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The Off-Label Use of Clozapine in Adolescents with Bipolar Disorder, Intermittent Explosive Disorder, or Posttraumatic Stress Disorder

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ABSTRACT

***Objective*: There are limited data in the literature regarding clozapine use in adolescents with diagnoses other than schizophrenia. This report describes the use of clozapine in adolescents with diagnoses of bipolar disorder, intermittent explosive disorder (IED), and posttraumatic stress disorder (PTSD).**

***Methods*: A chart review of 39 adolescents treated with clozapine at two residential facilities was undertaken. Data extraction included demography, illness variables, medication information, and clinical outcomes. Categorical outcomes were analyzed using contingency statistics, and continuous variables were analyzed using a paired *t* test.**

***Results*: The cohort included 26 females and 13 males with a mean age of 14 years. Clozapine was titrated slowly, and the mean daily dose was 102 mg. The diagnoses included bipolar disorder ($n = 7$), IED ($n = 9$), and PTSD ($n = 19$). There were significant reductions in polypharmacy once the clozapine dosage was stabilized. Prior to clozapine treatment, nearly 70% of the subjects were receiving either mood-stabilizing or antidepressant agents in combination with the previous antipsychotic drug. Once the clozapine dosage was stabilized, only 24% of the subjects required concomitant mood stabilizers ($p < 0.001$), and only 21% of the subjects required concomitant antidepressants ($p < 0.001$). Anxiolytic medication use was also significantly reduced during clozapine treatment. Most patients were discharged to a less restrictive setting. Eight subjects discontinued clozapine due to agranulocytosis ($n = 1$), neutropenia ($n = 2$), excessive weight gain ($n = 2$), or not requiring it long term ($n = 1$), and data were unavailable in 2 subjects. Significant weight gain (5% or greater change from baseline) was noted in 20 subjects.**

***Conclusions*: Clozapine, in relatively modest doses, appears to have clinical benefits for adolescent with bipolar disorder, IED, and PTSD. There is no labeled indication for clozapine use in these disorders. Clozapine is also associated with serious side effects in subsets of individuals. Therefore, a very careful evaluation of the risk-to-benefit ratio in each individual subject being considered for clozapine is highly recommended.**

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INTRODUCTION

CLOZAPINE IS USED in adults with treatment refractory schizophrenia (Kane et al. 1988). It has also shown to be effective in children and adolescents with treatment refractory schizophrenia (Chalasani et al. 2001; Kumra et al. 1996). Data regarding the off-label use of clozapine in conditions other than schizophrenia, especially in adolescents, are limited. The purpose of this article is to describe a clinical audit of clozapine treatment in a cohort of adolescent subjects with bipolar disorder, intermittent explosive disorder (IED), and posttraumatic stress disorder (PTSD) who were treated in two long-term residential care facilities.

METHODS

This was a retrospective chart review of 39 adolescents who were treated with clozapine at two long-term residential facilities by two child and adolescent psychiatrists. To familiarize the reader with the adolescents who were transferred to these two residential facilities, a description is provided below.

Typically, these subjects were admitted to these facilities following highly disruptive behaviors accompanying their severe mental illness that had not responded to multiple psychiatric treatments. In fact, all patients had been treated in several facilities and had been hospitalized mostly due to uncontrollable aggression, destructive behavior, and/or self-mutilation. They could no longer reside in group homes, foster homes, or other open residential treatment facilities. They had failed multiple psychotropic medication trials in different combinations, sometimes at high doses or blood levels. The medications included mood stabilizers such as lithium or valproate, antipsychotic agents, antidepressants, and anticonvulsants such as carbamazepine. Many of these patients were refused readmission to acute inpatient units due to their explosive behaviors. The intensity of services needed by them and the failure to respond to medication trials resulted in referral to these two locked residential treatment facilities. The average duration of stay in these two residential facilities was 5 months.

