VIOLENCE IN SCHIZOPHRENIA AND BIPOLAR DISORDER

Jan Volavka

New York University School of Medicine, New York, USA

SUMMARY

Background: Although most psychiatric patients are not violent, serious mental illness is associated with increased risk of violent behavior. Most of the evidence available pertains to schizophrenia and bipolar disorder.

Methods: MEDLINE data base was searched for articles published between 1966 and November 2012 using the combination of key words "schizophrenia" or "bipolar disorder" with "aggression" or "violence". For the treatment searches, generic names were used in combination with key words "schizophrenia" or "bipolar disorder" and "aggression" No language constraint was applied. Only articles dealing with adults were included. The lists of references were searched manually to find additional articles.

Results: There were statistically significant increases of risk of violence in schizophrenia and in bipolar disorder in comparison with general population. The evidence suggests that the risk of violence is greater in bipolar disorder than in schizophrenia. Most of the violence in bipolar disorder occurs during the manic phase. The risk of violence in schizophrenia and bipolar disorder is increased by comorbid substance use disorder. Violence among adults with schizophrenia may follow at least two distinct pathways-one associated with antisocial conduct, and another associated with the acute psychopathology of schizophrenia. Clozapine is the most effective treatment of aggressive behavior in schizophrenia. Emerging evidence suggests that olanzapine may be the second line of treatment. Treatment adherence is of key importance. Non-pharmacological methods of treatment of aggression in schizophrenia and bipolar disorder are increasingly important. Cognitive behavioral approaches appear to be effective in cases where pharmacotherapy alone does not suffice.

Conclusions: Violent behavior of patients with schizophrenia and bipolar disorder is a public health problem. Pharmacological and non-pharmacological approaches should be used to treat not only violent behavior, but also contributing comorbidities such as substance abuse and personality disorders. Treatment adherence is very important for successful management of violent behavior.

Key words: *schizophrenia - bipolar disorder – violence - aggression*

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Introduction

Most psychiatric patients are not violent. Nevertheless, there is a general consensus that severe mental illness, particularly schizophrenia and bipolar disorder, does increase violence risk. Violent behavior of psychiatric patients is a public health problem. It presents obvious risks of injuries or death of assailants and their victims. Furthermore, assaults by psychiatric patients significantly contribute to the stigma of mental illness (Torrey 2002). Caring for violent psychiatric patients presents difficult clinical challenges, and it complicates the efforts of caregivers. The emotional trauma of caring for a loved one who responds by violence should not be underestimated.

Finally, violence increases the cost of treatment. It is a frequent cause of hospitalization, and it may increase the length of hospital stay. Violent patients require disproportionate amounts of staff time. Additional costs are imposed on the criminal justice system.

In spite of its obvious practical importance, violence in psychiatric patients has attracted relatively little attention in the literature. The aim of this review is to examine the epidemiology, clinical features, and treatment of violent behavior in schizophrenia and bipolar disorder.

Definitions

Aggression is overt action intended to harm. This term describes animal and human behavior. Various rating scales are used to assess human aggression. These scales may separately assess verbal aggression, aggression against objects, against self, and against others (Yudofsky et al. 1986). The term *aggression* tends to be used in biomedical and psychological context. In this review, aggression against self will not be considered.

Violence denotes aggression among humans. The term is more commonly used in sociology and criminology (e.g., violent crime).The terms violence and aggression are used interchangeably, depending on context.

Agitation is excessive motor or verbal activity. Verbal aggression may include inarticulate screams, abuse, or threats.

Hostility denotes unfriendly attitudes. Overt irritability, anger, resentment, or verbal aggression is manifestation of hostility. Hostility is defined operationally by rating scales. The most frequently used method to assess hostility is the "hostility" item in the Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1989) or the Brief Psychiatric Rating Scale (BPRS) (Guy 1986).

The clinical importance of hostility is in its close association with violence and nonadherence to treatment.

Schizophrenia

Epidemiology

The groundbreaking epidemiological study that firmly established the link between violence and schizophrenia determined one-year prevalence of violent behavior in schizophrenia as 8.4%, compared with 2.1% in persons without any disorder (Swanson et al. 1990). The study has also clearly indicated that the risk of violence is further increased by comorbid substance use disorders. These landmark findings were further elaborated in a book chapter (Swanson 1994).

