

# Clozapine Reduces Violence and Persistent Aggression in Schizophrenia

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Violence and persistent aggression are serious problems in the general population and among certain psychiatric patients. Violence and persistent aggression have been associated with suicidal ideation and substance abuse, characteristics of chronically ill, and in many instances, treatment-resistant schizophrenia individuals. Assessment of dangerousness in psychiatric patients involves evaluation of sociodemographic and clinical factors. A substantial number of neurologic and psychiatric disorders are associated with pathologic anger and aggression; of these, the association between schizophrenia and violence/aggression is the best described. Neurotransmitters that have been implicated in aggressive and violent behavior include serotonin, norepinephrine, and dopamine. Current pharmacotherapy of pathologic aggression involves the use of multiple agents on a trial-and-error basis, with varying degrees of response. Unfortunately, this approach subjects patients to numerous side effects, including the extrapyramidal symptoms associated with the use of conventional antipsychotics. This paper will review evidence for the efficacy of clozapine in the treatment of aggression and violence in the treatment-refractory patient. The reduction in violence and persistent aggression with clozapine treatment should improve the chances for integration of the schizophrenia patient into the community and provide cost savings to society.

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The social, psychological, and financial consequences of violence in our society have become an increasing concern in recent years. The committing of violent acts by persons with psychiatric disorders has a powerful impact not only on the lives of the immediate victims, but on our society as a whole.

Broadly defined, a violent episode refers to an unwanted physical contact, an unwanted sexual act, or a threat that includes specific statements of intent to harm. Threats account for a significant percentage of violent episodes exhibited by psychiatric patients; in fact, threats alone (without physical or sexual assaults) may account for nearly half of all aggressive events in a mental health care setting.<sup>1</sup> Many studies of violence, however, do not take threats into account.

The overall rate of violent crime in the general population has increased significantly over the last 2 decades, with the largest increase occurring in aggravated assault. Homicide is the 11th most common cause of death in the United States, occurring at an average of > 21,000 inci-

dents per year.<sup>2,3</sup> Among 15- to 34-year-olds, homicide is a leading cause of death. It is the most common cause of death among black males and black females, the third most common cause of death among white males, and the fourth most common cause of death among white females.<sup>3</sup> Most violent crimes are committed among persons older than 18 years of age, yet the violence rate among teenagers has increased 2-fold to 2.5-fold since the 1970s. In contrast, among adults more than 30 years of age, rates have either remained the same or decreased.<sup>2</sup>

Lifetime prevalence of violent behavior is estimated to be about 25% of the general population.<sup>4</sup> There is an association between psychosis and violence directed toward others, particularly in schizophrenia.<sup>5,6</sup> Available data suggest that when they are not taking their antipsychotic medications, individuals with serious mental illnesses are more dangerous than members of the general population.<sup>7</sup> Hence, pharmacotherapeutic compliance with medications should be closely monitored in psychotic individuals with a violent predisposition. However, there are patients with schizophrenia who are persistently aggressive despite highly controlled environments, suggesting that treatment resistance (i.e., inadequate response to neuroleptics) may be a risk factor for violence.<sup>6</sup>

## PREDICTORS OF VIOLENCE

Assessment of dangerousness in psychiatric patients involves evaluation of sociodemographic and clinical factors (Table 1). In the case of patients who are hospitalized

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**Table 1. Sociodemographic and Clinical Factors With Predictive Value in the Assessment of Dangerousness**

Sociodemographic factors	
Previous history of violence and/or incarceration	
History of child abuse	
Young age	
Male sex	
Low socioeconomic status	
History of drug or alcohol abuse	
Unmarried/divorced status	
Clinical factors	
Early onset of psychiatric illness	
History of suicidal ideation and attempts	
History of frequent hospital admissions	
Presence of cognitive or neurologic impairment	
Presence of aggression at the time of referral	
Presence of aggression and anxiety at the time of hospital admission	

involuntarily for emergency psychiatric evaluation, immediate and ongoing assessment of dangerousness is especially important in order to (1) plan treatment interventions to prevent injury to self and others and (2) facilitate the decision as to whether to release patients or petition for longer periods of involuntary treatment.

