

Review Article

Aggression in Psychoses

Jan Volavka

New York University School of Medicine, P.O. Box 160663, Big Sky, MT 59716, USA

Correspondence should be addressed to Jan Volavka; janvolavka@gmail.com

Received 25 November 2013; Revised 16 December 2013; Accepted 18 December 2013; Published 12 February 2014

Academic Editor: Jane E. Boydell

Copyright © 2014 Jan Volavka. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Most individuals diagnosed with a mental illness are not violent, but some mentally ill patients commit violent acts. PubMed database was searched for articles published between 1980 and November 2013 using the combination of key words “schizophrenia” or “bipolar disorder” with “aggression” or “violence.” In comparison with the general population, there is approximately a twofold increase of risk of violence in schizophrenia without substance abuse comorbidity and ninefold with such comorbidity. The risk in bipolar disorder is at least as high as in schizophrenia. Most of the violence in bipolar disorder occurs during the manic phase. Violence among adults with schizophrenia may follow two distinct pathways: one associated with antisocial conduct and another associated with the acute psychopathology, particularly anger and delusions. Clozapine is the most effective treatment of aggressive behavior in schizophrenia. Emerging evidence suggests that olanzapine may be the second most effective treatment. Treatment nonadherence greatly increases the risk of violent behavior, and poor insight as well as hostility is associated with nonadherence. Nonpharmacological 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 is not sufficient.

1. Introduction

Many people believe that psychiatric patients are dangerous, and fear of violence is the most important part of the stigma of mental illness. This belief persists despite the fact that most psychiatric patients are in fact not violent and that they are much more likely to be victims rather than perpetrators of aggressive behavior.

Although the public fear of patients is overblown, there is a general consensus among experts that severe mental illness does increase the risk of violence. Indeed, violent behavior of the mentally ill presents a multitude of problems. There is the risk of injuries or death of victims and perpetrators. Caring for violent psychiatric patients challenges the clinician. It elicits fear, countertransference problems, and eventual burnout. It complicates the efforts of all caregivers. Caring for a violent relative is emotionally exhausting; it is obviously very difficult to live with an assaultive patient.

Importantly, violence affects the cost of treatment. Today, violent behavior is a leading cause of hospitalization, which may be prolonged if that behavior persists. Staff time is costly, and violent patients require a lot of it. Finally, there are societal costs such as the time spent by the police that have to

deal with assaultive patients in the community, and the enormous stress imposed on the jails and prisons where many assaultive psychiatric patients are incarcerated.

This review will examine the epidemiology, underlying mechanisms and pathways to violence, and the management of aggression in schizophrenia and bipolar disorder.

2. Methods

PubMed database was searched for articles published between 1980 and November 2012. For the general searches on aggression in psychoses, the combinations of key words “schizophrenia” or “bipolar disorder” with “aggression” or “violence” were used. For the treatment searches, generic names of medications 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.

Additionally, the review draws on the author’s own experimental and other studies in the area of violence in psychoses over the past 30 years. Published and unpublished materials were included.

3. Definitions and Assessment Methods

Many definitions of *aggression* have been offered [1]. The most useful and parsimonious (albeit imperfect) definition states that aggression is overt action intended to harm. This term may describe animal or human behavior. Human aggression can be assessed quantitatively with various rating scales designed for this purpose. The overt aggression scale (OAS) [2] and its modification (modified overt aggression scale (MOAS)) [3, 4] have been frequently used to separately assess verbal aggression and physical aggression against objects, against self, and against others. Aggression against self is outside the scope of this review and it will not be discussed here. The term *aggression* is typically used in biomedical and psychological literature.

Aggressive behavior has been classified into various subgroups. A useful classification defines two subtypes: impulsive or premeditated aggression. Impulsive aggression is a hair-trigger aggressive response to environmental provocation, characterized by a loss of behavioral control. This is in contrast with premeditated aggression which is defined as a planned aggressive act that lacks spontaneity and behavioral agitation.

This discussion leads us back to the definition of aggression stated above: “an overt action *intended* to harm.” Without the intent, the definition would make no sense: any unintentional error resulting in an injury to another person would be misclassified as aggression. But some cases of impulsive aggression represent a response to provocation that comes so fast that we may have some doubts about the assailant’s ability to fully form an intent in a fraction of a second. Even more seriously, that ability may be impaired or lost in cases of intoxication. The ability to form an intent is in doubt in psychotic or demented persons. To make things even more difficult, we do not fully understand the term “intent.” Thus, the definition of aggression offered here is imperfect. But so are all the other definitions that have been published. We have to keep these imperfections in mind when using the definition of aggression. A more extensive discussion of these issues can be found elsewhere [1].

Violence is defined as physical aggression among humans. This term tends to be more commonly used in sociology and criminology (e.g., *violent crime*). Some authors use the terms *violence* and *aggression* interchangeably, depending on context and style.

Violence perpetrated by psychiatric patients in the community can be assessed (and defined) by the MacArthur community violence interview that distinguishes two levels of severity: minor violence, corresponding to simple assault without injury or weapon use, and serious violence, corresponding to any assault using a lethal weapon or resulting in injury, any threat with a lethal weapon in hand, or any sexual assault [5–8].

The US Bureau of Justice Statistics’s definition of violent crime includes murder, rape and sexual assault, robbery, and assault (<http://www.bjs.gov/index.cfm?ty=tp&tid=31> accessed 11 20 2013).

Agitation is excessive motor and/or verbal activity. It may include verbal aggression manifested by threats, abuse,

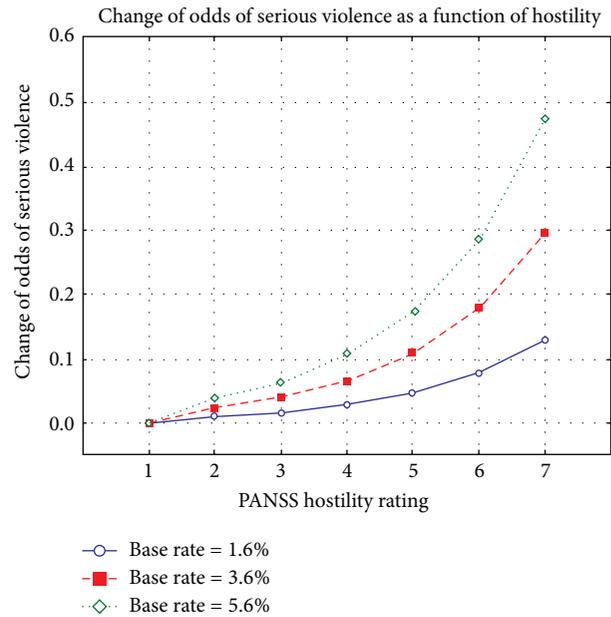


FIGURE 1: Change of odds of serious violence as a function of hostility. The computation and display were provided by Pal Czobor, PhD, using the data published by Swanson et al. [8].

or incoherent screams. Agitation may be assessed using the excited component of the positive and negative syndrome scale (PANSS) [9]. The excited component consists of five PANSS items: tension, excitement, hostility, uncooperativeness, and poor impulse control; each item is rated from 1 (absent) to 7 (extreme).