Swanson's study was conducted in the United States. Many subsequent epidemiological studies done in various countries have confirmed and expanded Swanson's original findings (Volavka 2002).

A meta-analysis of 20 studies compared risks of violence in 18,423 patients diagnosed with schizophrenia and other psychoses with general population. There was a modest but statistically significant increase of risk of violence in schizophrenia with an odds ratio (OR) of 2.1 (95% confidence interval [CI] 1.7–2.7) without comorbidity, and an OR of 8.9 (95% CI 5.4–14.7) with comorbidity with substance abuse. Risk estimate of violence in individuals with substance abuse (but without psychosis) showed an OR of 7.4 (95% CI=4.3-1) (Fazel et al. 2009).

A study analyzed data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), a two-wave project (N = 34,653: Wave 1: 2001-2003; Wave 2: 2004-2005). Indicators of mental disorder in the year prior to Wave 1 were used to examine violence between Waves 1 and 2 (Elbogen & Johnson 2009). Surprisingly, severe mental illness did not independently predict future violent behavior. Comorbid substance use disorder was one of the independent predictors.

However, we argued that the Elbogen analyses could be improved and consequently we re-analyzed the same NESARC data (Van Dorn et al. 2012). We found that individuals with severe mental illness, irrespective of substance abuse status, were significantly more likely to be violent than those with no mental or substance use disorders. Those with comorbid mental and substance use disorders had the highest risk of violence. Historical and current conditions were also associated with violence, including childhood abuse and neglect, household antisocial behavior, binge drinking and stressful life events (Van Dorn et al. 2012).

Thus, substance abuse is a very important risk factor for violence in schizophrenia. However, the weight of evidence suggests that features of schizophrenia such as psychotic symptoms and comorbid personality disorders are also likely to be independent risk factors for violence in individuals with schizophrenia (Volavka & Swanson 2010).

Clinical features

Violence in schizophrenia is heterogeneous in its origin and manifestations. It may be directly related to clinical symptoms. One hypothesis links elevated rates of violence among people with mental illness to a small set of delusional psychotic symptoms-so called threat/control-override (TCO) symptoms (Link et al. 1998, Link & Stueve 1994). These symptoms are elicited by questions like "dominated by forces beyond you", "thoughts put into your head", and "people who wished you harm".

However, a large study suggested that although delusions can precipitate violence in individual cases, they do not increase the overall risk of violence (Appelbaum et al. 2000). Delusional motivation of violence appears to be rare (Junginger et al. 1998).

Command hallucinations to harm others may increase risk of violence, although the level of compliance with such commands varies (Junginger 1995, Junginger & McGuire 2001). In general, positive symptoms of schizophrenia are associated with an increased risk of violence, whereas negative symptoms show the opposite relationship (Swanson et al. 2006). Finally, there is consistent evidence linking impaired insight to violence (Alia-Klein et al. 2007, Antonius 2005, Ekinci & Ekinci 2012, Lera et al. 2012). This effect may be indirect, mediated through the reduced adherence to treatment that is associated with poor insight (Alia-Klein et al. 2007, Coldham et al. 2002) (Czobor et al. 2013).

Contrary to the belief of many clinicians, much of the violence committed by schizophrenia patients does not seem so be directly related to psychotic symptoms. Recent evidence suggests that violence among adults with schizophrenia may follow at least two distinct pathways-one associated with premorbid conditions, including antisocial conduct, and another associated with the acute psychopathology of schizophrenia (Swanson et al. 2008b). In that study, adherence with antipsychotic medications was associated with significantly reduced violence only in the group without a history of conduct problems. In the conduct problems group, violence remained higher and did not significantly differ between patients who were adherent with medications and those who were not (Swanson et al. 2008b). Since the outcome did not depend on whether these patients actually did take the medication, we can infer that a history of conduct disorder is associated with reduced effectiveness of antipsychotics. This hypothesis remains to be tested.

These findings are consistent with previous observations indicating that only about 20% of assaults on a psychiatric ward was directly attributable to psychotic symptoms like delusions or hallucinations (Nolan et al. 2003). The other assaults appeared to be due to confusion, impulsiveness, or comorbid antisocial personality disorder/psychopathy. Thus, there are multiple pathways to violence in schizophrenia, and this etiological heterogeneity has implications for treatment (Volavka & Citrome 2011).