Sociodemographic factors with predictive value in the assessment of dangerousness include history of violence and/or incarceration,<sup>8,9</sup> history of child abuse,<sup>10</sup> male sex,<sup>11,12</sup> young age,<sup>8,12</sup> low socioeconomic status,<sup>12</sup> history of drug or alcohol abuse, and unmarried status.<sup>8</sup> Generally speaking, the best predictor of future behavior is past behavior.<sup>8</sup>

Clinical factors with predictive value in the assessment of dangerousness include early onset of psychiatric illness,<sup>13</sup> history of suicidal ideation and attempts,<sup>14,15</sup> history of frequent hospital admissions, cognitive or neurologic impairment,<sup>13,16,17</sup> aggression at the time of referral,<sup>18</sup> and aggression and anxiety at the time of hospital admissions.<sup>17</sup>

In the case of schizophrenia inpatients, it is important to differentiate between violent patients who are likely to inflict physical injury and violent patients who are not. In a retrospective analysis of violent and nonviolent patients admitted to a psychiatric emergency ward,<sup>18</sup> the best single predictor of violence was a history of previous violence by the patient. Patients with a history of 3 or more violent acts, those who were violent for a longer period of time, those with a diagnosis of schizophrenia, and those with a greater level of aggression at referral were more likely to inflict injury.

Of the clinical risk factors, violence is closely linked to suicidal behavior<sup>14,15</sup> and/or substance abuse.<sup>14,19</sup> An analysis of psychiatric outpatients<sup>14</sup> showed that as many as 92% of patients who attempted homicide also attempted suicide. Likewise, 86% of patients with homicidal ideation also reported suicidal ideation.<sup>14</sup> In another study, 55% of assaultive treatment-resistant schizophrenia patients had a history of suicide attempts.<sup>20</sup>

In a study of a prison population,<sup>19</sup> as many as 90% of prisoners with schizophrenia exhibited comorbid sub-

stance abuse. Substance abuse has been linked with violence; this association may be due to the fact that schizophrenia patients with comorbid substance abuse are notorious for medication noncompliance and, in general, exhibit poor outcomes.<sup>21</sup>

The risk factors of substance abuse, suicidal ideation and attempts, history of frequent hospital admissions, cognitive and neurologic impairment, and history of violence are temporally related in that these factors are characteristic of chronically ill, and in many instances, treatment-resistant schizophrenia patients. However, the relationship between treatment-resistant schizophrenia and violence remains to be explained.

## NEUROBIOLOGY OF AGGRESSION AND VIOLENCE

The connection between serotonin (5-hydroxytryptamine; 5-HT) and violence has been established with the repeated observation that abnormalities in central 5-HT function correlate with persistent aggression. Several studies show that the major metabolite of serotonin, 5-hydroxyindoleacetic acid (5-HIAA), is reduced in the cerebrospinal fluid (CSF) of subjects with a history of aggression and violence, as compared to those with no such history.<sup>22,23</sup> There is also preliminary evidence for a genetic disturbance in serotonergic function that might predispose individuals to impulsive aggressive behavior. Part of the gene for tryptophan hydroxylase (the rate-limiting enzyme for serotonin synthesis) has been shown to exist as at least 2 alleles, U and L. Preliminary study in human subjects suggests that the presence of either the UL or LL genotype may be associated with persistent aggressive and suicidal behavior and low levels of CSF 5-HIAA in violent offenders.<sup>24</sup>

Central dopaminergic and noradrenergic systems may also play a role in the genesis of persistent aggression. Evidence for a dopaminergic role comes largely from preclinical studies—it has been shown that increasing brain dopamine activity in animals renders them more likely to respond impulsively and aggressively to environmental stimuli.<sup>25</sup>

