# Clozapine Reduces Severe Self-Mutilation and Aggression in Psychotic Patients With Borderline Personality Disorder

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***Background:*** Clozapine has been reported to be effective in diminishing violence toward others in psychotic patients. This article describes the impact of clozapine on severe self-mutilation among patients with the dual diagnoses of borderline personality disorder and persistent psychoses.

***Method:*** Seven subjects known to the authors were selected for careful chart audits. These subjects had been admitted to 2 state psychiatric hospitals owing to severe self-mutilation and/or violence and subsequently treated with clozapine. A mirror-image design anchored to the start date of clozapine treatment and extending in either direction to a maximum of 1 year was used to extract data. Data extracted included incidents of self-mutilation (restraint), seclusion, the as and when needed (p.r.n.) use of medications, injuries to staff and peers, hospital privileges, and Global Assessment of Functioning (GAF) scores.

***Results:*** The subjects were all white women with a mean age of 37 years. All subjects carried DSM-III-R or DSM-IV borderline personality disorder diagnoses and an Axis I disorder diagnosis. They had received trials of several psychotropic agents, often in combination and mostly without benefit. After clozapine treatment, there were statistically significant reductions in incidents of self-mutilation (restraint), seclusion, the use of p.r.n. antianxiety medications, and injuries to staff and peers. These subjects received higher levels of hospital privileges, and their GAF scores nearly doubled following clozapine treatment. Four subjects were subsequently discharged from hospital.

***Conclusion:*** These preliminary but nonetheless favorable results suggest that clozapine deserves careful consideration for a controlled study in patients with borderline personality disorder and psychoses, especially if the clinical issues include severe self-mutilation, aggression, and violence. Until such studies are done, the risk-to-benefit ratio of clozapine treatment needs to be carefully evaluated on an individualized basis in such subjects.

*(J Clin Psychiatry 1999;60:477–484)*

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*The authors thank Mr. William Suvak, Librarian, Mayview State Hospital for obtaining articles of interest; the staff of the Medical Records Department, Mayview State Hospital for help with data extraction; Ms. S. Dumpman and Drs. A. Gopalani, J. Karambelkar, and A. Palmer for their advice and comments; and Tracy Anderson for help with data organization.*

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Clozapine, the prototype of the newer class of "atypical" antipsychotic agents, is arguably the most effective of this class of agents for neuroleptic-refractory or intolerant psychoses.[1] The broad spectrum of its neuroreceptor pharmacology, negligible extrapyramidal side effect induction, and dramatic improvements noted in some patients has led to its off-label use in related psychiatric conditions. For instance, clozapine has been noted to be effective in bipolar psychoses,[2] L-dopa–induced psychoses among subjects with Parkinson's disease,[3] and psychoses associated with the dementias.[4] The therapeutic benefits of clozapine beyond its direct impact on psychoses have also been noted; for instance, reduction of seclusion and restraint,[5–8] hostility,[9,10] self-mutilation,[11] and polydipsia in psychiatric patients has been reported.[12] We were impressed by clozapine's beneficial effects on hostility and aggression during and after our participation in the pivotal trial that led to the approval of clozapine in the United States,[1] and particularly in a subject with severe self-mutilation accompanying borderline personality disorder.[11] At the time the data were extracted for the present study, one previous report had evaluated the impact of clozapine in patients with the dual diagnosis of atypical psychoses and borderline personality disorder according to DSM-III-R.[13] In that study, patients treated with clozapine had shown significant im-

provements in Brief Psychiatric Rating Scale (BPRS) and Global Assessment of Functioning (GAF) scores. Since the submission of the present study and subsequent review process, a recent study[14] has been published indicating the benefits of low doses of clozapine (mean dosage = 44 mg/day) in 12 subjects with borderline personality disorder in the absence of a DSM-IV Axis I diagnosis.[15]

The purpose of the present case series is to describe the impact of clozapine on self-mutilation and related aggressive behavior in psychotic patients with additional diagnoses of borderline personality disorder at 2 state psychiatric hospitals. This study had a qualitative, descriptive aspect as well as a quantitative dimension to its design. For instance, quantitative data were available for certain parameters such as the use of as and when needed (p.r.n.) medications, the numbers of episodes of restraint and seclusion and the time in hours and minutes spent in each intervention, hospital privileges, and GAF scores. These served as proxy data for clinically relevant and important functional outcomes in the absence of specific and general psychopathology scales (e.g., BPRS).