Hostility signifies unfriendly attitudes. Manifestations of hostility include overt irritability, anger, resentment, or verbal aggression. Hostility is assessed and operationally defined by rating scales. The most frequently used method to assess hostility is the “hostility” item in the PANSS [9] or in the brief psychiatric rating scale (BPRS) [10]. The principal clinical importance of hostility is in its close association with violence. Hostility item in the PANSS is rated from 1 (absent) to 7 (extreme). For each unit increase on this 7-point rating of hostility, the odds of serious aggression (assessed with MacArthur community violence interview) were reported to increase by a factor of 1.65 ($P < 0.001$) [8] (see Figure 1).

The association of hostility rating with overt physical aggression has led to its widespread use as a proxy measure of violence. Hostility is also associated with nonadherence to medication [11] and difficulties in psychological treatments. Hostility interferes with therapeutic alliance.

Psychopathy is currently defined by assessment instruments developed by Hare and his group. The psychopathy checklist-revised (PCL-R) [12] is a 20-item instrument. Each item is scored on a three-point scale (0 = does not apply, 1 = applies to an extent, and 2 = applies). Items are summed, the total score range is 0–40. PCL-R can be used as a dimensional instrument (employing the total score) or as a categorical classifier using a cut-off score. The recommended cut-off

score is 30 [12], but sometimes lower cut-off scores are used [13].

Psychopathy Checklist. Screening version (PCL:SV) was developed as a shorter variant of PCL-R, suitable for administration to individuals with major psychiatric disorders [14]. It has 12 items that are scored in the same way as the PCL-R. The total score range is 0–24. The cut-off score for the diagnosis of psychopathy is 18. Analyses of the PCL:SV (and PCL-R) yielded two factors: factor 1 reflects personal and affective characteristics. Some of these items, such as lack of remorse and empathy, cannot be reliably distinguished from blunted affect in persons with schizophrenia. Factor 2 comprises behaviors manifesting continued socially deviant, unstable lifestyle and thus may be indexing the same syndrome as diagnoses of conduct disorder and antisocial personality disorder. Much of the research work on comorbidity of psychopathy with schizophrenia used the PCL:SV.

It should be noted that the antisocial personality disorder in the DSM-IV-TR and the DSM-5 [15] is partly defined by acts of violence, but the diagnosis can be given in the absence of aggressive behavior.

The American Psychiatric Association Board of Trustees recognized the numerous shortcomings of the current DSM-5 system for the classification of personality disorders. Nevertheless, the decision was to preserve the current system to maintain continuity with clinical practice. At the same time, an alternative DSM-5 model for personality disorders was developed and presented [15, page 761]. For the Antisocial Personality Disorder, the alternative system introduces “psychopathic features” as a diagnostic specifier, and “psychopathy” is introduced as a “distinct variant.” The main new alternative criteria for antisocial personality disorder are somewhat closer to Hare’s concept of psychopathy in that they pay more attention to personality functioning than the current system.

These modifications introduced in the alternative model represent partial improvements in comparison with the current system. Hopefully, work on these modifications will continue, and DSM-6 will switch from the current model to a new system for the diagnosis of personality disorders.

4. Schizophrenia

4.1. Prevalence of Violent Behavior in Schizophrenia. The National Institute of Mental Health (NIMH) supported the epidemiological catchment area surveys (ECA), an epidemiological study that provided prevalence estimates for mental disorders in the United States [16, 17]. The data were based on structured diagnostic household interviews conducted at five sites in the United States. It should be noted that this classical study had different sampling and time frames than most other studies. It included prisoners and it was conducted in the early 1980s before deinstitutionalization was fully completed and when antipsychotic medications differed from those used today.

The surveys included questions pertaining to any history of violent behavior. Analyses of these data yielded a one-year prevalence of violent behavior of 8.4% in persons

diagnosed with schizophrenia and 2.1% in those without any mental disorder [18, 19]. Males were more violent than females. Comorbid substance abuse substantially increased the prevalence of violent behavior in schizophrenia.

A longitudinal study assessed the population rates of violence in schizophrenia linking nationwide Swedish registry data of hospital admissions for schizophrenia and data on criminal convictions between 1973 and 2006 [20]. The study comprised a total of 80,025 individuals, 8,003 of whom were diagnosed with schizophrenia. In this schizophrenia subset, 13.2% of individuals had a record of at least one violent criminal offense, compared with 5.3% of individuals in general population (odds ratio (OR) = 2.0, 95% confidence interval (CI) = 1.8–2.2). The risk of violence was particularly elevated in individuals with schizophrenia and comorbid substance abuse: in individuals without substance abuse, OR = 1.2 (95% CI = 1.1–1.4), whereas with substance abuse OR = 4.4 (95% CI = 3.9–5.0) [20].

To study familial confounding, Fazel et al. also investigated risk of violence among unaffected siblings ($n = 8123$) of patients with schizophrenia. The risk increase among the patients with substance abuse comorbidity was significantly less pronounced when unaffected siblings were used as controls (28.3% of those with schizophrenia had a violent offense compared with 17.9% of their unaffected siblings; adjusted OR = 1.8; 95% CI = 1.4–2.4; $P < .001$ for interaction), suggesting significant familial confounding of the association between schizophrenia and violence [20]. These results are further discussed in a subsequent section on genetic influences.

A meta-analysis of 20 studies comparing risk of violence in schizophrenia and other psychosis with general population controls [21] confirmed and expanded the results reviewed above [20]. The meta-analysis comprised data from 18,423 individuals diagnosed with schizophrenia that were compared with 1,714,904 individuals in general population. There was a modest but statistically significant increase of risk of violence in schizophrenia (OR = 2.1, 95% CI = 1.7–2.7) without comorbidity and OR = 8.9 (95% CI = 5.4–14.7) with substance abuse comorbidity. Risk estimate of violence in individuals with substance abuse (but without psychosis) showed an OR of 7.4 (95% CI = 4.3–1) [21].

The national epidemiologic survey on alcohol and related conditions (NESARC) was a two-wave project conducted in the United States ($N = 34,653$; Wave 1: 2001–2003; Wave 2: 2004–2005). Indicators of mental illness in the year prior to Wave 1 were used to predict violence between Waves 1 and 2 [22]. Violence was assessed by self-report in a structured interview. Contrary to prior published evidence, severe mental illness did not independently predict violent behavior. Comorbid substance use disorder was one of the independent predictors.

We reanalyzed the same NESARC data using different methods [23]. Contrary to the results reported by Elbogen and Johnson [22], we found that individuals with severe mental illness with or without comorbid substance abuse were significantly more likely to be violent than those with no mental or substance use disorders. As expected, those with comorbid mental and substance use disorders had the highest risk of violence. Male gender, history of childhood abuse and

neglect, household antisocial behavior, binge drinking, and stressful life events were also associated with violence [23].

The epidemiological studies reviewed above used samples that aimed to represent populations. Other studies, however, used samples that were selected clinically; that is, they selected individuals who were ascertained to be diagnosed with schizophrenia.