Clozapine was used to target symptoms of extreme mood lability, explosive hostility, self-mutilation, delusions, or hallucinations. Due to complex comorbidity, some symptoms were common among the three different diagnostic groups noted below in the results, whereas some target symptoms were diagnostically specific. The data were extracted from the charts of 39 subjects who received clozapine for demographic and illness variables, psychotropic medication use, restrictive interventions (seclusion and restraint), height and weight, as well as pulse and blood pressure measurements. The diagnoses of patients were made by two child psychiatrists based on *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV; American Psychiatric Association 1994), criteria. All available information was used in making the diagnoses, including interviews with the subjects and their family members and medical records. Body mass index (BMI) was calculated using the nonmetric conversion: BMI (kg/m^2) = Weight (in lbs) $\div$ Height (in inches)$^2 \times 704.5$. Also, any reported or elicited side effects that were noted in the charts were recorded. Global Assessment of Functioning (GAF [DSM-IV, axis V]; American Psychiatric Association 1994) scores prior to and at the end of the clozapine treatment were recorded. The types of discharge placements were noted. To protect the confidentiality of the subjects, a person independent of the study delinked personal identifiers to the data, assigned a research identification number, and then provided it to the authors for analyses. The Institutional Review Board of the University of Pittsburgh approved the study.

Data analyses involved an enumeration of the demographic and illness characteristics of the cohort. The use of each class of concomitant psychotropic medicines prior to and during clozapine treatment was analyzed as categorical variables using a Fisher's exact chi-square test. Continuous variables such as weight and BMI were analyzed using the paired *t* test.

RESULTS

The mean age of the subjects was 14 years, and their mean duration of illness was 5 years. They had been hospitalized an average of three times prior to this hospitalization (see Table 1). They were admitted to these facilities over a period of 4 years. The majority were Caucasian, and two thirds of the subjects were female. As a group, their mean Full Scale IQ on the Wechsler Adult Intelligence Scale, third revision (Wechsler 1997), was 70, which falls in the upper end of the mild mental retardation category. Six subjects (15.4%) had an IQ below 70. Nineteen subjects had a primary axis I diagnosis (DSM-IV); American Psychiatric Association 1994) of posttraumatic stress disorder (PTSD), 9 subjects had a diagnosis of intermittent explosive disorder (IED), 7 subjects had a diagnosis of bipolar I disorder, and 4 subjects had other psychiatric diagnoses.

TABLE 1. DEMOGRAPHIC AND ILLNESS CHARACTERISTICS OF THE ADOLESCENT SUBJECTS (*N* = 39)

Age in years (mean ± SD)	14 ± 2
Sex, *n* (%)	
Male	13 (33.3)
Female	26 (66.7)
Ethnicity, *n* (%)	
Caucasian	35 (89.7)
African American	4 (10.3)
Primary diagnosis (DSM-IV), *n* (%)	
Bipolar I disorder	7 (17.9)
IED	9 (23.1)
PTSD	19 (48.7)
Others[a]	4 (10.3)
Onset of illness (years of age)	
Mean ± SD	9 ± 3
Duration of illness (in years)	
Mean ± SD	5 ± 1
Number of previous hospitalizations	
Mean ± SD	3 ± 2
Education (mean ± SD)	
Grade	8 ± 1
WAIS, 3rd revision (mean ± SD)	
IQ Verbal	72 ± 16
IQ Performance	71 ± 16
Full Scale IQ	70 ± 16

DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition; IED = intermittent explosive disorder; PTSD = posttraumatic stress disorder; WAIS = Wechsler Adult Intelligence Scale.

[a]Other diagnoses include depressive disorder not otherwise specified and pervasive developmental disorder.