Long-term treatment

Pharmacological treatment

Atypical antipsychotics are the mainstay of the long-term treatment of aggressive behavior in schizophrenia.

Clozapine is the gold standard for the treatment of schizophrenia patients exhibiting violent behavior (Frogley et al. 2012, Topiwala & Fazel 2011). Two randomized controlled double-blind trials confirmed the antiaggressive effects of clozapine. The first trial compared clozapine, olanzapine, risperidone, and haloperidol in patients with schizophrenia or schizoaffective disorder (Volavka et al. 2002). Analyses of the hostility item of the PANSS have demonstrated superior efficacy of clozapine in comparison with risperidone and haloperidol (Citrome et al. 2001b). Neither risperidone nor olanzapine showed superiority to haloperidol.

Additional analyses of the same trial focused on incidents of overt physical aggression instead of hostility (Volavka et al. 2004). The results demonstrated overall superiority in antiaggressive efficacy of all three atypicals over haloperidol.

The second trial compared clozapine, olanzapine, and risperidone in patients with schizophrenia or schizoaffective disorder who were selected for being violent (Krakowski et al. 2006). Efficacy of clozapine to reduce incidents of overt physical was superior to olanzapine, which was in turn superior to haloperidol.

Although its antiaggressive efficacy is firmly established, clozapine is not a panacea (Volavka 2012). Many patients, perhaps as many as 50% , fail to respond to this medication (Lieberman et al. 1994). These non-responders could be the patients with a history of conduct disorder as discussed above (Swanson et al. 2008b).

Furthermore, clozapine does not exhibit its full antiaggressive effect until an effective dose – around 500 mg/day – is reached (Volavka et al. 2004). Also, patients sometimes refuse or discontinue clozapine for various reasons, including the need for blood monitoring. Finally, some patients cannot receive or continue clozapine treatment for medical contraindications or adverse effects.

Olanzapine is effective against overt physical aggression (Krakowski et al. 2006) and against hostility (Volavka et al. 2002) in long-term schizophrenia patients. Olanzapine's antiaggressive effects were weaker than those of clozapine (Krakowski et al. 2006), and not distinguishable from other atypical antipsychotics (Swanson et al. 2008a). However, in first episode schizophrenia, it was superior to haloperidol, quetiapine, and amisulpride in its effect against hostility (Volavka et al. 2011).

Risperidone reduced violent behavior and hostility in open studies of schizophrenia (Chengappa et al. 2000, Bitter et al. 2005). An analysis of a randomized double-blind study of risperidone in schizophrenia patients confirmed its superiority over placebo in reducing hostility (Czobor et al. 1995). Other comparisons of risperidone with various antipsychotics in randomized trials showed mostly no significant differences in antiaggressive effects (Swanson et al. 2008a).

Aripiprazole. Five randomized, double-blind studies of patients with schizophrenia or schizoaffective disorder compared aripiprazole with placebo. Three of the studies included haloperidol as a comparator. Post-hoc analyses showed that aripiprazole was superior to placebo and not significantly different from haloperidol in reducing hostility (Volavka et al. 2005).

Quetiapine. Open studies supported effectiveness of quetiapine against hostility and aggression (Citrome et al. 2001a, Villari et al. 2008). These observations were confirmed by post-hoc analyses of randomized double-blind trials demonstrating superiority of quetiapine over placebo in reducing aggression in schizophrenia patients (Arango & Bernardo 2005). In another study, quetiapine's antiaggressive effects were similar to other atypical antipsychotics, but they were weaker than those of perphenazine (Swanson et al. 2008a).

Ziprasidone. Post-hoc analyses of effects on hostility used data from a randomized, open-label study comparing ziprasidone with haloperidol in schizophrenia and schizoaffective disorder (Citrome et al. 2006). Both drugs reduced hostility; ziprasidone was superior to haloperidol only during the first week of the study. Ziprasidone's antiaggressive effect were similar to other antipsychotics (Swanson et al. 2008a).

Other medications

Anticonvulsants and lithium are widely used for the adjunctive treatment of aggressive behavior in schizophrenia patients. However, this treatment is not supported by adequate empirical evidence. While it may be effective in individual patients, such treatment must be closely monitored, and it must be stopped if it fails to show clear benefits (Citrome 2009).