In humans, hyperactivity of noradrenergic functioning has been found to correlate with aggressive behavior. For example, there is increased  $\beta$ -adrenergic receptor binding in the prefrontal and temporal areas of the cerebral cortex in the brains of violent suicide victims compared with accident victims.<sup>26</sup> In addition, CSF 3-methoxy-4-hydroxyphenylglycol levels are elevated in violent suicide attempters compared with nonviolent suicide attempters.<sup>27</sup> More recently, an association between catechol-*O*-methyltransferase (COMT) activity and aggressiveness was reported.<sup>28</sup> COMT catalyzes the *S*-adenosyl-L-methionine-dependent methyl conjugation of catecholamine neurotransmitters and catecholaminergic drugs, thereby leading to inactivation. Two variants of COMT were characterized

in the study: a low-activity variant and a high-activity one. After screening schizophrenia patients, it was found that those who were homozygous for the low-activity allele were judged to be at greater risk for aggressive and dangerous behavior than those who were homozygous for the high-activity allele.<sup>28</sup> These results suggest that the functional polymorphism of COMT may modify aggressive behavior in individuals with schizophrenia.

Neuroanatomical studies of subjects with intractable behavioral and neurologic illness have provided clues to areas of the brain that are involved in pathologic emotional behaviors such as violence. Deep and surface electrorecordings have shown that emotional behavior (e.g., rage) is associated with activity in the hippocampus, medial amygdala, and mesencephalic tegmentum.<sup>29</sup>

Hyperprolactinemia in nonschizophrenia women has been associated with psychological distress, notably anxiety, depression, and hostility,<sup>30,31</sup> independent of its effect of lowering estrogen levels. Whether normalization of prolactin levels and/or estrogen status contributes to psychiatric improvement and secondarily decreases risk of violence in some women with schizophrenia is currently unknown. Relationships of prolactin and estrogen are likely to be complex and specific to the individual. With correction of hyperprolactinemia, menstrual periods absent on typical neuroleptic therapy may resume, secondary to reestablishment of normal hormonal cyclicity. Premenstrual exacerbation of psychosis has been reported<sup>32,33</sup> and may become more common clinically, given the introduction of prolactin-sparing neuroleptics.

In male patients, short-term studies of typical neuroleptics<sup>34,35</sup> have shown that these drugs may lower testosterone levels, particularly at higher doses, possibly as a consequence of hyperprolactinemia. The relationship of testosterone to aggressive behavior is complex.<sup>36</sup> Clozapine does not elevate prolactin levels<sup>37</sup> as all traditional neuroleptics and risperidone do.<sup>38</sup> The clinical behavioral implications of this have not been studied and are poorly understood. As clozapine does not cause hyperprolactinemia, its antiaggressive effects cannot be attributed to indirect lowering of testosterone levels; i.e., in this sense, clozapine may be endocrine sparing.

### **SCHIZOPHRENIA AS A RISK FACTOR FOR VIOLENCE**

Many neurologic and psychiatric disorders are associated with pathologic anger and aggression. These include schizophrenia, panic disorder, personality disorders, posttraumatic stress disorder, bipolar disorder, and major depressive episode.<sup>39</sup> Of these, the association between schizophrenia and violence and aggression is the best described.

Pathologic aggression and violence can result from psychotic states, particularly when patients have persecu-

tory delusions or mistakenly perceive themselves as being under threat. Many violent offenses committed by patients with schizophrenia occur during an acute psychotic episode.<sup>40</sup> Violence in acutely psychotic patients appears to be closely linked to the immediate psychopathology and usually subsides within the first several weeks of antipsychotic treatment.<sup>40</sup>

From a staff perspective, seclusion of aggressive patients is a form of preventive intervention. In one study<sup>41</sup> in which 26 of 100 frequently hospitalized schizophrenia or schizoaffective patients required seclusion during their hospital stays, patient views about seclusion were recorded. From the patients' perspective, the experience of seclusion was painful, associated with feelings of helplessness, fear, sadness, and anger. Their responses did not support the widely held perception that patients feel safe or protected in seclusion. Secluded patients tended to have been involuntarily committed and to have longer inpatient stays than patients who did not require seclusion.<sup>41</sup>