After a careful discussion of the risks and benefits with the family members or guardians and the subjects, and after obtaining consent, clozapine was initiated. Nearly all subjects were receiving multiple psychotropic agents at clozapine initiation (see Table 2). Clozapine was titrated relatively slowly, and the target dose was typically set at a lower dosage range than that used in adults with schizophrenia. The mean daily dose of clozapine was 102 mg (±57), and the range was 25–250 mg/day. Typically, the target doses were achieved in 2 months as the previous antipsychotic agent was cross-tapered slowly. Prior to clozapine initiation, 13 subjects were receiving risperidone, 7 subjects were receiving olanzapine, 6 subjects were receiving quetiapine, and 7 subjects were receiving first-generation antipsychotic agents. Most of these agents had been used for more than 3 months at adequate daily doses. These antipsychotic agents were tapered within a 1- to 2-month period following clozapine initiation. Clozapine was administered for an average of 120 days to this group of adolescents. The subjects had been residents

TABLE 2. THE USE OF CONCOMITANT MEDICATIONS PRIOR TO AND DURING CLOZAPINE TREATMENT

Class of medications	*Prior to clozapine* (N = *39*)	*During clozapine* (N = *34*)	χ^2	df	*Fisher's exact* p *(two-tailed)*
Mood stabilizers	27 (69%)[a]	8 (24%)[b]	15.2	1	0.0001
Antidepressants	27 (69%)	7 (21%)	17.3	1	0.0000
Anxiolytics	9 (23%)	0 (0%)	6.94	1	0.0027
Stimulants	8 (21%)	4 (12%)			ns

Note. Data from 5 subjects were unavailable for clozapine treatment.

[a]Lithium (*n* = 6), valproate (*n* = 16), carbamazepine (*n* = 2), and gabapentin (*n* = 3).

[b]Lithium (*n* = 5) and valproate (*n* = 3).

in these two facilities for an average of 55 days prior to receiving clozapine. Other psychotropic agents such as mood stabilizers, antidepressants, anxiolytic agents, and stimulants were tapered and discontinued over 1–month if it was clinically appropriate to do so.

As noted in Table 2, following clozapine initiation there was a statistically significant reduction in the use of concomitant mood stabilizers, antidepressants, and anxiolytic agents. Even though there was a reduction in the use of stimulant medications after the subjects received clozapine, these results were not statistically significant. Subjects with bipolar disorder showed clinically discernable improvements in manic or mixed symptoms, and those with a rapid cycling course exhibited longer euthymic intervals. Interestingly, among the seven bipolar subjects, four were discharged on a combination of lithium and clozapine, and two were discharged on clozapine monotherapy. One bipolar subject received clozapine for a brief period and then received an antidepressant and mood-stabilizer at discharge. Hallucinations and flashbacks in subjects with PTSD improved. Incidents of aggression and self-mutilation decreased impressively following clozapine use in all three diagnostic groups.

There were minor changes in the resting pulse rate and in measurements of systolic and diastolic blood pressure prior to and during the first 4 weeks of treatment with clozapine. However, none of these parameters achieved statistical significance (see Table 3). Nonetheless, four subjects did experience clinically significant orthostatic hypotension; this side effect was resolved by lowering the dose of clozapine. One of these hypotensive subjects had previously received clonidine for attention deficit hyperactivity disorder, and discontinuation of this agent resolved orthostatic hypotension. Two adolescents experienced neutropenia (and clozapine was discontinued), and one additional subject discontinued clozapine due to agranulocytosis. Eighteen subjects experienced sedation especially in the first 4–6 weeks of clozapine treatment. Six subjects experienced troublesome salivation, but none of the subjects discontinued clozapine due to this side effect. Four subjects experienced constipation that required assertive laxative treatment. Interestingly, 11 subjects did not experience side effects.

Table 3. Change in Global Assessment of Functioning (GAF) Scores, Body Mass Index, Pulse, and Blood Pressure Prior to and During Clozapine Treatment ($N = 39$)[a]

Variable	*Prior to clozapine*	*During clozapine*
GAF		
Mean ± SD	36 ± 9	58 ± 7
Range	20–50	35–70
Weight (in lbs), $n = 33$		
Mean ± SD	152 ± 44	168.4 ± 50
Range	44–233	44–268
Body mass index (kg/m^2), $n = 27$		
Mean ± SD	27 ± 6	30 ± 7
Range	12.7–44.5	13.4–48.9
Resting pulse (beats/min), $n = 28$		
Mean ± SD	91 ± 15	Week 1: 93 ± 24 Week 2: 90 ± 25 Week 3: 90 ± 24 Week 4: 98 ± 23
Sitting systolic BP (mm Hg), $n = 30$		
Mean ± SD	110 ± 16	Week 1: 107 ± 24 Week 2: 105 ± 24 Week 3: 107 ± 21 Week 4: 115 ± 11
Sitting diastolic BP (mm Hg), $n = 30$		
Mean ± SD	67 ± 9	Week 1: 67 ± 17 Week 2: 66 ± 16 Week 3: 68 ± 9 Week 4: 70 ± 8

BP = blood pressure.
[a]Data are missing for a few subjects.