Adrenergic beta-blockers showed antiaggressive action in several studies and case reports (Sheppard 1979, Whitman et al. 1987, Yorkston et al. 1977, Caspi et al. 2001, Newman & McDermott 2011), and this approach has been recommended for violence in schizophrenia as a second-line treatment (Kane et al. 2003) (p. 39).

Beta-blockers reduce blood pressure and pulse rate; and these adverse effects are partly responsible for the recent lack of interest in exploring beta-blockers as a treatment of violence. Beta-blockers have been supplanted by antipsychotics. Nevertheless, antipsychotics are not always effective; efficacy of adjunctive beta-blockers in the treatment of persistently aggressive schizophrenia patients should be studied further. Recently published meta-analyses indicating an association between the polymorphism of the catechol-o-methyl transferase (COMT) gene and violence in schizophrenia may rekindle interest in this area (Singh et al. 2012) (Bhakta et al. 2012).

Non-pharmacological treatment

Aggressive behavior in many schizophrenia patients fails to respond adequately to pharmacological treat-

ments. This is due, in part, to an etiological heterogeneity of this behavior. As discussed above, history of conduct disorder, as well as comorbid antisocial personality disorder, constitute alternative pathways to violence in schizophrenia. Aggressive behavior in schizophrenia patients with these problems is not directly caused by psychosis, and therefore it is less likely to respond to antipsychotics.

Furthermore, there are patients whose violent behavior does respond to antipsychotics, but who become non-adherent to treatment and start abusing drugs or alcohol after they are discharged from the hospital. Non-adherence to pharmacological treatment and substance abuse elevate the risk of violence in schizophrenia (Alia-Klein et al. 2007, Swartz et al. 1998b, Volavka & Citrome 2011).

Standard psychiatric treatment programs have limited success in reducing recidivistic violent and criminal behavior in such patients. Some studies show that outpatient civil commitment may reduce violence in such cases (Swanson et al. 2000).

A specialized, cognitive behavioral treatment program was developed for such population. The program, called STAIR (Service for Treatment and Abatement of Interpersonal Risk), has been operating since 1997 at a state hospital providing treatment to the severely mentally ill in the New York City region. This inpatient treatment program specifically targets the factors associated with violent and criminal behavior. Substance abuse programs complete the curriculum. The Cognitive Skills Training course is the core of the program. The program has reduced rates of arrest and hospitalization and improved adherence to treatment (Yates et al. 2010). Similar programs have been developed elsewhere (Haddock et al. 2009, Cullen et al. 2012).

Bipolar disorder

The prevalence of violent behavior in bipolar disorder is at least as high as in schizophrenia. Clinicians have been aware of the problems with violent behavior in bipolar disorder for a long time. However, research efforts in this area have lagged behind analogous work in schizophrenia (Latalova 2009).

Epidemiology

A sample representing the population of the United States was collected for National Comorbidity Survey (NCS) between 1990 and 1992. Diagnoses ("lifetime" and "last year") and history of aggressive behavior during the preceding year were determined by interviews (Corrigan & Watson 2005). Aggressive behavior (or its proxy, "trouble with the police or the law") was reported by 12.2% of individuals with the diagnosis of bipolar disorder, 8.2% with alcohol abuse, 10.9% with drug abuse and 1.9% with no disorder. All diagnoses mentioned above are lifetime. The analogous numbers for "last year" diagnoses were 16.0%, 9.1%,

19.8%, and 2.0% (Corrigan & Watson 2005). Thus, when the patient was exhibiting symptoms of bipolar disorder (or substance abuse) during the 12-month period covered by the aggression survey, the frequency of reported aggression increased. Thus, comorbidities increased the frequency of aggressive behavior.

The NESARC study conducted in 2001-2002 involved interviews to assess lifetime prevalence of aggressive behavior as well as the lifetime DSM-IV psychiatric disorders in 43093 adults representing the population of the United States (Pulay et al. 2008). The lifetime prevalence of aggressive behavior after age 15 was 0.66% in persons without lifetime psychiatric disorder, but 25.34% and 13.58% in bipolar disorder I and II, respectively. The respective odds ratios were 3.72 (2.94-4.70) and 1.77 (1.26-2.49). These numbers represent a mixture of pure bipolar disorders (without comorbid diagnoses) and bipolar disorders with comorbid diagnoses. The prevalence of aggressive behavior in pure bipolar (without comorbidity) was 2.52% and 5.12%, respectively. Comparable prevalence of aggressive behavior for pure alcohol dependence and drug dependence was, respectively, 7.22% and 11.32%. The rates of comorbidity of bipolar disorder with alcohol dependence, drug dependence, paranoid personality disorder, and antisocial personality disorder were significantly elevated (Grant et al. 2005). These comorbidities increase the risk of violence.