The differentiation of aggressive from nonaggressive schizophrenia patients may be aided by thorough examination of underlying psychopathology. Psychopathologic correlates of aggressive behavior in schizophrenia patients include conceptual disorganization, excitement, suspiciousness, hostility, uncooperativeness, poor attention, poor impulse control, preoccupation, and social avoidance.<sup>42</sup> Patients may give verbal cues of aggression in the form of expressions of distrust, anger, and negativism.

A review of the literature shows that since the 1950s, individuals with schizophrenia have been involved in crime and arrested more frequently than the general population.<sup>16</sup> Moreover, injury-inflicting psychiatric inpatients more frequently have a diagnosis of schizophrenia than do non-injury-inflicting psychiatric inpatients.<sup>18</sup>

### **PHARMACOTHERAPEUTIC APPROACHES TO VIOLENCE AND PERSISTENT AGGRESSION**

The complex biological substrate of violence and persistent aggression is not fully understood, but is probably not explainable by any single biochemical process. Neurotransmitter systems that have been implicated in aggressive and violent behavior include gamma-aminobutyric acid (GABA), serotonin, norepinephrine, and dopamine. Serotonergic drugs in particular have been studied for use in aggression. Drugs with 5-HT<sub>2</sub>-antagonist and those with 5-HT<sub>1</sub>-agonist properties show an antiaggressive effect.<sup>43,44</sup> Other neurotransmitters implicated in the etiology of aggression include acetylcholine, adenosine, histamine, and the endogenous opioid system, but the precise role of these agents in promoting aggressive behavior remains unclear.<sup>44,45</sup>

Currently, there is no medication approved by the Food and Drug Administration (FDA) for the treatment of aggression. Current pharmacotherapy of aggression often in-

volves the use of polypharmacy on a trial-and-error basis, with varying degrees of response. Unfortunately, this approach often leads to untoward side effects that further complicate management.

Management of aggression and violence begins with a complete physical examination, including thorough neurologic and psychiatric evaluations. A detailed medication and substance abuse history must be obtained. Coexisting disorders, if any, should be identified and treated. Non-pharmacologic therapy, while not the focus of this review, including behavioral therapy and comprehensive psychosocial treatment, is necessary to optimize treatment outcomes.<sup>19</sup>

Pharmacotherapy for acute episodes of aggression and violence often utilizes a benzodiazepine, an antipsychotic, or a combination of both. The decision to implement chronic therapy for persistent aggression and violence is based on the patient's past response to pharmacotherapeutic intervention and discontinuation as well as how problematic a relapse may be to the patient's treatment plan. A large number of psychoactive agents have been tried for the treatment of persistent aggression. These include lithium, carbamazepine, valproic acid, buspirone, trazodone,  $\beta$ -blockers such as propranolol, serotonin reuptake inhibitors such as fluoxetine, and clozapine.<sup>45</sup> While haloperidol is frequently prescribed for aggression and violence, it may, particularly at higher doses, aggravate violent behavior in a subgroup of patients.<sup>46</sup> This may be related to the motor and mental dysphoria associated with neuroleptic treatment.<sup>47</sup> These problems can be minimized with the new generation of "atypical" antipsychotics.

Clozapine is currently approved by the FDA for use in patients with severe refractory schizophrenia and in patients who experience intolerable adverse effects with conventional antipsychotics.<sup>38,48</sup> The ability of clozapine to reduce aggression adds a behavioral dimension to the management of treatment-resistant schizophrenia.

Risperidone has also been shown to have antiaggressive effects.<sup>49</sup> The effect of the other novel antipsychotics on violence and persistent aggression still needs to be assessed. Since clozapine is the only antipsychotic medication that is specifically approved for use in treatment-refractory patients, we will focus our attention on studies that have measured its effect on violent and aggressive behavior.