As a group, there was a clinically and statistically significant increase in body weight and BMI (see Table 4). Body weight increased by a mean of 16.4 lbs (±20); $t = 4.7$, $df = 32$, $p < 0.001$. BMI increased by a mean of 3.06 (±3.4); $t = 4.6$, $df = 26$, $p < 0.001$. Five subjects lost weight (−2% to −6.7%) of baseline body weight, 1 subject had no weight change, 7 subjects gained between 1% and 5%, 8 subjects gained between 5% and 10%, 7 subjects gained between 10% and 20%, and 5 subjects gained more than 20% of their baseline body weight.

Data on body weight changes in 6 subjects were unavailable. As a group, the subjects moved from an overweight BMI category (mean of 27) to an obese category (mean of 30) during clozapine treatment.

Other than the 3 subjects who discontinued clozapine due to either neutropenia or agranulocytosis, 5 additional subjects discontinued clozapine. Two subjects discontinued clozapine due to excessive body weight gain (63 lbs and 35 lbs, respectively). Neither of these subjects showed clinical laboratory evidence of diabetes mellitus or dyslipidemia. One subject with psychotic bipolar depression did not require clozapine treatment following remission. Reasons for discontinuing clozapine in 2 subjects were unavailable.

Seclusion and passive physical restraint episodes occurred in a few subjects at different time points. These events were enumerated using seclusion or restraint events per days of hospitalization per subject prior to clozapine treatment and during clozapine treatment. Twenty-one subjects experienced restraint events at a mean of 1.0 (±2.6) prior to clozapine treatment, and 12 subjects experienced these events after clozapine initiation at a mean of 0.34 (±0.70); the reduction was not statistically significant. Similarly, 8 subjects experienced a mean of 0.50 (±1.0) seclusion events prior to receiving clozapine, and 7 subjects experienced a mean of 0.06 (±0.08) interventions after receiving clozapine; however, the reduction was statistically nonsignificant.

GAF scores increased significantly from a mean of 36 (±9.9) at baseline to 58.8 (±7.5) at discharge; $t = -11.0$, $df = 36$, $p < 0.001$. Clinically, patients showed a robust improvement in their social, behavioral, and emotional functioning compared with the period prior to clozapine. All patients were discharged to an open and less restrictive environment, including home with either the biological or foster family.

DISCUSSION

Similar to the use of clozapine in adults with conditions other than schizophrenia (Chengappa et al. 1999; Frankenburg and Zanarini 1993; Zarate et al. 1995), even in this group of adolescents without schizophrenia, clozapine appears to have provided some useful clinical benefits. It is interesting that the majority of subjects had failed to respond to the second- or first-generation antipsychotic agents, yet several of them eventually responded to clozapine. There was a significant reduction of polypharmacy, especially the decreased use of mood stabilizers, antidepressants, and anxiolytic agents. Even though the GAF score increases were relatively modest, the majority of the subjects were discharged either home or to a less restrictive but structured facility. Although there were reductions noted in seclusion and restraint events, the results were not statistically significant. Clinically, however, there were notable improvements in aggres-

TABLE 4. SIDE EFFECTS DURING CLOZAPINE TREATMENT

Type of side effects	N = *39*[a]	*Comments*
Body weight gain (>5% baseline)	20	Two subjects discontinued
Leukopenia	2	Both subjects discontinued
Agranulocytosis	1	Discontinued
Seizures	0	
Hypotension	4	Dose was lowered, and side effect was resolved
Hypersalivation	6	Troublesome, especially in first few weeks, none discontinued
Sedation	18	Resolved with the passage of time
Constipation/flatulence	4	Resolved with laxative use
No side effects	11	
Data not available	2	

[a]Some subjects had more than one side effect.

sive and suicidal behavior and gestures that permitted discharge to a less restrictive setting. Other clinically notable improvements were in the areas of improved socialization and participation in individual, group, and milieu therapy. Notable improvements were also noted in their ability to relate to staff, peers, and family.