Another set of analyses of the NESARC study sought to determine the prevalence of criminal justice involvement during episodes of mania and to identify whether specific manic symptoms contribute to this risk (Christopher et al. 2012). Analyses aimed to determine the rate of legal involvement (being arrested, held at the police station, or jailed) of individuals with bipolar I disorder during the most severe lifetime manic episode. Among the 1,044 respondents (2.5%) who met criteria for having experienced a manic episode, 13.0% reported legal involvement during the most severe manic episode. Legal involvement was more likely among those with symptoms of increased self-esteem or grandiosity, increased libido, excessive engagement in pleasurable activities with a high risk of painful consequences, having more manic symptoms, and having both social and occupational impairment (Christopher et al. 2012).

Data on diagnoses, sociodemographic information, and violent crime in Sweden from January 1, 1973, through December 31, 2004 were obtained for a study of bipolar disorder (Fazel et al. 2010b). Individuals with 2 or more discharge diagnoses of bipolar disorder (n=3743), general population controls (n=37 429), and unaffected full siblings of individuals with bipolar disorder (n=4059) were the subjects. After the first diagnosis, 355 individuals with bipolar disorder (9.5%) committed violent crime compared with 629 general population controls (1.7%) (adjusted odds ratio, 6.6; 95% confidence interval, 5.8-7.6) (Fazel et al. 2010a). The risk was most increased in patients with substance

abuse comorbidity (adjusted odds ratio, 19.9; 95% confidence interval, 14.7-26.9). However, there was still a significant risk increase even in patients without substance abuse comorbidity (adjusted odds ratio, 3.1; 95% confidence interval, 2.6-3.8) (Fazel et al. 2010a).

Clinical observations during hospitalization and immediately prior to it suggest that the risk of violence is high during acute manic episodes (Binder & McNiel 1988, Barlow et al. 2000).

A study compared the prevalence of aggression in bipolar disorder patients with persons showing other psychopathology and healthy controls (Ballester et al. 2012). Subjects with bipolar I and bipolar II disorder (n=255), other psychopathology (n=85), and healthy controls (n=84) were recruited. Aggression was measured using a questionnaire. Bipolar disorder patients showed significantly higher aggression scores than the other groups. Independent of the severity of bipolar disorder and polarity of the episode, those in a current mood episode showed significantly higher aggression scores than those not in a current mood episode. Subjects with current psychosis showed significantly higher total aggression scores, hostility, and anger than those without current psychosis (Ballester et al. 2012).

Clinical features

A factor analysis showed that aggression in bipolar disorder was associated with paranoia and irritability (Cassidy et al. 1998a). This irritable aggression remained stable in time across consecutive manic episodes (Cassidy et al. 2002).

In a more detailed study, aggression was associated with irritability, uncooperativeness, impatience, and lack of insight. Subsequent cluster analysis of this data set revealed four subtypes of mania, one of them labeled as "aggressive" (Sato et al. 2002). In a study of patients with bipolar disorder, manic or mixed, aggression appeared with similar frequency in the two subtypes (Cassidy et al. 1998b).

Thus, aggression is a feature of manic and mixed episodes of bipolar disorder, develops in the context of irritability, and may be an enduring individual trait.

The preceding studies investigated symptoms occurring contemporaneously with aggression. We will now take a broader perspective, looking at concomitants of aggression in bipolar disorder that are not necessarily contemporaneous with aggressive behavior.

Psychological links between inward and outward aggression have been of interest to psychiatrist since Freud. Relation between suicide and aggression in bipolar disorder is particularly important. Patients with bipolar disorder who had a history of suicide attempt were compared with those without such a history (Oquendo et al. 2000).The attempters scored higher on scales assessing hostility and lifetime history of aggression. In a similar study of bipolar patients, suicide attempters were compared with non-attempters (Michaelis et al. 2004). The attempters scored signi-

ficantly higher on a hostility scale (Buss & Durkee 1957), particularly on the subscale that assesses overt physical aggression. They also showed higher level of impulsiveness. Impulsiveness and hostility were correlated in the attempter subset.