Clozapine has relatively weak dopaminergic activity. Like conventional antipsychotic drugs, clozapine blocks receptors for the  $D_2$  dopamine subtype. However, compared with similar drugs, it has a lower affinity for  $D_2$  receptors and binds more strongly to  $D_1$  receptors.<sup>48</sup> Clozapine is also a potent 5-HT<sub>2</sub>-serotonergic and  $\alpha_1$ -adrenergic receptor antagonist.<sup>48</sup> The unique binding characteristics of clozapine are probably responsible for its ability to be therapeutically efficacious while causing few, if any, extrapyramidal side effects.

Preclinical animal studies have shown that clozapine significantly decreases attack and threat behaviors.<sup>50</sup> In humans, studies show marked efficacy in the treatment of aggression in schizophrenia patients. These studies are summarized in Table 2.

Buckley et al.<sup>51</sup> studied the effects of clozapine in schizophrenia patients with and without a history of violent behavior. The violent group showed a significant reduction in aggressive behavior during the first 6 months of clozapine therapy, as evidenced by fewer hours of seclusion and restraint.

Spivak et al.<sup>52</sup> reported the results of a prospective, open-label trial in which 14 neuroleptic-resistant schizophrenia patients were treated with clozapine for 18 weeks. Clozapine treatment induced a marked decrease in impulsiveness (32% on the Impulsivity Scale,  $p < .0001$ ) and aggressiveness (98% on the Overt Aggression Scale,  $p < .0001$ ).

Rabinowitz et al.<sup>53</sup> performed a retrospective chart review of incident reports involving aggression and restraint on 75 patients who had been taking clozapine in doses ranging from 100 to 600 mg/day for at least 6 months and had been hospitalized for at least 3 months before beginning clozapine therapy. There were significantly fewer incidents of physical aggression per month per patient taking clozapine than before clozapine treatment, and there was a similar decline in verbal aggression.

Ratey et al.<sup>54</sup> studied aggressiveness in a unit designed to house severely aggressive patients. Nonblinded raters retrospectively reviewed the charts of 5 patients treated with clozapine and quantified episodes of violent behavior. Clozapine treatment resulted in a decrease in assaultive and self-injurious behavior and the need for sedatives.

Volavka et al.<sup>55</sup> examined the effect of clozapine on hostility and aggression as part of a larger open-label study assessing the safety and efficacy of clozapine in 123 treatment-refractory inpatients. The 18-item Brief Psychiatric Rating Scale (BPRS) was administered to patients at baseline, 6 weeks, 12 weeks, and at endpoint (1 year or time of discharge). Hostility and psychosis factor scores of the BPRS were compared, and Pearson correlation coefficients for changes in hostility scores were determined after statistically accounting for changes in the psychosis factor scores. Clozapine had a significant effect on hostility, with correlation coefficients for changes in the hostility score at 6 weeks, 12 weeks, and endpoint of 0.46, 0.38, and 0.36, respectively ( $p < .001$  for all).

Mallya et al.<sup>56</sup> retrospectively reviewed restraint and seclusion records of 107 patients who received clozapine in a state mental hospital. Patterns of restraint and seclusion were compared before and after treatment with clozapine. The frequency of restraint dropped by 92% and the number of seclusion incidents dropped by 83%. The average length of time in restraints per incident decreased by 66%, and the average seclusion time per incident decreased by 72%.