## METHOD

The medical records of 7 patients with severe self-mutilation and aggressive behavior in 2 state hospitals were reviewed for relevant clinical details. Two subjects were residents in a forensic unit at one of the state hospitals. Five subjects were residents in another state hospital and were among nearly 250 patients who received clozapine after it was generally available at that hospital. The subjects were known to the authors, the senior clinicians, and the administrative staff of the hospitals owing to the extremely aggressive nature of their behaviors, which often led to clinical or administrative reviews and consultations.

The demographic and illness characteristics of these subjects were noted and verified by careful chart review. The diagnoses were verified by review of all available medical records and knowledge of the patients by the authors, and in 3 cases, additional data were obtained from the previous treating psychiatrists. Quantitative data extraction was anchored to the start date of clozapine and extended to a maximum of 1 year in either direction. Detailed review of concomitant and p.r.n. psychotropic medication use prior to and during clozapine use and, in a couple of instances, after discontinuation of clozapine was obtained. A similar strategy was used to obtain details of the seclusion and restraint incidents, description of the actual incidents of self-mutilation from the clinical notes, injuries to staff or peers due to assaultive behavior, and clinical outcome based on progress notes, hospital privilege levels, and general assessment of functioning (GAF, DSM-III-R or DSM-IV Axis 5). Information about seclusion and restraint interventions was recorded on a database maintained by the state hospitals and the Office of Mental Health and Substance Abuse Services, Harrisburg, Pa., for quality assurance and monitoring purposes. This database captures each incident of restraint and seclusion in hours and minutes and codes the interventions, as well as the final justification (for instance, failure of one-on-one intervention, the use of p.r.n. medications, etc.), prior to the use of each of these particular interventions. A careful review of the justification codes suggested that restraint interventions were nearly always applied in instances of severe self-mutilating behavior and that seclusion was invariably used during episodes of aggression toward peers or staff. Thus, the quantitative data on the restraint intervention were a proxy for self-mutilating behavior.

These data were extracted for the mirror-image period (i.e., anchored to the start date of clozapine) to a maximum of 1 year for each subject in this study. Hospital privileges included passes to walk on the grounds unescorted, to go off grounds with staff, to go on overnight visits with family, or to participate in at least 50% of recreational activities, occupational therapy, or vocational adjustment services. The awarding of these privileges was scored as 0 (not awarded) to 1 (awarded), with a minimum score of 0 to a maximum score of 5, and each point increase or decrease amounted to a 20% change in privileges. GAF scores were dictated by the psychiatrist at each admission and subsequently at the annual evaluation following admission, and were scored from 1 to 100 in DSM-IV,[15] with higher scores indicating improved symptoms and judgment and a better level of functioning. The nonparametric Wilcoxon signed rank test (2-tailed) was used to assess statistical significance among the variables such as privilege levels, use of seclusion or restraint interventions (number of incidents and duration in hours), use of p.r.n. medications, number of injuries to staff and peers, and GAF scores pre- and post-clozapine usage.

## RESULTS

All 7 subjects were white women and ranged in age from 26 to 47 years with a mean age of 36.6 years (Table 1). They had DSM-III-R or DSM-IV Axis I diagnoses of psychosis not otherwise specified (N = 2), schizoaffective disorder (N = 2), bipolar I disorder (N = 1), chronic paranoid schizophrenia (N = 1), or impulse-control disorder (N = 1). A review of previous hospital admissions indicated that the diagnoses were stable except for the subject with schizoaffective disorder bipolar type, who had been diagnosed with bipolar I disorder during earlier admissions. All subjects had an Axis II diagnosis of borderline personality disorder. Five of the subjects had experienced severe and prolonged sexual and/or physical abuse during childhood. The personality disorder diagnosis had per-

  

