Impact of Complete Blood Count Sampling Time Change on White Blood Cell and Absolute Neutrophil Count Values in Clozapine Recipients

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Abstract

Introduction: Despite its superior efficacy, clozapine is typically reserved for treatment-refractory schizophrenia due to the risk of agranulocytosis with an occurrence of up to 1% in recipients. The FDA has rigid treatment guidelines for hematologic monitoring for clozapine patients. If the white blood cell (WBC) count or absolute neutrophil count (ANC) falls below predetermined values, clozapine treatment must be held or discontinued. Diurnal and ethnic variations in complete blood count (CBC) values, somewhat dependent upon blood sampling time have been reported, and called pseudoneutropenia, which appears independent of clozapine therapy. Unnecessary treatment interruption or discontinuation is costly and may lead to disease relapse. The purpose of this study was to evaluate the effect of a time change in CBC sampling on WBC and ANC values in a group of clozapine patients in a regional public inpatient psychiatric facility. **Methods:** Facility CBC sampling for clozapine patients was switched from 0630 to on or after 0830. A retrospective record review was conducted for all patients who were receiving clozapine before and after the time switch, with a minimum of six values pre- and post-change. CBC values sampled on or after 0830 were accepted as applicable post data, as patients are awakened daily at 0630, and a minimum of two hours of wakefulness/mobility had occurred. Patient medical records, automated lab information system, and the Clozapine National Registry were data sources. Data extracted included WBC/ANC values (with date/time of sampling) and demographic information (DOB, sex, weight, height, BMI, and ethnicity). The data were analyzed using repeated measures ANOVA. **Results:** Ten patients (80% male, 90% Caucasian, mean age=55.7 years) met study criteria. The difference in the pre/post time change WBC values was marginally significant (mean increase=667/mm^3, p=.07), with a significant difference (mean increase=1,130/mm^3, p=.003) between the pre/post time change ANC values. ANC values were more positively impacted by the sampling time change than WBC values in this sample. The mean sampling time change across all subjects pre/post was 5 hours 24 minutes. **Conclusions:** All reasonable steps should be considered to safely continue an effective therapy in treatment-refractory schizophrenia. A larger, more ethnically diverse sample is needed to validate the present work; however, changing the timing of CBC sampling for clozapine patients from early morning to after a minimum two-hour period of wakefulness/movement may have potential to improve WBC and ANC values. Marginal improvements in resultant WBC/ANC values could potentially allow clozapine therapy to continue uninterrupted per FDA monitoring guidelines.

Key Words: Clozapine, Pseudoneutropenia, Agranulocytosis, Treatment-Resistant Schizophrenia

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Submitted: July 21, 2009; Revised: December 4, 2009; Accepted: March 24, 2010

Introduction

There are approximately 1.5 million people in the United States diagnosed with schizophrenia. While atypical antipsychotics are routinely used to treat schizophrenia and other psychiatric conditions, between 20 to 30% of these patients are unresponsive to first-line antipsychotic therapy (1). Unlike other atypicals, clozapine is indicated for resis-

Clinical Implications

Changing the timing of complete blood count (CBC) sampling from early morning to after a two-hour minimum period of wakefulness and mobility may have the potential to improve white blood cell (WBC) and absolute neutrophil count (ANC) values by minimizing potential instances of pseudoneutropenia and could potentially allow clozapine therapy to continue uninterrupted in certain cases, per current FDA-mandated CBC monitoring guidelines. It is critically important to differentiate between benign and malignant neutropenia. The present work does not differentiate between these two conditions; rather, the methodology outlined may assist clinicians to avoid responding to transiently low WBC or ANC values by sampling later in the day. Further, until additional studies are published, it is suggested that all WBC values obtained in the early morning, which are falling or below normal, should be repeated after a delay of several hours before a final decision is made to terminate clozapine therapy. The present findings suggest that even a minimal delay in sampling time may provide more robust results and potentially allow continued clozapine therapy. A larger, more ethnically diverse study sample is needed to validate the results from the current study. Further discussion should occur at the FDA level regarding special consideration for subjects with pseudoneutropenia. Finally, another area for additional study might be that of determining the extent of diurnal variation in those individuals who go on to develop more malignant neutropenia. It is clear that all reasonable steps should be considered in order to appropriately maintain therapy in the treatment-refractory population typically receiving clozapine therapy.

tant or refractory to treatment cases which have failed an adequate trial of two other atypicals (1-3). The superiority of clozapine over other antipsychotic agents in treatment-resistant cases is well established (1-3). Further, the CATIE II (Clinical Antipsychotic Trials of Intervention Effectiveness II) trial results demonstrated the superiority of clozapine over other second-generation antipsychotics in patients who prospectively failed an optimized antipsychotic regimen (4). However, clozapine, while highly effective in the treatment of schizophrenia, is often held in reserve due to the risk of the potentially life-threatening side effect of agranulocytosis and rigid requirements for complete blood count (CBC) monitoring.