**Table 2. Studies of Clozapine in Aggression**

Study	Type of Study	Methodology	Results
Buckley et al <sup>51</sup>	Open-label, prospective	30 male and female subjects (violent and non-violent) were treated with clozapine	Significant reduction in aggression in violent schizophrenia patients
Spivak et al <sup>52</sup>	Open-label, prospective	14 antipsychotic-resistant patients were treated with clozapine for 18 weeks and evaluated for aggressiveness and impulsiveness	Significant decrease in aggressiveness (98%) and impulsiveness (32%) with clozapine
Menditto et al <sup>58</sup>	Open-label, prospective comparison to typical agents	22 chronic psychiatric inpatients (many of whom had high rates of aggressive behaviors)	Number of aggressive acts significantly declined 6 months after clozapine initiation compared with treatment with typical antipsychotics
Ebrahim et al <sup>59</sup>	Open-label, prospective	27 patients of forensic status who had either schizophrenia or schizoaffective disorder or were treatment-resistant or treatment-intolerant patients	70.3% of patients on clozapine achieved a given level of patient privileges only achieved by 3.7% of patients before clozapine treatment; diminished hostility, aggression, restraint, and seclusion with clozapine
Chiles et al <sup>61</sup>	Open-label, prospective	115 patients with treatment-resistant schizophrenia or schizoaffective disorder	Clozapine treatment associated with a significant reduction in the use of seclusion and restraint
Volavka et al <sup>55</sup>	Open-label, prospective	Safety and efficacy of clozapine studied in 123 inpatients who failed conventional antipsychotic therapy	Significant reduction in hostility scores at 6 weeks, 12 weeks, and endpoint (1 year or discharge)
Wilson <sup>60</sup>	Open-label, prospective	37 patients who were treatment-resistant or treatment-intolerant	Number of violent episodes increased prior to clozapine treatment but steadily decreased after clozapine initiation
Rabinowitz et al <sup>53</sup>	Retrospective review	Incident reports involving aggression and restraint were reviewed for 75 patients who received clozapine 100–600 mg/day for at least 6 months	49% of clozapine-treated patients had fewer incidents of physical aggression; 70% had fewer incidents of verbal aggression; significant decreases in BPRS <sup>a</sup> hostility, positive, negative, and psychosis scores with clozapine
Ratey et al <sup>54</sup>	Retrospective review	Chart review of 5 aggressive patients treated with clozapine	31.8% decrease in assaults; 65% decrease in self-injurious behavior; 78.6% decrease in amount of time spent in restraints
Mallya et al <sup>56</sup>	Retrospective review	Review of restraint and seclusion records of 107 patients	Restraint use dropped by 92%; number of seclusion incidents decreased by 83%; average length of time in restraints decreased by 66%; average seclusion time per incident decreased by 72% with clozapine
Maier <sup>57</sup>	Retrospective review	Study of forensic status among 25 treatment-refractory schizophrenia or schizoaffective patients who received clozapine	13/25 patients improved with clozapine, as manifested by release or advancement to a lower-security unit

<sup>a</sup>BPRS = Brief Psychiatric Rating Scale.

Maier<sup>57</sup> reported the use of clozapine in 25 treatment-refractory schizophrenia or schizoaffective patients in a forensic hospital. Of these patients, 52% improved, as manifested by release granted by the judicial system or by advancement to a lower-security unit. No standardized reporting measures were used in this study.

Menditto et al.<sup>58</sup> compared 2 groups of 11 subjects each (1 group taking clozapine and 1 taking traditional antipsychotics) based on clinical functioning as measured by the Time-Sample Behavioral Checklist. Data on frequency of aggressive behaviors were aggregated into three 6-month time periods. The number of aggressive acts declined significantly in the 6 months following the initiation of clozapine treatment. The study is, to our knowledge, the only prospective study in which clozapine's effect on violence is compared with a standard agent.

Ebrahim et al.,<sup>59</sup> in a prospective study involving 27 patients (most of whom had paranoid schizophrenia), re-

ported a significant decline in hostility, aggression, and use of seclusion and restraint following clozapine initiation. As a result of diminished aggressiveness with clozapine treatment, 70% of patients attained a level of patient privileges that had been attained by only 4% of patients before clozapine initiation.

Wilson,<sup>60</sup> in analyzing records of 37 patients 6 months before and 6 months after clozapine treatment, found that the number of violent episodes among schizophrenia patients on clozapine treatment steadily decreased during the study period.