**Table 1. Demographics and Clinical Characteristics[a]**

| Case | Age (y) | Diagnosis (Axis I, II) | Duration of Illness (y) | Previous Hospitalizations (N) | Descriptions of Self-Mutilation or Aggression | Previous Medication Trials |
|---|---|---|---|---|---|---|
| 1 | 38 | Psychosis, NOS<br>Borderline personality disorder | 28 | 0 | Cutting wrists<br>Banging head<br>Drug overdoses | High-potency neuroleptics, oral and im<br>Lorazepam |
| 2 | 26 | Impulse-control disorder, NOS<br>Borderline personality disorder | 14 | 12 | Cutting wrists<br>Burning self with cigarettes<br>Banging head, arms, knuckles<br>Kicking and hitting others | High-potency neuroleptics, oral and im<br>Valproate, lithium<br>Clonazepam<br>SSRI antidepressants |
| 3 | 33 | Schizoaffective disorder, bipolar type<br>Borderline personality disorder<br>H/O polysubstance abuse | 15 | 21 | Burning self on the chest with a lighter<br>Running headlong into a glass partition in the nursing station, head butting<br>Punching peers and staff | High- and low-potency neuroleptics, oral and im<br>Valproate, lithium, carbamazepine<br>SSRI antidepressants<br>Lorazepam, clonazepam |
| 4 | 38 | Psychosis, NOS<br>Borderline personality disorder | 16 | 13 | Cutting wrists, forearm, and feet<br>Inflicting abdominal wounds on self that would be intentionally reopened<br>Burning self with cigarettes or a lighter<br>Drug overdoses | High- and low-potency neuroleptics, oral and im<br>Risperidone, 12 mg/d (6 mo)<br>Valproate, carbamazepine, lithium<br>Lorazepam, oral and im<br>SSRI antidepressants<br>High-dose β-blockers |
| 5 | 37 | Schizoaffective disorder, depressed<br>Borderline personality disorder | 15 | 11 | Slashing wrists/forearm<br>Frequent banging of head, hand<br>Unprovoked hitting of staff and peers<br>Drug overdoses | High- and low-potency neuroleptics<br>Lorazepam, oral and im<br>Tricyclic antidepressants<br>SSRI antidepressants<br>Lithium, valproate, carbamazepine |
| 6 | 47 | Bipolar I, mixed with psychotic features<br>Borderline personality disorder | 32 | 11 | Banging head<br>Pulling out clumps of hair<br>Attacking staff and peers<br>Screaming | Lithium, valproate, carbamazepine<br>Clonazepam, lorazepam<br>High- and low-potency neuroleptics, oral and im<br>Risperidone, 10 mg/d (5 mo)<br>Verapamil |
| 7 | 37 | Chronic paranoid schizophrenia<br>Borderline personality disorder<br>H/O alcohol abuse | 14 | 8 | Slashing of wrists, forearms<br>Inflicting burns on self<br>Drug overdoses | High- and low-potency neuroleptics<br>Lithium, valproate<br>Lorazepam<br>SSRI antidepressants<br>Tricyclic antidepressants |

[a]All cases were white women. Abbreviations: H/O = history of, NOS = not otherwise specified, SSRI = selective serotonin reuptake inhibitors.

sisted from the earliest admissions, the duration of illness ranged from 14 to 32 years, and 6 subjects had numerous psychiatric hospitalizations. Descriptions of the aggressive and self-mutilating behavior are provided in Table 1; these behaviors usually resulted in hospitalization. If the subjects were already in hospital, these incidents resulted in the use of restrictive interventions such as seclusion or restraint combined with the use of parenteral lorazepam or neuroleptic agents. In addition to injuries to the subjects themselves, some of these incidents resulted in injuries to peers or staff. All subjects had trials of neuroleptic agents, often in combination with mood-stabilizing drugs, benzodiazepines, and selective serotonin reuptake inhibitor antidepressants. While the data are not shown here, all took moderate-to-high doses of these agents for extended periods (months) with equivocal benefits. Some experienced neuroleptic-induced extrapyramidal side effects (N = 5) or akathisia (N = 3) that responded to either anticholinergic agents or β-blocker drugs.