The MacArthur violence risk assessment study enrolled 1136 patients with mental disorders at three acute inpatient facilities in the United States and followed them up during their first year after discharge from the hospital to monitor their violent behavior [5]. The comparison group consisted of 519 people residing in the same neighborhoods. A special assessment tool, the MacArthur community violence interview, was developed for this project (see above). The interview was conducted with the subjects and collateral informants. The one-year prevalence of violence was 17.9% for patients with a major mental disorder and without a substance abuse diagnosis and 31.1% for patients with a major mental disorder and a substance abuse diagnosis. The results showed no significant difference between the prevalence of violence by patients without substance abuse and the prevalence of violence by comparison group members who were also without substance abuse. Substance abuse raised the rate of violence in both groups. The methods and interpretation of this influential study raised certain concerns [24].

The NIMH supported clinical antipsychotic trials of intervention effectiveness (CATIE) [25] enrolled a national sample of 1,445 schizophrenia patients from 57 United States sites. Information on violent behavior during the 6 months prior to enrollment was collected using a version of the MacArthur Community Violence Interview (see above). The results showed that 4% had committed serious acts of violence involving weapons or causing injury to another individual, and 16% had engaged in less serious acts that would be described as simple battery, such as slapping, pushing, and shoving [8]. Minor violence was associated with co-occurring substance abuse. Females were significantly more likely to be violent than males; this effect appeared to be attributable to a group of young women with a history of substance abuse and arrest.

Homicide is the violent crime that is almost always reported to the police, and its investigation results more frequently in the identification of the perpetrator in comparison with other crimes. The Finnish police have been able to solve about 95% of all homicides committed during several decades. The prevalence of various mental disorders among 693 Finnish homicide offenders was determined [26]. The prevalence of schizophrenia and schizophreniform psychoses was 6.4% in male and 6.0% in female offenders. Primary or secondary diagnosis of alcoholism was detected in 32.9% of male and 32.1% of female offenders. Comparing the prevalence of schizophrenia and schizophreniform psychoses in offenders with the general population, the age-adjusted OR = 9.7, 95% CI = 7.4–12.6 for males and 9.0, 95% CI = 3.6–22.2 for females.

Other data suggested that females diagnosed with schizophrenia may be more at risk for committing homicide than their male counterparts. A study of 1087 homicide offenders

(convicted or exculpated) in Austria [27] detected that 4.3% male and 13.5% female offenders had schizophrenia. Comorbid substance abuse/dependence was diagnosed in 46.3% of the male (39% alcohol and 24.4% nonalcohol) and 11.8% of the female schizophrenics (5.9% alcohol and 11.8% nonalcohol). A comparison of risk for schizophrenia or schizophreniform disorder in offenders with the general population in Austria showed age-adjusted ORs in men 5.85, 95% CI = 4.3–8.0; in women OR = 18.4, 95% CI = 11.2–31.6 [27]. For males and females combined, the proportion of offenders with schizophrenia or schizophreniform disorder (with or without alcohol use or abuse comorbidity) was 5.3%, OR = 8.8, 95% CI = 6.6–11.5. For those *without* that comorbidity, the respective numbers were 3.8%, OR = 7.1, 95% CI = 5.1–9.8. The numbers for subjects with alcohol comorbidity were substantially higher.

Psychiatric diagnoses of 2005 individuals convicted of homicide or attempted homicide in Sweden were analyzed [28]. It was found that 8.9% of homicide offenders had schizophrenia, 2.5% had bipolar disorder, and 6.5% had other psychoses. It should be noted that 47.5% of offenders with complete information had a primary or secondary diagnosis of substance use disorder. A meta-analysis of 10 studies indicated that the risk of homicide in psychosis is maximal during the first episode before the start of treatment [29].

Thus, schizophrenia may be associated with a somewhat higher risk for homicide than for less serious violent behavior. However, caution is required when comparing the homicide studies with the other studies of violence risk in mental illness. It should be noted that, except for Schanda et al. [27], the homicide studies do not present separate estimates of the risk for homicide in schizophrenia without substance abuse comorbidity. That comorbidity is high in homicide offenders and may be responsible for a substantial proportion of risk variance. There may be a gender difference in the risk for homicide in schizophrenia patients, but the evidence is unreliable (note the large CI for the OR in females in the Schanda et al. study [27]). The risk elevation in the first episode of psychosis is well supported and it underscores the need for early treatment and monitoring.

When interpreting the prevalence and risk data reviewed above, it is important to remember that they largely apply to schizophrenia patients dwelling in the community. Except for the ECA study [18, 19], hospitalized and incarcerated patients did not contribute to these estimates. Violent behavior is a frequent reason for hospitalization and arrest of schizophrenia patients. Thus, the estimates of prevalence and risk of violent behavior in the community are lowered by a constant removal of the most violent schizophrenia patients to hospitals and jails. In many cases, violent behavior continues inside these institutions [30, 31]. Furthermore, it is important to point out that only some incidents of aggressive behavior lead to prosecution. Therefore, studies based on self-reports must be distinguished from those based on convictions.

In summary, prevalence estimates of violent behavior in patients diagnosed with schizophrenia vary depending on the severity of violence. The six-month prevalence of serious violence perpetrated by community-dwelling schizophrenia patients in the United States is approximately 4%.

Schizophrenia patients without substance abuse comorbidity are about twice as likely to perpetrate violent acts as their counterparts in the general population and about nine times as likely if that comorbidity is present. Thus, substance abuse is a major risk factor for violence in schizophrenia. Future efforts at tertiary prevention and management of schizophrenia should be targeted at the diagnosis and systematic treatment of comorbid substance use disorder.

4.2. Comorbidity of Schizophrenia and Psychopathy/Antisocial Personality Disorder. Studies in prisoners have established that psychopathy alone (without any comorbidity) is associated with violent behavior [32]. A meta-analysis involving 15,826 individuals indicated that the PCL-R had a moderate effect size in predicting interpersonal violence [33]. Another meta-analysis showed a similar result [34].

The PCL:SV was administered to 26 persistently violent patients and 25 matched nonviolent patients, all diagnosed with schizophrenia or schizoaffective disorder [35]. Mean psychopathy scores were higher for violent patients than nonviolent patients. Higher psychopathy scores were associated with earlier age of onset of illness and more arrests for both violent and nonviolent offenses.

The relationship between schizophrenia/psychopathy comorbidity and violence was addressed with ratings on the PCL-R that were used to test the hypothesis that psychopathy predicts violent recidivism in a Swedish forensic cohort of 202 male violent offenders with schizophrenia. Psychopathy was strongly associated with violent recidivism [13].

Interestingly, Finnish homicide offenders with schizophrenia ($N = 72$) had significantly *lower* mean score on PCL-R than a comparison sample of homicide offenders without schizophrenia [36].

The relationship between psychopathy and violence was confirmed in a sample of 94 Australian men diagnosed with schizophrenia-spectrum disorders [37]. The predictive validity of PCL-R scores remained significant after controlling for substance abuse.