Treatment resistance in chronic schizophrenia remains a national public healthcare issue due to lack of effective therapies, and in many cases, reluctance to use clozapine. The rate of clozapine-associated agranulocytosis was generally thought to occur in 0.8 to 1% of patients (1, 5, 6). However, a review of over 99,000 patients enrolled in the Clozapine National Registry from 1990–1994 and monitored according to accepted guidelines found the rate of agranulocytosis to be lower at 0.38% (7). Clozapine-associated agranulocytosis is not dose related, and risk increases with increasing age, Ashkenazi Jewish or Asian ethnicity, and female gender. The risk decreases after six months of therapy without leukopenia (6, 8).

As a result of the potential for blood dyscrasias, the U.S. Food & Drug Administration (FDA) has mandatory treatment guidelines for hematologic monitoring for clozapine recipients (see Table 1) (9). Patients on clozapine must follow strict hematological monitoring of white blood cell (WBC) and absolute neutrophil count (ANC) weekly when first initiating treatment (9). If the WBC count or ANC falls below predetermined values, treatment must be held or discontinued. This treatment interruption or discontinuation is costly and time-consuming, may adversely impact the therapeutic alliance, and may lead to disease relapse. Further, diurnal and ethnic variations in WBC values have been reported in healthy subjects, which are independent of clozapine therapy (10, 12-16, 20-22). These variations, in some instances, may be somewhat dependent upon CBC sampling time and could, if acted upon, lead to unnecessary termination of clozapine therapy. Pseudoneutropenia or transient neutropenia is a more pronounced variant of the normal diurnal variation in circulating WBC values and has been noted to occur in many patients treated with clozapine, but has not been associated with progression to agranulocytosis (10, 12-16, 20-22). In a treatment-refractory population of persons with schizophrenia, every effort must be made to assure that appropriate, safe, and effective pharmacotherapy can continue, while assuring ongoing optimal patient safety. Unnecessary discontinuation of clozapine due to spurious WBC or ANC findings should be avoided due to the potential for psychiatric relapse.

In clozapine-treated individuals, transient neutropenia is defined as a return of the neutrophil count to normal values without changing the clozapine dose (8, 13). Transient neutropenia cases among clozapine recipients were first reported in the late 1980s. More recently, transient neutropenia was shown to occur in 22% of 68 patients receiving clozapine for the first time (13). Discontinuation of clozapine with a reluctance to reinitiate therapy is especially of concern in cases of clozapine-related pseudoneutropenia, when discontinuation may in fact be clinically unnecessary (14, 17, 19, 23). It is, therefore, critical to distinguish between benign pseudoneutropenia and emerging clozapine-induced agranulocytosis (19, 23). The former may precipitate a process leading to the loss of access, or limit the access,

Table 1 FDA Suggested Clinical Management of Abnormal WBC or ANC Results for Clozapine Patients

Situation	Hematological Values for Monitoring	Frequency of WBC and ANC Monitoring
Substantial drop in WBC or ANC	Single drop or cumulative drop within 3 weeks of WBC≥3,000/mm^3 and ANC≥1,500/mm^3	1. Repeat WBC and ANC 2. If repeat values are WBC≤3,500/mm^3 and ANC≤2,000/mm^3, then monitor twice weekly
Moderate leukopenia Moderate granulocytopenia	If WBC between 2,000/mm^3 and 3,000/mm^3, and/or ANC between 1,000/mm^3 and 1,500/mm^3	1. Interrupt therapy 2. Monitor daily until WBC>3,000/mm^3 and ANC>1,500/mm^3 3. Monitor CBC twice weekly until WBC>3,500/mm^3 and ANC>2,000/mm^3 4. May rechallenge when WBC>3,500/mm^3 and ANC>2,000/mm^3
Severe leukopenia Severe granulocytopenia	WBC<2,000/mm^3 and/or ANC<1,000/mm^3	1. Discontinue treatment and do not rechallenge patient 2. Monitor until normal and for at least 4 weeks from day of discontinuation
Agranulocytosis	ANC≤500/mm^3	1. Discontinue treatment and do not rechallenge patient 2. Monitor until normal and for at least 4 weeks from day of discontinuation WBC>3,500/mm^3

to a needed therapy, while the latter could potentially be life-threatening (10, 19, 23).