A study compared impulsivity and aggression between 143 controls, 138 bipolar disorder and 186 major depressive disorder patients with or without a history of suicide attempt (Perroud et al. 2011). The patient groups showed higher impulsivity scores and more severe lifetime aggression than controls. Impulsivity distinguished major depressive disorder subjects without a history of suicide attempt from those with such a history, but not in bipolar disorder subjects. Impulsive and aggressive traits were strongly correlated in suicide attempters (independently of the diagnosis) but not in non-suicide attempters. Thus, impulsivity may be a suicide risk marker in major depressive disorder but not in bipolar disorder, and its strong correlation with aggressive traits seems specifically related to suicidal behaviors (Perroud et al. 2011)

As noted in the epidemiological studies described above, comorbidity with other disorders elevates the risk of aggression in patients diagnosed with bipolar disorder, and the comorbidity rates are high. Clinical studies are consistent with the epidemiological ones. A study showed that alcohol abuse/dependence comorbidity ranged between 31.9% and 47.3%, drug abuse/dependence abuse range was 15.1-34.2% , depending on age of onset (Perlis et al. 2004). Early onset was associated with higher risk of comorbidity. Other studies yield a range of 17-64% for substance abuse comorbidity with bipolar disorder (Baldassano 2006).

The impact of alcohol abuse on symptom presentation was examined in patients with acute bipolar mania with and without current alcohol abuse (Salloum et al. 2002). The comorbid group showed higher levels of impulsivity and aggressive behavior. In general, the evidence for the role of substance use disorders in the pathophysiology of aggression in the mentally ill is overwhelming (Swartz et al, 1998a, Fazel et al. 2010a).

Comorbidity of bipolar disorder with antisocial personality disorder was demonstrated in the NESARC sample as described above (Grant et al. 2005). It was also described in clinical vignettes (Thorneloe & Crews 1981) and observations in forensic facilities and prisons (Good 1978). This comorbidity would of course elevate the risk of aggression since the diagnosis of antisocial personality disorder is partly defined by it.

The NESARC analysis does not give specific comorbidity rate of bipolar disorder with borderline personality disorder (Grant et al. 2005). However, that comorbidity does elevate the risk of aggressive behavior, as demonstrated by a study of bipolar patients (Garno et al. 2008). In that study, trait aggression was assessed by the Brown-Goodwin scale (Brown et al. 1979), and history of childhood trauma was ascertained by a questionnaire. Trait aggression was strongly related to the presence of comorbid borderline personality

disorder as well as the history of childhood trauma and the severity of current manic and depressive symptoms (Garno et al. 2008).

In addition to elevating the risk of aggression, comorbidity with borderline personality disorder is also associated with higher impulsiveness in patients with bipolar disorder (Carpiniello et al. 2011). This is not surprising, since impulsive aggression is a core component of borderline personality disorder (Latalova & Prasko 2010).

Executive dysfunction predicted aggressive behavior among psychiatric inpatients (N=85, 27.6% diagnosed as bipolar) (Serper et al. 2008). Bipolar patients who were stable and euthymic performed significantly worse on neuropsychological tests of executive function than controls, and showed a relative lack of inhibition (Mur et al. 2007).

It is now clear that "remitted" euthymic bipolar patients have distinct impairments of executive function, verbal memory, psychomotor speed, and sustained attention (Latalova et al. 2011). It is possible that a neuropsychological dysfunction, perhaps as a trait, is a predisposing factor for aggressive in bipolar patients. These neuropsychological findings, plus the elevated trait hostility and impulsivity mentioned before, could be seen as a part of a diathesis that predisposes some bipolar patients to become aggressive when experiencing the stress of a manic episode.

Finally, bipolar disorder is associated with poor insight (Latalova 2012). Impaired insight is linked to aggressive behavior in psychiatric disorders (Alia-Klein et al. 2007, Antonius 2005, Ekinci & Ekinci 2012, Lera et al. 2012). Thus, impaired insight may be one of the mechanisms that raise the risk of violence in bipolar disorder.

Management of aggression in bipolar disorder

Aggression during manic episode in the context of acute agitation

Acute agitation is a common presentation of a manic episode. Staff training in behavioral management of acute agitation is extremely important, since their intervention may prevent an escalation of behavioral dyscontrol. The first interventions include clearing the room, having staff available to assist, and encouraging the patient to talk about his\her needs and concerns (Volavka et al. 2012). Prompt use of sedating or calming agents is important.