Several studies examined relative contributions of psychopathy, psychotic symptoms, and other factors to the development of aggressive behavior. One of them assessed the contributions of psychosis, disordered impulse control, and psychopathy to assaults perpetrated by inpatients with schizophrenia or schizoaffective disorder [38]. A semistructured interview aimed to elicit reasons for assaults from assailants and victims. Consensus ratings indicated that approximately 20 percent of the assaults were directly related to positive psychotic symptoms. Factor analysis revealed two psychosis-related factors, one related to positive psychotic symptoms and the other to psychotic confusion and disorganization, as well as a third factor that differentiated impulsive from psychopathic assaults [38].

In an English study, 33 violent and 49 nonviolent forensic patients were assessed using neuropsychological tasks and measures of psychotic symptoms and psychopathy (PCL:SV) [39]. The “violent” group had significantly higher psychopathy scores. Personality factors (factor 1 of PCK:SV) rather than symptoms and neuropsychological function predicted violence [39].

A multisite study examined the correlates of antisocial personality disorder among 232 men with schizophrenic disorders and comorbid antisocial personality disorder [40]. Comparisons of the men with and without antisocial personality disorder revealed no differences in the course or symptomatology of schizophrenia. By contrast, individuals with antisocial comorbidity committed significantly more crimes and significantly more nonviolent crimes than those without that comorbidity. The mean total number of *violent* crimes was 5.1 (SD = 8.6) for patients with antisocial comorbidity and 1.9 (SD = 3.0) without antisocial comorbidity; $t = 2.6$, $P = 0.01$. This P value was uncorrected for multiple comparisons; the significance was lost after Bonferroni correction [40].

Thus, comorbid psychopathy or antisocial personality disorder in patients with schizophrenia or schizoaffective disorder is associated with violent behavior. This risk increase is statistically independent of comorbid substance use disorders and the severity of psychotic symptoms that also elevate the risk.

As stated above in the section on definitions and assessment methods, Factor 2 of the PCL:SV may be indexing a pattern of aggressive behavior since childhood that is captured by a diagnosis of conduct disorder in childhood. Recent imaging findings suggest that schizophrenia preceded by conduct disorder represents a distinct subtype of schizophrenia [41].

4.3. Risk Factors and Pathways to Violence in Schizophrenia.

Risk factors for violence can be classified in several ways. One of them is a classification depending on the temporal proximity to a violent event: proximal factors act to some extent as triggers, whereas the role of distal factors is less direct. Another classification is based on the factor’s modifiability: static factors such as genotype and demographics are not modifiable, whereas dynamic factors such as symptoms are amenable to change. The latter classification is somewhat more clinically oriented.

4.3.1. Static Factors. These factors include age, gender, genetic influences, childhood maltreatment, development of childhood conduct disorder, history of arrest and conviction, and history of adult victimization.

There is robust evidence indicating that young age is a risk factor for violence in general population as well as in psychotic patients [1, 42]. As mentioned in the preceding section on prevalence, the effect of gender is somewhat equivocal. A large recent review reported that male gender was modestly associated with violence in psychotic patients (OR = 1.6, 95% CI = 1.2–2.1) [43]. This systematic review and metaregression analyzed 110 studies involving 45,533 psychotic individuals, 87.8% of whom were diagnosed with schizophrenia. A total of 8,439 of these individuals (18.5%) were violent [43].

Genetic Influences. In a nonpatient sample, heritability of assaultiveness was shown to be approximately 50% [44]. A large epidemiological project focusing primarily on the risk of violent crime among schizophrenia patients had a genetic component to study familial confounding [20]. This project

was reviewed in the section on prevalence. The main genetic finding was that the variation in violence risk depended on the degree of relatedness between the patient and the control group. Compared with unrelated general population controls, the risk of violent crime in individuals with schizophrenia and violent crime was increased approximately 4-fold. However, unaffected siblings had higher rates of substance abuse compared with unrelated general population. Therefore, the risk increase for schizophrenia with substance abuse comorbidity compared with these siblings was substantially reduced from 4-fold to approximately 2-fold. This reduction suggested familial confounding of this association. It is not clear if this familial confounding occurred through genetic susceptibility or early environmental effects [20].

Efforts to explore a molecular basis of genetic influences in this area have focused on neurotransmitters and their genes. Enhancement of central dopaminergic or noradrenergic function facilitates aggressive behavior in most animal studies [45]. Drugs that increase central dopaminergic transmission, such as amphetamines and cocaine, may elicit psychosis with violent behavior [1]. Furthermore, drugs that diminish noradrenergic activity (such as propranolol) have antiaggressive effects in humans [46, 47]. Thus, the preponderance of the evidence suggests that catecholamines generally enhance violence.

However, the information on genetic influences on violence in schizophrenia is limited. Much of the molecular genetic work in schizophrenia and violence has focused on catechol-O-methyltransferase (COMT), one of the enzymes involved in the catabolism of catecholamines; amines in the brain. A functional single nucleotide polymorphism involves a Val (valine) to Met (methionine) substitution at codon 158 of the COMT gene. The Val allele at this locus is associated with high enzymatic activity, whereas the Met allele is associated with low enzymatic activity. Homozygosity for the Met allele confers a 3- to 4-fold reduction in COMT activity relative to Val homozygotes; heterozygotes have intermediate activity.

Male heterozygous COMT knockout mice exhibit increased aggressive behavior [48]. When mouse strains were ranked according to their aggressivity, the ranking correlated with the expression of the COMT gene in the hippocampus: the lower the level of expression, the more aggressive the strain [49]. Thus, consistent with the enhancing effects of catecholamines on aggression, low expression of the COMT is associated with increased aggression in animal models. Based on the findings discussed above, it would seem appropriate to hypothesize that, in general, the COMT polymorphism would exert an effect in humans such that the Met allele would be associated with increased violent behavior.

COMT had originally been explored as a candidate gene for schizophrenia, and the association of COMT polymorphism with violence in schizophrenia patients was first tested in this context. Initial association studies yielded encouraging results [50, 51], and numerous attempts at replication followed. Two meta-analyses of such association studies have been published to date. One of them included 15 studies comprising 2,370 individuals with schizophrenia [52]. Evidence of a significant association between the presence of

a Met allele and violence was found such that men's violence risk increased by approximately 50% for those with at least one Met allele compared with homozygous Val individuals (diagnostic OR = 1.45; 95% CI = 1.05–2.00; $z = 2.37$, $P = 0.02$). No significant association between the presence of a Met allele and violence was found for women [52].

A meta-analysis testing the same association in 14 studies was independently conducted by another group [53]. Similarly, it was found that the Met158 allele of the COMT gene confers a significantly increased risk for violent behavior in schizophrenia. Taken together, these findings have potential implications for pharmacogenetics of schizophrenia. Future research could test the usefulness of this genetic information for personalized treatment.

Childhood Maltreatment. In a classical cohort study of 908 child abuse and neglect court cases, Widom established that being maltreated as a child increases risk for delinquency, adult criminal behavior, and violent criminal behavior [54]. However, she observed that the majority of abused and neglected do not become delinquent, criminal, or violent. The interaction between childhood maltreatment and MAOA polymorphism described above [55] partially explained the differences in the effects of maltreatment on violent behavior [56]. More recent reports confirm the association between childhood maltreatment and adult criminal violence in individuals without schizophrenia [57, 58].