Chiles et al.<sup>61</sup> compared the seclusion and restraint patterns of 115 patients 12 weeks prior to and 12 weeks following clozapine initiation. The results show a dramatic reduction in seclusion and restraint apparent from the second week after clozapine initiation.

The antiaggressive effects of clozapine suggested by the results of these studies may be attributable to at least 5

factors: (1) decrease in psychosis; (2) decrease in negative symptomatology; (3) lack of associated motor disorders, especially akathisia; (4) decrease in substance abuse; and (5) decrease in suicidality. In the absence of randomized, double-blind comparative studies, it is as yet unclear how clinicians should choose among the various atypical antipsychotic agents for the management of aggressive behaviors. Available research strongly suggests that clozapine will be effective for this component of treatment-refractory conditions. Guidelines for this area await comparative studies.

### **COST-EFFECTIVENESS OF CLOZAPINE THERAPY**

The overall costs of untreated aggression and violence within the health care system and on society in general are difficult to estimate, but are believed to be enormous. Inpatient violence is also a significant source of staff injury.<sup>62,63</sup> In one hospital alone,<sup>64</sup> assault-related penetrating injuries generated more than \$2 million in charges during a 3-year period. Sixty-seven percent of this amount was incurred by patients who had no source of third-party payment. Reimbursement covered only 30% of the charges. Uncompensated costs like these place a huge burden on the health care system. Violence may also prolong hospital stays, adding to the economic burden. In a retrospective review of 253 patients admitted to an acute inpatient unit of a university-based hospital,<sup>65</sup> 50% of violent schizophrenia patients remained in the hospital more than 21 days. In contrast, very few of the nonschizophrenia violent patients (10%) remained in the hospital for more than 21 days.

More than half of psychiatric inpatients may require seclusion and/or restraint at least once.<sup>66</sup> Antiaggression therapy may lessen the need for seclusion and restraint, thereby reducing the overall use of hospital resources. In one study evaluating the effect of clozapine therapy on seclusion and restraint over a 12-week period in a sample of 115 state mental-hospital patients,<sup>61</sup> there was a dramatic reduction in the need for restraint and seclusion during clozapine treatment.

In another state facility, schizophrenia patients receiving clozapine treatment sustained a reduction in bed days by an average of 132 days per year after 1.5 years, increasing to 201 days per year after 2.5 years ( $p < .001$ ). This reduction in hospitalization corresponded to gross cost savings of \$33,000 per patient per year at 1.5 years, and \$50,250 per patient per year at 2.5 years.<sup>67</sup>

### **LEGAL ISSUES INVOLVING VIOLENCE**

A legal dimension is added to the case for treating aggression and violence in psychiatric patients when one considers that psychiatrists are subject to being sued for malpractice when a patient commits a violent act.<sup>68</sup> The

case of *Tarasoff v Regents of the University of California* (1976)<sup>69</sup> established a psychiatrist's liability if a patient unintentionally harms another under foreseeable circumstances. According to the Tarasoff court, "When a psychotherapist determines, or pursuant to the standards of his profession should determine, that his patient presents a serious danger of violence to another he incurs an obligation to use reasonable care to protect the intended victim against such danger."<sup>69</sup>

### **CONCLUSION**

Schizophrenia is a risk factor for violence; other factors such as young age, male sex, unmarried status, suicidal ideation, and frequent hospital admissions are shared risks for suicide and violence. A history of substance abuse, violence, and/or persistent aggression are strong predictors of violence. Numerous studies have shown that clozapine is an efficacious antipsychotic for the management of treatment-resistant schizophrenia patients, without causing extrapyramidal side effects. Because of the high costs of violent behavior to patients, families, care providers, and society, the intensive and comprehensive treatment of schizophrenia patients who have aggressive and violent tendencies is warranted.

*Drug name:* buspirone (BuSpar), carbamazepine (Tegretol and others), clozapine (Clozaril), fluoxetine (Prozac), haloperidol (Haldol and others), propranolol (Inderal and others), risperidone (Risperdal), trazodone (Desyrel and others), valproic acid (Depakene and others).

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