Clozapine has been used off-label in conditions other than schizophrenia. In a review of such off-label use, Frankenburg and Zanarini (1994) described clozapine being given to patients with borderline personality, bipolar disorder, psychogenic polydipsia, and other conditions. In these situations, it is likely that a combination of factors may be responsible for the clinical improvements noted on clozapine treatment. These include significant improvements in psychoses, manic or mixed depressive mood symptoms, aggressive and suicidal acts, and behavior. Due to a broad neuroreceptor antagonist pharmacological profile, clozapine may be associated not only with several side effects but may also provide benefits for symptom domains beyond the traditional psychoses symptom cluster.

In terms of safety and tolerability, orthostatic hypotension, hypersalivation, sedation, and constipation were important clinical issues for some patients. These side effects could be managed symptomatically or by a reduction in the dosage of clozapine, and they did not lead to discontinuation of clozapine. However, as per treatment guidelines, 3 adolescents experienced either severe neutropenia or agranulocytosis, and this led to the discontinuation of clozapine. Curiously, 11 subjects had no reported or elicited side effects. The slow titration and lower daily target dosage of clozapine may have mitigated some of the side effects. Furthermore, a reduction in polypharmacy may have helped in this regard as well. Clearly, as noted by others in the adult literature, weight gain was substantial with clozapine treatment even in this adolescent population. Two subjects discontinued clozapine due to excessive weight gain. This issue certainly may be a limiting factor in the long-term use of clozapine, especially if medical conditions associated with obesity either emerge or worsen. Weight gain should be addressed assertively right at the initiation of clozapine treatment and should be monitored regularly in treatment.

The limitations of this study are that it was a retrospective chart review. Further, no specific scales were used to assess psychopathology, and there was no random assignment to clozapine or a comparator treatment. Finally, as the number of subjects of each diagnostic group was relatively small, it is difficult in such a retrospective chart study to specifically evaluate whether target symptoms that improved (mood lability, hostility or aggression, or psychoses) in these subjects were due to clozapine. Due to the comorbid conditions noted in these subjects, more than one set of target symptoms improved in some subjects; therefore, a selection bias toward clozapine responders may have occurred. Also, as seclusion and restraint events typically occur early in the course of admission, any improvement in these restrictive interventions may have been erroneously attributed to clozapine. However, other data also support a reduction in aggression with clozapine treatment (Chengappa et al. 2001; Frankenburg and Zanarini 1993). Further, it is possible that all the extra attention that accompanies the initiation and administration of clozapine may have been responsible for the clinical improvements that were recorded, but it is pertinent to note that these subjects had received considerable and significant attention even prior to clozapine treatment from various agencies, caregivers, and parents due to the highly disruptive behaviors they exhibited. Nevertheless, it is possible that the milieu and nonpharmacological interactions may also have influenced the clinical outcomes independent of a clozapine effect. Finally, as we do not have systematic follow-up after discharge, it is not clear from these data what the benefits or risks are from longer term clozapine treatment. Still, if data were extrapolated from the adult psychiatric literature, clozapine does appear to reduce suicidal behavior over the longer term (Meltzer et al. 2003). It is possible that clozapine may help appropriately selected adolescent subjects as well.

In summary, these data suggest that clozapine may benefit some adolescents with bipolar disorder, IED, or PTSD who are refractory to treatment and who display severe aggression or self-mutilation. However, it is also important to note that there is no labeled indication for the use of clozapine in these diagnostic groups. Therefore, it would be clinically prudent to weigh the risk-to-benefit ratio in each subject prior to obtaining consent for clozapine treatment, especially as there are serious side effects to consider in both the short- and long-term use of clozapine.

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