The evidence for that association in schizophrenia is more tentative, although individuals with schizophrenia report more childhood adversities than controls [59]. History of childhood physical abuse was one of the factors associated with the occurrence of incidents of assaultive behavior among 183 male patients of a forensic psychiatric hospital, 106 of whom were diagnosed with schizophrenia [30]. A group of 60 male psychotic patients legally detained at a forensic unit was assessed for history of violence; the participants were also asked about any history of childhood abuse, substance use, medication adherence, and current insight in terms of awareness of mental illness [60]. Multiple regression analysis indicated that the history of childhood abuse was associated with the severity of violence independently of substance use, medication adherence, and insight ($\beta = 0.18$, $P < 0.01$) [60]. In a group of 28 schizophrenia patients with a history of violence, 46% had experienced child abuse and/or neglect [61]. Childhood physical (OR = 2.2, 95% CI = 1.5–3.1) or sexual abuse (OR = 1.9, 95% CI = 1.5–2.4) was moderately associated with violence [43].

Thus, similar to robust evidence in general population indicating a relationship between childhood maltreatment and violent behavior in adulthood, there are data indicating that this relationship also exists in psychotic patients. Interactions between genes and environment that affect risk for violent behavior have been studied in general population.

Childhood Conduct Problems. Males diagnosed with schizophrenia are at increased risk to have exhibited conduct disorder before age 15. A study examined the consequences of conduct disorder among 248 adult men with schizophrenia or schizoaffective disorder [62]. Participants were assessed at

hospital discharge and repeatedly during the subsequent two years. In adulthood, the diagnosis and symptoms of conduct disorder were associated with increased nonviolent and violent criminal offending, after adjusting for diagnoses of substance use disorders. During the 2-year follow-up period, conduct disorder diagnosis and the number of conduct disorder symptoms were associated with aggressive behavior, controlling for lifetime diagnoses of substance use disorders, substance misuse measured objectively and subjectively, and medication compliance. During the two-year follow-up period, neither the diagnosis of conduct disorder nor the number of conduct disorder symptoms was associated with levels of positive and negative symptoms, compliance with medication, substance use, or readmission. Thus, it appears that conduct disorder is a distinct comorbid disorder proceeding alongside the course of schizophrenia and elevating the risk of violent behavior independently of psychotic symptoms [62].

These results have implications for understanding etiology and for treatment. If the relationship between the history of conduct disorder and aggression in schizophrenia is independent of comorbid substance use disorder and of medication, then “reduction of substance use disorder would reduce violent behavior only among patients with no history of aggressive behavior prior to the onset of schizophrenia. Among adults with schizophrenia and a history of conduct disorder, treatments designed to reduce aggressive and antisocial behaviors, in addition to treatment of substance use disorder, may be necessary to reduce violence” [63]. These implications for treatment remain to be tested experimentally.

The findings reported by the Hodgins group are consistent with evidence suggesting 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. That evidence came from a reanalysis of data from the CATIE [64]. The prevalence of violence was higher among patients with a history of childhood conduct problems than among those without this history (28.2% versus 14.6%; $P < 0.001$). In the conduct-problems group, violence was associated with current substance use at levels below diagnostic criteria. Positive psychotic symptoms were linked to violence only in the group without conduct problems. 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 [64].

History of Violent and Criminal Behavior. Past violence is one of the strongest predictors of future violence [1]. Detailed confirmation of this rule has been provided in a recent analysis demonstrating that history of assault, imprisonment, arrest, and conviction for any offense were all showing strong associations with violent behavior, with ORs ≥ 4.2 [43].

Most offenders diagnosed with schizophrenia get their first conviction before their first psychotic episode [65].

A study examined offending among 301 individuals experiencing their first episode of psychosis [66]. The results showed that 33.9% of the men and 10.0% of the women had a record of criminal convictions, and 19.9% of the men and 4.6% of the women had been convicted of at least one violent crime. This increased their risk for future violent behavior. These findings have important implications for the understanding, prevention, and treatment of violent behavior in psychotic patients.

Adult Victimization. Relationships between victimization and offending were addressed by several studies. In individuals diagnosed with serious mental illness, history of a criminal conviction was associated with having been robbed ($r = 0.09$, $P < 0.05$), threatened with a weapon ($r = 0.12$, $P < 0.001$), and beaten ($r = 0.10$, $P < 0.01$) [67].

Relationships between victimization and crime were examined in a sample of 331 involuntarily admitted patients with serious mental illness [68]. Being a victim of a crime predicted patients' violence significantly and independently of age and substance use (OR = 1.76 [95% CI = 1.11–2.79], $P < 0.05$).

Logistic regression was used to estimate the bivariate association between being violent towards others and violent victimization. The OR = 7.12 ($P \leq 0.001$) [69]. Patients with serious mental illness charged with a criminal offense were more likely (OR = 4.80 [95% CI = 3.71–6.20], $P \leq 0.001$) than patients who were nonoffenders ($n = 2,413$) to have a record of violent victimization and more likely (OR = 3.07 [95% CI = 2.55–3.69], $P \leq 0.001$) to have a record of nonviolent victimization, controlling for the effects of age, gender, and substance use disorders [70]. Thus, relationship between victimization and violent behavior by patients with serious mental illness has been established.

4.3.2. Dynamic Factors. These factors include psychotic symptoms, comorbid substance use disorders and psychopathy, lack of insight, and nonadherence to treatment. Some of these factors that are in close temporal proximity to a violent assault act as triggers. Immediate environmental provocation, intoxication, and current clinical symptoms play a role.

The environmental provocation can be real. A study using video recordings of interactions between psychiatric inpatients has revealed that threatening and intrusive behaviors in assailants and victims preceded 60% of assaults [71]. When psychiatric inpatients are asked by staff to do (or to stop doing) something, they may respond by assaulting the staff member. Such situation was in fact listed by staff members as the most frequent reason for assaults on a maximum security psychiatric unit [72]. However, the assaulters in the same study listed being teased or “bugged” as the most frequent reason. Some of this “bugging” may have been delusional.

Intoxication. As discussed repeatedly in previous sections, comorbid substance use disorders substantially elevate the risk of violence in individuals diagnosed with schizophrenia. Acute intoxication is one of the mechanisms for this effect. Binge drinking, the pattern of alcohol consumption that is most likely to lead to intoxication, was significantly related to

violence in an analysis of the NESARC data mentioned earlier [23]. Recent alcohol misuse was moderately associated with violence in psychotic patients (OR = 2.2, 95% CI = 1.6–2.9) in a recent meta-analysis of risk factors for violence in psychosis [43].

Schizophrenic individuals who also abuse drugs may be particularly likely to become assaultive under the influence of alcohol [73]. Furthermore, the lifetime prevalence of comorbidity between schizophrenia and any substance use or dependence was estimated at 47.0% (OR = 4.6), and the analogous numbers for alcohol abuse or dependence were 33.7% (OR = 3.3) [74]. These data were determined from 20,291 interviews in the ECA study mentioned earlier in the section on prevalence. Thus, schizophrenia patients may be more vulnerable to acute alcohol effects and are more likely to abuse alcohol than members of the general population.