Clozapine treatment was initiated following a discussion of the risks and benefits with each subject, and in consultation with a colleague. In most instances, clozapine was titrated over 5 to 8 weeks and was added to the previous cocktail of medications that were gradually tapered and discontinued, except for mood-stabilizing agents (lithium and valproate) in the subjects with diagnoses of bipolar or schizoaffective disorder. Aside from the usual side effects of sedation, excessive salivation, and orthostatic dizziness, there were no problems with the titration and stabilization phase of clozapine treatment. Two patients gained about 20 lb (9 kg) over the 6 to 12 months after initiation of clozapine, and 1 subject gained 30 lb (13.5 kg) during this period. One subject experienced a speech impediment that resolved upon lowering the dose. Clozapine treatment in subject 3 was discontinued owing to leukopenia (total white blood cell count = 3000/μL; absolute neutrophil count = 1500/μL). She decompensated rapidly, most of the clinical gains with clozapine were lost in a month, and attempts to control her self-mutilating behavior with risperidone in doses up to 10 mg/day failed. Eventually, she was rechallenged with clozapine, with significant improvements again evi-

dent in 6 weeks, and she remained on clozapine therapy without neutropenia prior to her discharge from the hospital. Subject 4 was discontinued as the phlebotomy was very difficult, and she eventually refused to take the drug. She, too, experienced fairly rapid decompensation, and several of the aggressive and self-mutilating behaviors returned. These behaviors have been partially controlled with risperidone, 9 mg/day, combined with valproate, and she remains in the hospital.

The doses of clozapine and the duration of treatment for each subject are described in Table 2. The mean dose of clozapine was 421 mg/day (range, 300–550 mg/day). As noted from Table 2, there were significant reductions in the use of seclusion and restraint interventions following clozapine treatment. The number of seclusion incidents decreased from a mean ± SD of 26 ± 26 to 2.3 ± 2 ($p < .02$), and the number of hours secluded decreased from 185 ± 171 to 5.6 ± 7.2 hours ($p < .02$). The number of restraint incidents decreased from 37.4 ± 49.7 to 1.3 ± 1.9 ($p < .03$), and the number of hours restrained decreased from 242.2 ± 310.5 to 5.3 ± 10.5 hours ($p < .03$). There was a significant reduction in the use of p.r.n. lorazepam prescriptions (mean ± SD of 82 ± 62.2 to 28 ± 21; $p < .05$), and a trend toward reduced p.r.n. use of neuroleptic drugs (mean ± SD of 18.4 ± 13.5 to 2 ± 1.6; $p < .07$) after the initiation of clozapine. Injuries to peers and staff also diminished significantly following clozapine treatment from 4.14 ± 3.9 to 0.3 ± 0.49 incidents ($p < .03$). Functional outcome improvements were noted in 2 additional ways: (1) subjects received higher hospital privileges following clozapine treatment, improving from a mean ± SD of 0.43 ± 0.5 to 3.4 ± 1.8 privileges ($p < .03$), and (2) there were modest though significant improvements in the GAF scores, which nearly doubled from 27.8 ± 5.7 to 53.6 ± 5.6 ($p < .02$). The hospital privileges were scored from 0 (no privileges) to 5 (maximum privileges); thus, each point gained amounted to a 20% increase, and in this instance, the mean amounted to a 60% increase. The GAF scores in DSM-IV[15] are scored from 1 to 100, with higher scores indicating improvement. Scores in the 20s indicate behavior affected by delusions and hallucinations or serious impairment in communication or judgment or inability to function in most areas. Scores in the 50s indicate moderate symptoms and moderate difficulty in social, occupational, or school functioning.

One subject remains in a forensic setting for legal reasons, and the other forensic subject has reduced security but still remains in hospital. Four subjects were discharged from hospital receiving clozapine, and 1 remains in the state hospital receiving risperidone, having discontinued clozapine. Among the 4 subjects who were discharged, 2 have remained in the community without hospitalization for 6 and 4 years, respectively, and continue to receive clozapine, and 2 subjects have had 2 brief community hospitalizations and continue to receive clozapine and mood stabilizers. At the time of discharge, 2 patients continued to evidence psychotic symptoms, but these did not have an impact on their ability to be discharged into the community.

