC = absolute neutrophil count, BEN = benign ethnic neutropenia, FDA = US Food and Drug Administration.

conditions (eg, post-chemotherapy) that predispose these patients to benign neutropenia, however, it should be noted that BEN may not be entirely African descent and may include Yemenite Jews and Arab populations.

Since this study was conducted, the FDA has made changes to the United States clozapine monitoring parameters. In this new system, all patients, prescribers, and pharmacies will be registered in a shared Risk Evaluation and Mitigation Strategy (REMS) called the Clozapine REMS Program rather than the 6 individual manufacturer registries used previously. Monitoring for neutropenia now only requires ANC, rather than both ANC and WBC. Furthermore, the ANC thresholds have been modified with 2 new algorithms, 1 for the general population and 1 developed for BEN patients. We have included the new guidelines for BEN patients in Table 1. In light of our results, we fully support the changes made by the FDA to accommodate lower ANC values in patients with BEN. This modification will lead to reduced frequency of blood draws and may lead to more widespread use, improved compliance, greater patient satisfaction, and more willingness to continue this potentially life-saving medication. However, as shown by the results of this study, not all patients with a low baseline ANC and possibly BEN are of African descent. Further research is needed in these patients to determine the cause of their low ANC as well as the appropriate course of clozapine treatment.

Limitations of the Study

This was a retrospective study so the process for how each patient was identified as having benign neutropenia was varied. No genetic markers were evaluated in this sample, so it is unknown if the patients carried the genetic polymorphism commonly seen in BEN. Furthermore, the findings in this small sample size may not be generalizable to a larger population. Nonetheless, this is the first systematic collection of a group of patients with benign neutropenia treated in the United States using modified monitoring guidelines.

Future Research

Our research group has recently been funded by the NIMH (NCT #02404155) to prospectively study the safety of using clozapine in patients with BEN and to assess possible genetic biomarkers for this condition. Conducted in the United States and Nigeria, the study will use modified guidelines that were approved by the FDA under an Investigational New Drug Application prior to the 2015 REMS changes. Our hopes are that the study results will contribute to future modification of the US guidelines and will contribute to clinician awareness and recognition of benign neutropenia and BEN, so as to give patients with this condition the opportunity to benefit from the unique advantages of clozapine.

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Previous presentation: Presented as a poster at the College of Psychiatric and Neurologic Pharmacists Annual Meeting, April 2015, Tampa, Florida.
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