Current Clinical Symptoms. Current clinical psychotic symptoms play a role in the development of violent behavior in schizophrenia. As described in the preceding section, approximately 20% of assaults perpetrated by psychotic inpatients are attributable to positive psychotic symptoms [38]. Positive symptoms of schizophrenia were associated with an increased risk of violence, whereas negative symptoms showed the opposite relationship [8]. In a large metaregression study, the relation between positive symptoms and violence was very modest (OR = 1.2, 95% CI = 1.0–1.5), whereas negative symptoms had no effect on violence [43]. Command hallucinations to harm others may increase risk of violence, although the level of compliance with such commands varies [75, 76].

Mentally ill patients sometimes make threats to kill, and such threats need to be evaluated by clinicians. An Australian study addressed this problem [77]. A total of 613 individuals convicted of threats to kill had their prior contact with public mental health services established at the time of this offense. The group's subsequent criminal convictions were established 10 years later using the police database. Within 10 years, 44% of threateners were convicted of further violent offending, including 19 (3%) homicides. Those with histories of psychiatric contact (40%) had a higher rate (58%) of subsequent violence. Homicidal violence was most frequent among threateners with a schizophrenic illness. Sixteen threateners (2.6%) killed themselves, and three were murdered. Thus, this study revealed high rates of assault and even homicide following threats to kill [77].

A group of delusional psychotic symptoms—so-called threat/control-override (TCO) symptoms—was reported to lead to violence [78, 79]. These symptoms are elicited by questions like “dominated by forces beyond you,” “thoughts put into your head,” and “people who wished you harm”.

An analysis of the data from the MacArthur violence risk assessment study [5] suggested that although delusions can precipitate violence in individual cases, they do not increase the overall risk of violence. An early analysis suggested that the threat/control-override symptoms were not associated with violent behavior in that study [80].

However, when the same MacArthur data set was reanalyzed using methods that considered the temporal proximity of the symptoms to violent events, the results indicated

relationships between specific delusions and violence [81]. The delusions included being spied upon (OR = 1.62, 95% CI = 1.06–2.47, $P = 0.027$), being followed (OR = 1.90, 95% CI = 1.29–2.80, $P = 0.001$), being plotted against (OR = 1.70, 95% CI = 1.14–2.52, $P = 0.009$), being under control of person/force (OR = 1.92, 95% CI = 1.24–2.97, $P = 0.003$), thought insertion (OR = 1.63, 95% CI = 1.00–2.66, $P = 0.048$), and having special gifts/powers (OR = 1.95, 95% CI = 1.31–2.92, $P = 0.001$). All these delusions were associated with angry affect ($P < 0.05$). Inclusion of anger in the model significantly attenuated the main effects (except grandiose delusions), indicating an indirect pathway. Thus, temporal proximity is important when investigating relationships between delusions and violence. Anger due to delusions is the key factor in this pathway [81]. The importance of temporal proximity for research on causes of violence is now being increasingly accepted [23].

Similar findings were reported by the same group of investigators using data from the East London first episode psychosis study [42]. The participants were 458 patients with first episode psychosis who were 18 to 64 years of age. Patients were clinically assessed and interviewed about their overt violent behavior while experiencing psychotic symptoms during the 12-month period prior to interview. The prevalence of violence was 38% during the 12-month period, and 12% of the sample engaged in serious violence. Anger was the only affect due to delusions that was positively associated with violence. Three highly prevalent delusions demonstrated pathways to serious violence mediated by anger due to delusional beliefs: persecution, being spied on, and conspiracy. Thus, anger due to delusions is a key factor that explains the relationship between violence and acute psychosis [42].

Patients with first episode of psychosis who had a record of criminal convictions prior to contact with mental health services showed impaired performance on neuropsychological studies in comparison with their nonoffending patient counterparts. Offenders had significantly lower IQ scores than nonoffenders, both current and premorbid. The offenders were further distinguished by significantly poorer performance on the verbal learning and short-term verbal recall, visual recall memory, a measure of visual-spatial perception and organization, and three subtests of the WAIS, digit symbol, which assesses processing speed and vocabulary and comprehension, which index verbal intelligence [66].

Lack of Insight. A prospective study of 63 inpatients diagnosed with schizophrenia or schizoaffective disorder provided what was probably the first rigorous demonstration of the relationship between insight and violence [82]. Similar observations regarding the lack of insight into illness and into legal consequences of their illness were described in a sample of 115 violent patients with schizophrenia in a jail or court psychiatric clinic [83].

The German national crime register was searched for records of criminal offenses committed by 1662 patients with schizophrenia treated between 1990 and 1995 at a German hospital. Analyses were performed to determine predictors of later criminal behavior, and psychopathology was assessed. Sixty-two (3.7%) patients were convicted for physical injury

offenses in the 7–12 years after discharge. Significantly higher rates of criminal conviction and recidivism were found for patients with lack of insight at discharge. Analyses also showed a significantly higher risk of nonviolent and violent crimes in patients with a hostility syndrome at admission and discharge. There was a significantly lower incidence of criminal behavior in subjects with a depressive syndrome [84].

In a study of pretrial detainees that was described in the segment on childhood maltreatment [60], impaired insight (lack of awareness of having a mental illness) was significantly related to the severity of reported violence, and that relationship was statistically independent of the effects of substance use, medication adherence, and childhood abuse. Schizophrenia patients without concomitant substance abuse or Axis II disorders ($N = 133$) were recruited for a Turkish study of violence [85]. History of violence, lower self-reflectiveness, worse insight, and delusion severity were significant predictors of violence in a comparison of 47 violent with 86 nonviolent patients.

In a study of 168 psychotic patients (86 with schizophrenia and 43 with bipolar disorder) in Spain, it was found that patients showing poor insight showed higher hostility and impaired impulse control; these variables were assessed as PANSS items [86]. The authors hypothesized that lack of insight was the primary problem, leading to increased hostility and impairment of impulse control. Lack of insight was moderately associated with violence in a large metaregression analysis ($OR = 2.7$, $95\% CI = 1.4-5.2$) [43].

However, a study of 209 schizophrenia patients has shown that while insight was associated with aggression in univariate analysis, the association was no longer significant after controlling for psychopathy scores and positive symptoms [87].

In summary, preponderance of evidence links violence in psychotic individuals to their impaired insight into mental illness. This effect may be indirect, mediated through the reduced adherence to treatment that is associated with poor insight.

Nonadherence to Treatment. Nonadherence to antipsychotic medication treatment is a major problem in treating schizophrenia. Less than 50% of schizophrenia patients are adherent to their medication [88, 89]. Nonadherence has been associated with symptom worsening, including aggressive behavior [90]. Non-adherence with medication was modestly associated with violence in a large metaregression study ($OR = 2.0$, $95\% CI = 1.0-3.7$) [43]. Somewhat surprisingly, the effect of non-adherence with psychological therapies on violence appeared considerably stronger ($OR = 6.7$, $95\% CI = 2.4-19.2$) [43]. It should be noted that only three studies of non-adherence to psychological therapies were used for the computation of the OR, whereas nine studies were used for medication non-adherence.