## DISCUSSION

### Diagnoses

All but one of the subjects had persistent psychoses in addition to a diagnosis of borderline personality disorder. Unlike the transient psychosis-like phenomena that occur in patients with borderline personality disorder,[15] these subjects had psychotic episodes or symptoms that were long-standing and consistent with the Axis I diagnoses. Prolonged (rather than transient) psychotic states have been described in patients with borderline personality disorder.[16,17] However, the validity of a diagnosis of borderline personality disorder in the face of an Axis I diagnosis of persistent psychosis remains controversial, and the literature and research in this area remain sparse. Nonetheless, using the Structured Clinical Interview for DSM-III-R (SCID-I for Axis I for DSM-III-R),[18] the Revised Diagnostic Interview for Borderlines,[19] and the Revised Diagnostic Interview for Personality Disorders,[20] Frankenburg and Zanarini[13] established that 15 subjects (nearly 14%) from a cohort of 110 patients with treatment-resistant psychosis met the dual criteria for atypical psychosis (psychosis not otherwise specified) as well as borderline personality disorder under DSM-III-R nosology. Interestingly, nearly 50% of subjects (7/15) in Frankenburg and Zanarini's study[13] also met criteria for schizotypal disorder. A previous study also suggested a close link between borderline and schizotypal personality disorder.[21]

In the context of heritability, a family study evaluating the relationship among personality disorders, schizophrenia, and related psychoses suggested that schizotypal personality has a close link to schizophrenia and nonaffective psychoses.[22] Thus, it is possible that a subgroup of subjects with borderline personality disorder could also have persistent psychosis (affective and nonaffective) and, perhaps less commonly, overt schizophrenia. Five of the 7 subjects in our series experienced severe sexual and physical abuse during childhood and had the diagnosis of borderline personality disorder from the earliest admissions to hospital.

The individuals in our study had received trials of different classes of psychotropic agents, often in combination, and these strategies had mostly been ineffective in mitigating the severe and extreme self-mutilation or aggression directed toward others. Most of the subjects in our report had gained notoriety within the 2 hospitals and consequently had engendered intense negative reactions from some staff and peers alike. Treatment plans had em-

  

**Table 2. Clozapine Dosing, Privileges, Seclusions, Restraints, Injuries**[a]

| Case | Clozapine (mg/d) Duration (mo) | GAF Score: Admission or Preclozapine | GAF Score: During Clozapine Treatment or at Discharge | Medication[b]: Anxiolytic Pre | Medication[b]: Anxiolytic Post | Medication[b]: Antipsychotic Pre | Medication[b]: Antipsychotic Post | Privileges[c] Pre | Privileges[c] Post | Seclusion: Incidents[c] (N) Pre | Seclusion: Incidents[c] (N) Post | Seclusion: Duration (h) Pre | Seclusion: Duration (h) Post | Restraint: Incidents[c] (N) Pre | Restraint: Incidents[c] (N) Post | Restraint: Duration (h) Pre | Restraint: Duration (h) Post | Injury to Staff/Peers (Incidents, N) Pre | Injury to Staff/Peers (Incidents, N) Post | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 400/6 | 30 | 50 | NA | NA | NA | NA | 0 | 1 | 50 | 4 | 414.50 | 12.50 | 107 | 5 | 700 | 28.5 | 3 | 0 | Continues occasional wrist cutting, but much improved. No seclusion/ restraints. Forensic patient, cannot be discharged for legal reasons. |
| 2 | 300/5 | 30 | 45 | NA | NA | NA | NA | 1 | 1 | 70 | 6 | 376.80 | 18.80 | 111 | 2 | 667 | 2.3 | 4 | 1 | Much improved forensic patient, cannot be discharged for legal reasons. |
| 3 | 350/6 | 30 | 55 | 123 | 57 | 27 | 2 | 0 | 3 | 2 | 1 | 14.80 | 1.92 | 14 | 0 | 196.5 | 0 | 12 | 1 | Discontinued from clozapine due to neutropenia. Most gains lost within a month; reverted to preclozapine behaviors. Risperidone up to 10 mg/d without impact. Rechallenged with clozapine; significant improvements in 3 months without neutropenia. |
| 4 | 450/4 | 30 | 50 | 64 | 27 | 29 | 3 | 0 | 5 | 29 | 1 | 248.6 | 0.50 | 26 | 2 | 124.8 | 6.1 | 6 | 0 | Extremely difficult phlebotomy so she refused to have blood drawn after 4 months; CBC and differential were not obtained. Rapid decompensation, partially controlled with risperidone, 9 mg/d. |
| 5 | 550/12 | 20 | 60 | 168 | 39 | 28 | 4 | 1 | 4 | 18 | 1 | 193.50 | 0.80 | 2 | 0 | 4.2 | 0 | 2 | 0 | Discharged 2.5 years after clozapine was started. She also received valproate, sertraline, and lorazepam. Had done well in the community, no re-hospitalization in past 3.5 years. |
| 6 | 450/7 | 20 | 60 | 36 | 14 | 8 | 1 | 0 | 5 | 6 | 2 | 18.75 | 4 | 2 | 0 | 3 | 0 | 2 | 0 | Discharged after 7 months on clozapine, valproate, and lithium. 2 brief community hospitalizations over 2 years. |
| 7 | 450/7 | 35 | 55 | 19 | 3 | NA | NA | 1 | 5 | 6 | 1 | 26.5 | 0.50 | 0 | 0 | 0 | 0 | 0 | 0 | Significant improvement. Discharged. Has done well without rehospitalization for 6 years. No alcohol use for 6 years. |
| Mean % Change | | 48%↑ | | 67%↓ | | 89%↓ | | 60%↑ | | 91%↓ | | 97%↓ | | 97%↓ | | 98%↓ | | 93%↓ | | |