The focus of the present study was to evaluate the effect of a relatively minimal timing change in CBC sampling on WBC and ANC values in a group of clozapine recipients in a regional state psychiatric inpatient facility. The primary objective was to determine if this practice change might optimize the results obtained, minimizing benign neutropenia as a variable in the decision to continue therapy algorithm, thus, potentially enabling continued therapy with clozapine in selected cases.

Methods

After Institutional Review Board approval, a retrospective chart review was conducted at a regional state psychiatric inpatient facility. CBC sampling time for clozapine recipients at this facility had traditionally been at 0630 (military time) immediately upon awakening; CBC sampling was now moved to a minimum of two-hour post awakening and mobility. Patients were included in this study if they were receiving clozapine before and after the sampling time switch, with a minimum of six CBC values on or before 0630 and six values on or after 0830. CBC values sampled on or after 0830 were accepted as applicable post data, as patients are awakened at 0630 and a minimum of two hours of wakefulness/mobility had occurred. Data sources included patient medical records, the facility automated laboratory information system, and the Clozapine National Registry. Data extracted included WBC/ANC values (with date/time of sampling) and demographic information (DOB, sex, weight, height, BMI, ethnicity). Data were analyzed using repeated measures analysis of variance (ANOVA). Individual and group mean data for the six samples pre and post were tabulated, with the ANOVA performed, comparing the group mean for each sampling time pre and post. By comparing the group mean data for each sampling interval versus comparing an overall mean before and after sampling time change, the inherent variability of WBC and ANC values is clearly demonstrated.

Results

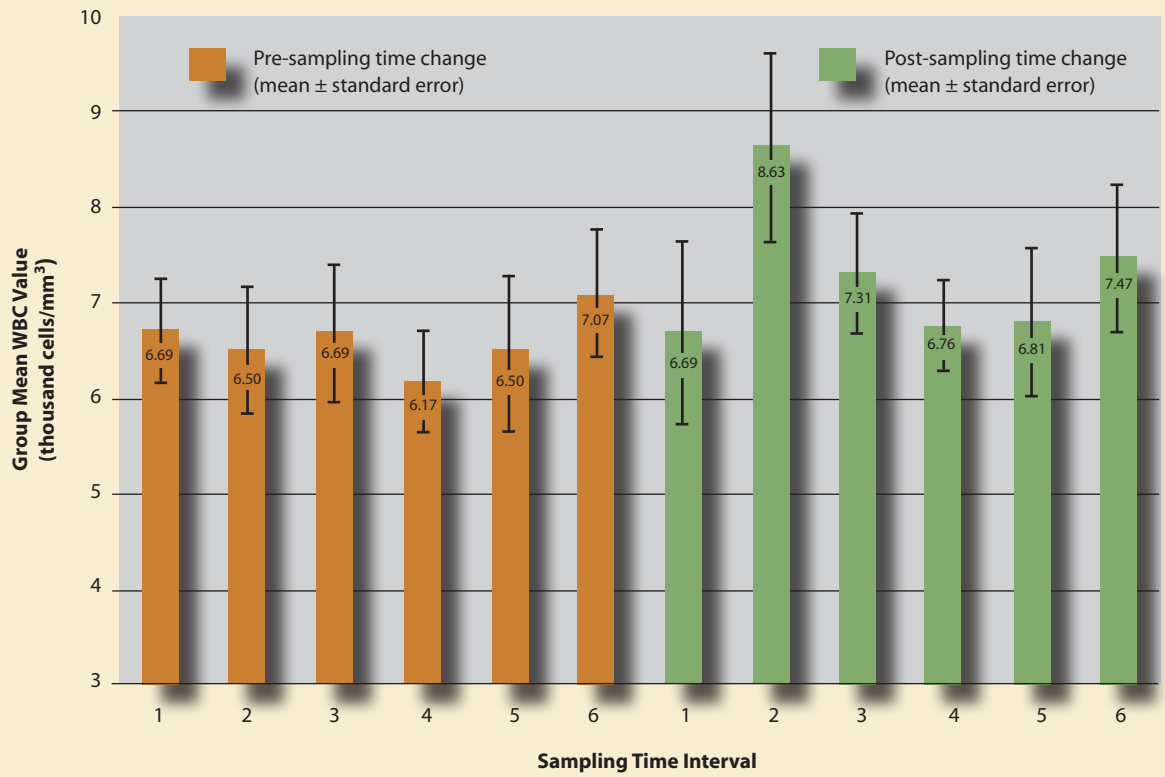
Ten patients (80% male, 90% Caucasian) met all study inclusion criteria. The subject mean age was 55.7 years (see Table 2). The difference in the group pre/post sampling time change WBC values was marginally significant (mean increase=667/mm^3, p=.07) (see Figure 1). The time periods in Figure 1 are the six sampling intervals prior to and the six intervals subsequent to the time change for sample acquisition. Inspection of Figure 1 suggests that a larger difference (pre vs. post) occurred for time periods 8–12 (i.e., that the pre to post difference emerges after time period 7).