Comorbidity of alcohol or other drug abuse with poor adherence to medication further elevates the risk of violent behavior among persons with severe mental illness [91]. As discussed in the preceding section, impaired insight may lead to reduced adherence. Canadian researchers noted that

poor insight was one of the predictors of poor adherence to medication in a sample of 200 patients with first episode psychosis [92]. Furthermore, medication adverse effects such as parkinsonism, weight gain, and loss of libido may additionally reduce the patients' willingness to take medication [88].

While non-adherence to medication certainly elevates the risk for violence, hostility also appears to contribute to the development of non-adherence in patients with schizophrenia or schizoaffective disorder [11]. However, rising hostility may be the result of inadequate treatment or inadequate antipsychotic response, leading to patient's unwillingness to continue treatment.

Antisocial personality disorder/psychopathy is perhaps also affecting adherence to medication treatment. This is suggested by the fact that history of aggressive behavior, arrest, or incarceration was strongly related to non-adherence to treatment in a large prospective naturalistic study of schizophrenia patients [93].

In the CATIE study [25], higher levels of insight at baseline were significantly associated with lower levels of schizophrenia symptoms at followup, and more positive medication attitudes, which were in turn associated with better adherence with medication treatment [94].

Relationships between insight, hostility, and adherence were examined in a post hoc analysis of the data obtained in the European First Episode Schizophrenia Trial (EUFEST) [95]. EUFEST was a randomized, one-year open trial comparing the effectiveness of haloperidol, amisulpride, olanzapine, quetiapine, and ziprasidone in first episode schizophrenia, schizoaffective disorder, or schizophreniform disorder. The primary outcome measure was all-cause treatment discontinuation. Secondary measures included the PANSS and the Hayward scale [96], a measure of adherence.

The reanalysis investigated concurrent and predictive associations to determine whether medication adherence varies as a function of hostility and lack of insight [97]. Predictive association of hostility and lack of insight (assessed as PANSS items) with non-adherence to medication (Hayward scale) was statistically significant at one month of treatment (Figure 2).

Thus, non-adherence to treatment is of central importance among pathways to violence in schizophrenia. It is closely related to substance use disorder. Furthermore, impaired insight and probably increased hostility are among the symptoms that are impairing adherence. Also, comorbid antisocial features are linked with non-adherence.

4.4. Treatment of Violent Behavior in Schizophrenia

4.4.1. Atypical Antipsychotics. Atypical antipsychotics are currently the principal treatment of aggressive behavior in schizophrenia.

Aripiprazole was compared with placebo in five randomized, double-blind studies of patients with schizophrenia or schizoaffective disorder, and haloperidol was used as a comparator in three of these studies. A meta-analysis of these five studies showed that aripiprazole was significantly superior to placebo, but not to haloperidol, in reducing hostility [98].

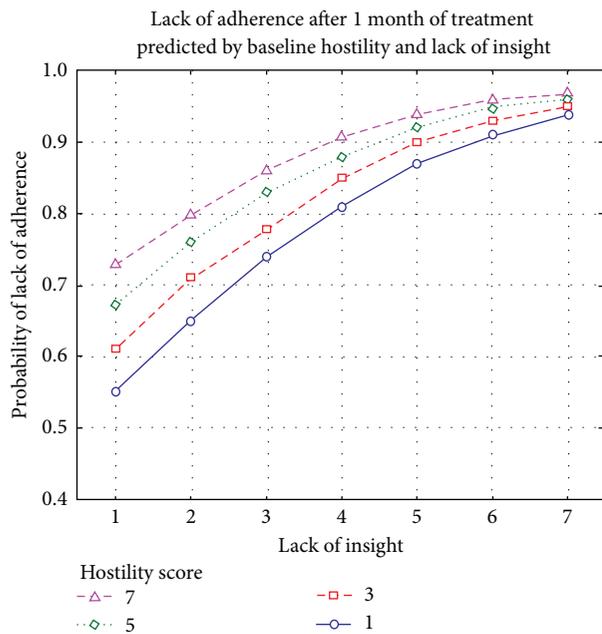


FIGURE 2: Lack of adherence after one month of treatment predicted by baseline hostility and lack of insight. Predictive relationship of hostility and lack of insight at baseline with medication adherence at 1 month of treatment in the study. Logistic regression analysis indicated that both predictor variables reached significance (hostility $P = 0.027$, lack of insight $P < 0.0001$). The figure illustrates the combined effect of the two predictors, that is, the probability of lack of full adherence at 1 month (any score of <7 on the Hayward scale) both as a function of lack of insight at baseline (x -axis) and hostility (y -axis strata depicting additive effects with increasing severity of hostility). Display and computations were provided by Pal Czobor, PhD, who used data collected in the EUFEST study [95, 97].

Clozapine is the most effective, evidence-based treatment for schizophrenia patients exhibiting violent behavior. The evidence for clozapine superiority in antiaggressive effects is based, in part, on randomized, double-blind, controlled trials. One trial compared clozapine, haloperidol, olanzapine, and risperidone in 157 treatment-resistant patients diagnosed with schizophrenia or schizoaffective disorder [99]. The scores on hostility item of the PANSS were used as the dependent variable in analyses that have demonstrated superior efficacy of clozapine in comparison with risperidone and haloperidol [100]. However, neither risperidone nor olanzapine was superior to haloperidol.

Further analyses of the same trial [99] examined incidents of overt physical aggression [101]. The results demonstrated superiority of clozapine over haloperidol, but this effect only became significant after 24 days of treatment when an effective dose of clozapine—around 500 mg/day—was reached. A principal limitation of this trial [99] was that the patients were not selected for being violent.

A more recent double-blind randomized controlled trial compared clozapine, olanzapine, and risperidone in 110 patients diagnosed with schizophrenia or schizoaffective disorder who were selected for being violent [102]. Efficacy of clozapine to reduce the number and severity of aggressive

incidents was superior to olanzapine, which was in turn superior to haloperidol.

Numerous observational studies and uncontrolled trials have indicated superior antiaggressive effectiveness of clozapine in psychotic patients [103–107]. These studies and similar literature are discussed elsewhere [108, 109].

Although its antiaggressive efficacy is firmly established [110, 111], clozapine is not appropriate or effective in all patients [112]. Perhaps as many as 50% of patients fail to respond to clozapine [113]. Patients whose aggressive behavior continues despite clozapine treatment are sometimes those with a history of conduct disorder and comorbid personality disorder [64, 114].

Furthermore, as mentioned above, clozapine is not fully effective during the dose escalation period [101]. The principal risk of clozapine is agranulocytosis which develops in approximately 1% of patients during the first three months of treatment [115]. This requires regular monitoring of white cell counts, which is one of the reasons why patients sometimes refuse or discontinue clozapine. Finally, some patients cannot receive or continue clozapine treatment for medical contraindications or adverse effects.

Olanzapine is effective against hostility [99] and overt physical aggression [102] in long-term schizophrenia patients. Olanzapine was less effective against aggression than clozapine [102]. In the CATIE study [25], its effects in reducing violence during the first 6 months of the study were not distinguishable from other atypical antipsychotics [116].