[a]Abbreviations: CBC = complete blood count, GAF = Global Assessment of Functioning, NA = not available, Post = postclozapine, Pre = preclozapine. Symbols: ↑ = increase, ↓ = decrease.
[b]Number of times prn medication administered in the mirror-image time periods.
[c]Privileges include ability to use a ground pass to walk unescorted on the grounds, to go off grounds with staff or unescorted, undertake recreational activities, participate in occupational therapy, and undertake passes with family.

phasized consistency and were also based on second and third opinions for pharmacologic and behavioral interventions, but this strategy had not helped these patients to any significant degree. The suggested management of the borderline patient involves brief crisis-type inpatient hospitalization, and in the current fiscal climate of health care, alternatives to inpatient hospital stay have also been recommended.[23] Among these subjects, such nonhospital interventions were impossible either for legal reasons or extreme parasuicidal behavior, aggression, or psychoses, or some combination thereof, and they were admitted to longer stay state psychiatric facilities.

### Possible Reasons for the Noted Improvements

It might be argued that the improvements noted in these subjects were merely part of the natural course of the disorder. However, the temporal sequence of the striking improvements noted within weeks of initiation of treatment suggests that these effects were most likely due to clozapine.

Were the noted benefits simply a reflection of improvement in psychosis and mood lability following clozapine treatment? Two of the patients who were discharged while receiving clozapine continued to have some psychotic symptoms, but their impulse control and judgment were no longer issues that prevented discharge back to the community. Two subjects with diagnoses of schizoaffective and bipolar disorder, respectively, were discharged with marked improvements in mood lability, suggesting that improvements in psychosis and mood lability may certainly explain some but not necessarily all the improvements noted with clozapine therapy. Others, too, have suggested that improvements noted in violent patients due to clozapine treatment may not necessarily be linked to or completely explained by improvements in psychosis.[8–10,24]

Using a series of linear regression statistical models and predictive equations, Rabinowitz et al.[8] found that improvement in hostility scores explained a substantial proportion of the variance in the overall improvement of clozapine-treated patients as compared to change in psychosis scores. In the 2 studies involving borderline personality disorder patients and clozapine,[13,14] overall improvements in general functioning and psychopathology (BPRS and Hamilton Rating Scale for Depression scores) were noted, as well as a significant reduction in suicidal attempts and physical fights.[14] In the Italian study,[14] none of the patients had an Axis I diagnosis, and the DSM-IV Axis II diagnoses were made using a structured clinical interview (SCID-II) for personality disorders. Not unexpectedly, and as noted in our report, the mean daily dose of clozapine was higher (250 mg/day) in the study of patients with dual diagnoses of borderline personality disorder and atypical psychosis[13] as compared with the mean clozapine dose in the study without an Axis I diagnosis[14] (44 mg/day; range, 25–100 mg/day). In this study, as in the one by Frankenburg and Zanarini,[13] the indication for longer term use of clozapine is dictated by the Axis I condition, but it is not clear how long clozapine treatment is needed in those without an Axis I condition.[14] The authors describe worsening and deterioration when 2 subjects discontinued clozapine, and 1 subject who resumed taking clozapine improved again.

Might the improvements among these subjects be due to the absence of side effects, such as akathisia, commonly associated with the older neuroleptic drugs? The much lower propensity of clozapine to induce akathisia[25,26] may be important among subjects vulnerable to this side effect, especially as the presence of neuroleptic-induced akathisia has been linked to violence in psychiatric subjects.[27] Akathisia had been successfully treated with β-blockers or anticholinergic agents among the patients reported in our series.