A statistically significant difference (mean increase= 1,130/mm^3, p=.003) between the pre/post time change ANC values is depicted in Figure 2. Inspection of Figure 2 suggests that the group mean pre/post difference was variable, with larger differences occurring for time periods 8, 9, 10, and 12 than for time periods 7 and 11. Based upon a review of the data, the ANC values were more positively impacted by the sampling time change than the WBC values. The mean time difference between sample collection times across all subjects pre/post was 5 hours 24 minutes (see Table 2).

Table 2 Subject Demographics

Subject #	Age	Sex	Race	Mean Pre WBC (thousand cells/mm^3)	Mean Post WBC (thousand cells/mm^3)	Mean Pre ANC (thousand cells/mm^3)	Mean Post ANC (thousand cells/mm^3)	Mean Time of Sampling Collection Pre- (military time)	Mean Time of Sampling Collection Post- (military time)	Difference in Mean Sampling Time Pre/Post (hours/minutes)
1	61	M	W	5.9	7.7	3.9	5.8	0600	1035	4 hr/35 min
2	50	M	W	5.2	5.7	2.7	3.6	0630	1235	6 hr/05 min
3	69	M	W	5.6	6.5	2.1	2.9	0605	1230	6 hr/25 min
4	62	M	W	11.6	12.3	6.1	7.8	0600	1040	4 hr/40 min
5	67	M	W	5.1	7.3	2.6	5.1	0610	1130	5 hr/20 min
6	37	M	AA	5.9	5.2	2.9	2.8	0635	1000	3 hr/25 min
7	53	M	W	7.2	6.9	3.6	3.9	0555	1305	7 hr/10 min
8	28	M	W	5.2	7.2	2.7	4.9	0630	1130	5 hr/00 min
9	73	F	W	8.1	7.4	4.9	4.8	0620	1245	6 hr/25 min
10	57	F	W	6.3	6.7	2.6	3.8	0620	1115	4 hr/55 min

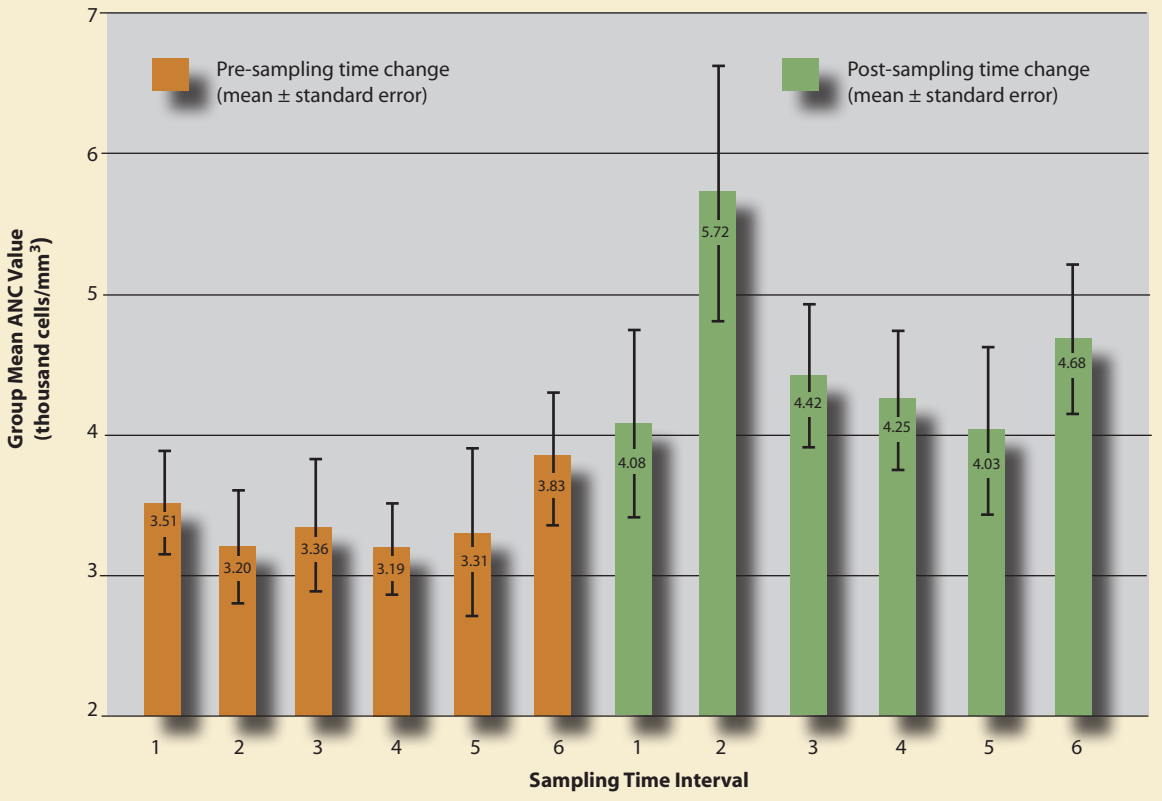
Figure 1 Mean WBC Values Pre and Post Sampling Time Change