Benzodiazepines

Benzodiazepines are commonly used, particularly where alcohol or sedative withdrawal is a possibility.

Lorazepam is a benzodiazepine that is reliably absorbed intramuscularly, has no active metabolites and has a half-life between 10 and 20 hours; usual dose is 0.5–2.0mg every 1–6 hours. Caution is required when respiratory depression is a possibility. Lorazepam is not recommended for long-term daily use because of the potential for tolerance and dependence.

Antipsychotics

First-generation antipsychotics have been used to manage agitated behavior in acute mania. These agents continue to be used, but are associated with extrapyramidal adverse effects, including akathisia (which can be confused with underlying agitation) and acute dystonia. Combination treatment of first-generation antipsychotics, such as haloperidol, with lorazepam is supported by the results of a randomized, double-blind, clinical trial that compared intramuscular haloperidol 5 mg, intramuscular lorazepam 2 mg or both in combination in psychotic, agitated and aggressive patients treated in emergency departments (n=98) (Battaglia et al. 1997). Adverse effects of haloperidol can be mitigated by concurrent administration of promethazine, as demonstrated by several studies identified in a Cochrane review (Huf et al. 2009).

Second-generation antipsychotics are also used to treat agitation. Three are available in short-acting intramuscular formulations (ziprasidone, olanzapine and aripiprazole), with effect sizes for the reduction of agitation similar to that observed for haloperidol or lorazepam (Citrome 2007). Their major advantage over first-generation antipsychotics is their lower propensity for extrapyramidal adverse effects.

In clinical development is inhaled loxapine, where the drug is delivered using a handheld device that produces a thermally generated condensation aerosol free of excipients or propellants, resulting in rapid delivery into the lung and then into the systemic circulation (Citrome 2012). Inhaled loxapine provided a rapid, well-tolerated acute treatment for agitation in patients with bipolar I disorder (Kwentus et al. 2012).

Long-term management

Pharmacological management

Irritability and aggression comprise a core feature of mania, and successful treatment of the underlying manic episode is therefore expected to reduce or eliminate the concurrent aggressive behavior. Thus, long-term antiaggressive pharmacological treatment of manic patients is co-extensive with the general management of bipolar disorder. Such general information is outside of the scope of this review. The reader is referred to generally available guidelines (Collins et al. 2010, Fountoulakis et al. 2012, Podawiltz 2012).

Non-pharmacological management

Cognitive-behavioral therapy (CBT) has been used to address many aspects of bipolar disorder that raise the risk of aggression, including comorbid personality disorders and substance use disorders as well as treatment nonadherence. A randomized controlled study of CBT in bipolar patients focused on treatment adherence (Cochran 1984). In comparison with a control group, the patients who received six CBT sessions demonstrated superior adherence to medication, better understanding of their treatment, and fewer hospitalizations. Manuals for the use of CBT in bipolar

disorder are available (Basco & Rush 2007). Parts of the manuals are specifically directed towards treatment adherence and substance use problems.

Family members are among the most frequent victims of assaults by patients diagnosed with mental disorders. Family-focus psychoeducational treatment addresses problems in communications in the family, lack of information about the illness, and lack of skills in conflict resolution (Herman et al. 2004).

Conclusion

Most patients with schizophrenia and bipolar disorder are not violent. Nevertheless, the risk of violence in patients with these disorders is greater than in general population. This risk is particularly high in schizophrenia and bipolar disorder with comorbid substance use disorders and personality disorders, but it exists even without such comorbidities. Pharmacological treatments are the principal tools to manage violence in psychoses. However, their effectiveness is limited due to inherent treatment resistance, treatment non-adherence, and the fact that some violent behavior in patients diagnosed with schizophrenia or bipolar disorder is not directly caused by psychosis. Comorbidities are frequently implicated in violent behavior of psychotic patients, and their detection and treatment are therefore of primary importance. Psychosocial treatments are necessary components of the management of violence in psychosis.

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Correspondence:

Jan Volavka, MD, Professor Emeritus of Psychiatry
New York University School of Medicine
PO Box 160663, Big Sky, MT 59716, USA
E-mail: janvolavka@gmail.com