Could it be that all the extra attention accorded to these individuals secondary to clozapine treatment helped bring about the improvements? This is most unlikely since these individuals had already received so much attention within the hospital system that the administration of clozapine was a relatively minor event for them. It might also be argued that the improvements were simply due to the highly sedative properties of clozapine. While this fact may explain some of the early benefits during titration, it does not explain the long-term and sustained improvements noted with clozapine. In our patients, the study lasted a maximum of 1 year in either direction unless the patients were discharged sooner. The finding of a sustained improvement after several weeks and months of clozapine treatment after subjects adjusted to the earlier sedating properties of clozapine has been noted by others as well.[6,7]

### Cost

It is difficult to determine a dollar figure of cost in terms of injuries to self, peers, or staff, not to mention the intense demoralization for all concerned in such difficult clinical situations. In general, the costs are likely to be high due to the assignment of extra nursing personnel for seclusion and restraint incidents, consultations with experts, or resultant injuries to self, peers, or staff that may require special medical or surgical attention and staff disability that may follow such interventions. Thus, treatments such as clozapine that appear to have a significant and positive impact in such difficult-to-treat clinical situations need careful study.

### Clozapine and Its Impact on Aggression

Previous case reports[11,28,29] and a case vignette in a preliminary report on the effects of clozapine in borderline personality disorder[13] suggest there are significant benefits for patients evidencing self-mutilation and aggression with clozapine treatment, at least among a subgroup of patients with this diagnosis. Other authors have also in-

  

dicated that clozapine has significant benefits for violent patients. For instance, significant decreases in seclusion, restraint, and aggression among clozapine-treated psychotic patients have been reported.[5–10,30] Similarly, decreases in aggression and explosive behavior have also been noted among patients with severe head injury[31] and in demented patients with psychoses,[4] suggesting that this benefit of clozapine is not limited to only those with the "functional" psychoses.

### Potential Explanation for the Mechanisms

What is the mechanism by which clozapine exerts its action on violent behavior, whether self-mutilation or other directed aggression? Clozapine has a wide range of effects on a variety of neuroreceptors that includes, among others, serotonin, dopamine, acetylcholine, and histamine.[32] Indices of a central serotonergic deficit have been linked to impulsive aggression,[33] and this finding has been used to explain why the serotonin reuptake inhibitors may be effective for such patients. In contrast, clozapine has antagonist effects at the postsynaptic serotonergic receptors, and so it is difficult to reconcile a serotonergic hypothesis to explain the benefits of clozapine in this regard. However, clozapine affects several serotonin receptor subtypes, including autoreceptors,[32] and as the functions of these subtypes are better understood, more explanations regarding clozapine's mechanism of action may be forthcoming. Clues to the benefits of clozapine for self-mutilating behavior are also available from animal models of such behavior. For instance, rats that as neonates had their brain dopaminergic neurons lesioned with 6-hydroxydopamine (6-OHDA) display self-mutilation when treated with levodopa. Dopamine $D_1$ receptor antagonists and clozapine are able to block these behaviors in a dose-dependent manner,[34] but predominantly $D_2$ receptor antagonists such as haloperidol and chlorpromazine do not.[35,36] Finally, in rodent models of aggression, clozapine produces a specific inhibition of aggressive behavior at doses that have minimal effects on motor function. These data would again suggest clozapine has antiaggressive effects that are not based only on its sedative properties.[37]

## CONCLUSION

The cases presented in this article suggest that patients with psychoses and borderline personality disorder who display severe self-mutilation may benefit from clozapine treatment. Clearly, these data must be considered preliminary, and until controlled investigations provide more definitive answers, the risk-to-benefit ratio for clozapine treatment in such instances must be considered on an individualized case-by-case basis and preferably in consultation with a colleague for a second opinion. Nonetheless, if benefits such as those described by us or others in the literature were to occur, then clearly the quality of the lives for such suffering individuals, their families, and their caregivers will be decidedly better.

*Drug names:* carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), clonazepam (Klonopin), clozapine (Clozaril), haloperidol (Haldol and others), lorazepam (Ativan and others), risperidone (Risperdal), sertraline (Zoloft), verapamil (Calan and others).

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