Discussion

The current FDA monitoring guidelines require minimum values of WBCs>3,500/mm^3 before initiation in clozapine therapy and discontinuation if WBC<3,000/mm^3 or an ANC<1,500/mm^3 (9). Clozapine has been suggested to cause neutropenia by several mechanisms, including a direct toxic effect of either clozapine or its major metabolite n-demethylclozapine, destruction of WBC precursors by an immune system-mediated effect, or a combination of both mechanisms (8, 11, 14-16). It is further hypothesized that

Figure 2 Mean ANC Values Pre and Post Sampling Time Change



a distinct mechanism is responsible for the development of the more severe agranulocytosis compared to mild to moderate neutropenia. Studies have found that in agranulocytosis, neutrophil precursors and mature neutrophils are affected, while in mild to moderate neutropenia, only peripheral cells are affected (11).

Repeated challenges after discontinuation related to leukopenia are routinely avoided, leaving the patient with few effective treatment alternatives (14, 17). Therefore, the potentially benign diurnal variations in WBC values and clozapine-related transient neutropenia are of particular interest owing to the rigid CBC monitoring guidelines and the potential for clinicians to discontinue therapy unnecessarily (18, 19, 23). Circulating blood cells are known to show circadian rhythms in healthy individuals, although little is confirmed regarding the mechanisms involved (10, 19). Clozapine appears to magnify the existing circadian variations in neutrophil counts in some individuals (11, 16, 19). The mechanism of action responsible for this is unclear; however, a proposed mechanism is that of clozapine impacting the endogenous production of hematopoietic cytokines (12). Of note is that morning pseudoneutropenia has also been reported in the published literature with risperidone and olanzapine (12, 21).

Previous case reports have suggested that postponing WBC sampling from early morning until late afternoon may improve WBC values (13, 15, 20-22). The present work suggests that it may be possible to provide more robust WBC values by only a minimum delay in sampling time. The minimum two-hour window for delaying the sampling was derived by reviewing facility patient care procedures. At 0630, patients are awakened and in the ensuing two hours, bathing, dressing, and going to breakfast occur, all prior to the 0900 community meeting, which is the beginning of the treatment day. It was hypothesized that the two hours of activity and mobility would improve the WBC/ANC values sufficiently to support the procedural change. In the present study, the results suggest that a sampling delay of a few hours, perhaps corresponding with noon medication administration or the noon meal, could provide more robust results than the early morning sampling.

Given the high cost of medication discontinuation, costs of rehospitalization, risk of relapse, and inadequate treatments for chronic schizophrenia, clozapine may be underutilized. Kelly and colleagues published an excellent review of the disproportionate use of clozapine relative to the treatment-refractory schizophrenia population in the United States, along with discussion regarding why this may

be occurring (17, 23). This underutilization is especially noteworthy in the African-American population, where clozapine use has been notably lower compared to Caucasians (17). Normal ranges for WBC counts tend to be lower in the African-American population (2,800–9,500/mm^3) compared to Caucasians (3,600–9,500/mm^3) (17, 23). Due to the phenomenon known as benign ethnic neutropenia, it has been estimated that approximately 20% of African Americans may be deemed ineligible and 25% discontinued after initiation of clozapine treatment (17). Benign ethnic neutropenia (BEN) is a sustained low neutrophil count that is normal for the individual and is not associated with increased infections (24). In a population with a propensity for neutrophil counts to be consistently below the typical standard, a clozapine-mediated pseudoneutropenia could be an additional risk factor for unnecessary discontinuation of therapy

Kelly and colleagues examined discontinuation rates due to leukopenia and agranulocytosis in 1,875 patients in the state of Maryland between 1989 and 1999 (17). A discontinuation rate of 5.3% (31/588) in African Americans compared to 2.4% (31/1,287) in Caucasians occurred due to leukopenia. Findings also revealed no cases of agranulocytosis in the African Americans in this study sample compared to eight Caucasians (0.62%) that developed blood dyscrasia. It is likely that this trial reveals an inappropriate discontinuation of clozapine therapy due to pseudoneutropenia or benign ethnic neutropenia. In the present study, one subject was African American and experienced a mean decrease in both WBC and ANC values after changing the sampling time.

Novartis, the pharmaceutical company marketing the innovator clozapine product, has recently revised its prescribing guidelines in the United Kingdom and Canada to include special consideration for patients with benign ethnic neutropenia (24). Despite these observations, clinical acknowledgments, and subsequent changes in other countries, a change of FDA-required monitoring guidelines based upon ethnicity in the United States has not yet occurred (17).

Clozapine remains the treatment of choice for treatment-resistant schizophrenia (1, 3, 4, 25, 26). The superior efficacy of clozapine relative to other antipsychotics merits increased efforts to encourage greater use in appropriate patients and to more efficiently monitor for side effects. The potential risk of agranulocytosis is not to be cavalierly dismissed, nor is the decision to stop a therapy that is efficacious in a patient who was previously treatment refractory (19). As there are a number of potential possibilities when a low WBC or ANC is identified, before interruption of clozapine therapy, a clinical distinction should be made between a transient versus malignant neutropenia (10, 15, 22, 23). The present work identifies one mechanism to potentially maintain uninterrupted clozapine therapy by optimizing WBC/ANC test results. As patients with transient neutropenia are not systematically predisposed to developing agranulocytosis, interruption in therapy may thus be avoided in at least selected cases. Laboratory screening tests are being developed and validated which can make a distinction regarding risk for agranulocytosis, such as monitoring endogenous G-CSF (28) and/or the use of a hydrocortisone test (29). However, the data supporting the use of the hydrocortisone test involved a study with only three patients. Until well-validated laboratory screening tests become available for routine use, increased frequency of WBC monitoring and/or alteration of the timing of WBC monitoring is recommended (23, 29). As an example, if the absolute neutrophil count is less than 1,500/mm^3 but greater than 1,000/mm^3 in the morning, and no clinical signs of infection are present (fever, malaise), another test may be repeated in the afternoon before the decision of discontinuing therapy is made.

Limitations of our study include lack of randomization of subjects, small sample size, limited number of pre/post CBC samples per subject, and no controlling for clozapine dose/duration or therapy/concomitant medications/patient medical comorbidities. In addition, it is not clear, within the duration of the study, if the changes seen in the WBC and ANC values have clinical relevance in terms of allowing continuation of clozapine therapy for specific patients.

Conclusions

Changing the timing of CBC sampling from early morning to after a two-hour minimum period of wakefulness and mobility may have the potential to improve WBC and ANC values by minimizing potential instances of pseudoneutropenia and could potentially allow clozapine therapy to continue uninterrupted in certain cases, per the current FDA-mandated CBC monitoring guidelines. It is critically important to differentiate between benign and malignant neutropenia. The present work does not differentiate between these two conditions; rather, the methodology outlined may assist clinicians to avoid responding to transiently low WBC or ANC values by sampling later in the day. Further, until additional studies are published, it is suggested that all WBC values obtained in the early morning, which are falling or below normal, should be repeated after a delay of several hours before a final decision is made to terminate clozapine therapy. The present findings suggest that even a minimal delay in sampling time may provide more robust results and potentially allow continued clozapine therapy. A larger, more ethnically diverse study sample is needed to validate the results from the current study. Further discussion should occur at the FDA level regarding special consideration for subjects with pseudoneutropenia. Finally, another

area for additional study might be that of determining the extent of diurnal variation in those individuals who go on to develop more malignant neutropenia. It is clear that all reasonable steps should be considered in order to appropriately maintain therapy in the treatment-refractory population typically receiving clozapine therapy.

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