However, when the treatment effects on PANSS hostility item scores acquired during the 18-month Phase 1 of the CATIE study were analyzed, significant differences between treatments were discovered ($F_{4,1487} = 7.78, P < 0.0001$). Olanzapine was significantly superior to perphenazine and quetiapine at months 1, 3, 6, and 9. It was also significantly superior to ziprasidone at months 1, 3, and 6 and to risperidone at months 3 and 6 [117]. These results were similar to those obtained in the EUFEST study [95], where olanzapine was superior to haloperidol, quetiapine, and amisulpride in its effect against hostility [118].

Quetiapine reduced hostility and aggression in open studies [119, 120]. These observations were confirmed by post-hoc analyses of randomized double-blind trials demonstrating superior antiaggressive effect of quetiapine in comparison with placebo in schizophrenia patients [121]. In CATIE patients, quetiapine's antiaggressive effects were similar to other atypical antipsychotics, but they were weaker than those of perphenazine [116].

Risperidone showed superiority over placebo in reducing hostility in a post-hoc analysis of a randomized double-blind study [122]. Reduction of hostility and violent behavior was seen as an effect of risperidone in open studies of schizophrenia [123, 124]. Other comparisons of risperidone with various antipsychotics in randomized trials showed mostly no significant differences in antiaggressive effects [116].

Ziprasidone effects on hostility were studied using data from a randomized, open-label study comparing ziprasidone with haloperidol in schizophrenia and schizoaffective disorder [125]. Post-hoc analyses showed that both drugs reduced hostility; ziprasidone was superior to haloperidol only during

the first week of the study [126]. Ziprasidone's antiaggressive effect was not significantly different from other antipsychotics in CATIE patients [116].

In summary, clozapine is the most effective antipsychotic in reducing hostility and aggression in patients diagnosed with schizophrenia or schizoaffective disorder. However, its use in clinical practice is limited by its adverse effects, particularly the risk of agranulocytosis. Olanzapine's effectiveness against hostility is inferior to clozapine, but superior to other antipsychotics. Other atypical antipsychotics are also effective, and there are apparently no major differences among them in terms of antiaggressive activity.

4.4.2. Other Medications. *Adrenergic beta-blockers* were demonstrated to possess antiaggressive properties [127–131], but cardiovascular adverse effects such as reduced blood pressure and pulse rate occurring at doses required for antiaggressive effect have limited their clinical use for this indication. Beta-blockers have been supplanted by antipsychotics. Nevertheless, antipsychotics are not always effective and have adverse effects of their own. Therefore, 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 [52, 53] have pointed to a role of catecholamines in the pathogenesis of violence in schizophrenia. These meta-analyses may therefore rekindle future interest in influencing noradrenergic system as a potential treatment for violent behavior in schizophrenia.

Anticonvulsants are widely used for the adjunctive treatment of aggressive behavior in schizophrenia patients. However, empirical evidence supporting efficacy of this treatment is missing. Although it may perhaps be effective in individual patients, such treatment must be monitored, and it must be discontinued if it fails to show benefits or if adverse effects develop [132].

4.4.3. Nonpharmacological Treatment. Pharmacological treatment of aggressive behavior in schizophrenia has variable effectiveness. Etiological heterogeneity of this behavior (and probably of schizophrenia itself) plays a role in this variability of treatment response [133, 134]. As discussed above, history of conduct disorder and current comorbidity with antisocial personality disorder or psychopathy constitute alternative pathways to violence in schizophrenia [64]. Aggressive behavior in schizophrenia patients with these problems may not be directly caused by psychosis, and therefore it is less likely to respond to antipsychotics.

Non-adherence to treatment constitutes a crucially important limit to the effectiveness of pharmacological treatment. Non-adherence to pharmacological treatment and substance abuse elevate the risk of relapse and violence in schizophrenia [60, 134, 135].

Standard psychiatric treatment programs relying only on pharmacological approaches have therefore limited success in reducing recidivistic violent and criminal behaviors. Some

studies show that outpatient civil commitment may reduce violence in such cases [136].

Various cognitive behavioral treatment programs were developed for recidivistically violent and criminal patients. One such program has been operating at a state hospital providing treatment to the severely mentally ill in New York City. The cognitive skills training course is the principal component of the program. Substance abuse programs are included. The program has effects after discharge from the hospital: its graduates exhibit reduced rates of arrest and rehospitalization, as well as improved adherence to treatment [137]. Reports of similar programs operating elsewhere have been published [138, 139]. Programs of this type have a potential to break the revolving-door cycle of hospitalization-discharge-nonadherence to medication and drug abuse-relapse with violent behavior-arrest-jail-hospitalization, and so on. Developing more of these programs in the future could improve the lives of patients and their families and reduce the cost of management of the chronically ill and violent individuals.

Promising practices for psychosocial treatment of schizophrenia include cognitive adaptive therapy, cognitive behavioral therapy for posttraumatic stress disorder, first-episode psychosis intervention, healthy lifestyle interventions, integrated treatment for co-occurring disorders, peer support services, physical disease management, prodromal stage intervention, social cognition training, supported education, and supported housing [140].

5. Bipolar Disorder

5.1. Prevalence of Violent Behavior in Bipolar Disorder. Clinical observations indicated that the risk of violence is particularly high during acute manic episodes during hospitalization and immediately prior to it [141, 142].

Between 1990 and 1992, diagnoses and history of aggressive behavior during the preceding year were determined by interviews in a representative US sample for the national comorbidity survey [143]. Aggressive behavior or "trouble with the police or the law" was endorsed by 12.2% of individuals with the lifetime diagnosis of bipolar disorder, 8.2% with alcohol abuse, 10.9% with drug abuse, and 1.9% with no disorder. The analogous numbers for "last year" diagnoses were 16.0%, 9.1%, 19.8%, and 2.0% [143].

The NESARC study (described in the previous segment on schizophrenia) determined that the lifetime prevalence of aggressive behavior after age 15 was 0.66% in persons without lifetime psychiatric disorder, but 25.3% and 13.6% in bipolar disorders I and II, respectively. The odds ratios were 3.72 (2.94–4.70) and 1.77 (1.26–2.49). These numbers represent a mixture of bipolar disorders with or without comorbid diagnoses. The prevalence of aggressive behavior in pure bipolars I and II (without comorbidity) was, respectively, 2.52% and 5.12%. Comparable prevalence of aggressive behavior for pure alcohol dependence and drug dependence was, respectively, 7.22% and 11.32% [144]. High rates of comorbidity of bipolar disorder with alcohol dependence, drug dependence, paranoid personality disorder, and

antisocial personality disorder were reported [145]. These comorbidities substantially increase the risk of violence.

A total of 3,743 individuals diagnosed with bipolar disorder were compared with 37,429 general population controls in a study using official Swedish records [146]. After the diagnosis, 9.5% of individuals with bipolar disorder committed violent crime compared with 629 general population controls (1.7%) (adjusted OR = 6.6, 95% CI = 5.8–7.6) [147]. Substance abuse comorbidity further increased the risk (adjusted OR = 19.9, 95% CI = 14.7–26.9). In patients without substance abuse comorbidity, there was still a significant risk increase (adjusted OR = 3.1, 95% CI = 2.6–3.8) [147].

Prevalence of criminal justice involvement during episodes of mania and contribution of manic symptoms to such involvement were the subject of additional analyses of NESARC data. Among the 1,044 respondents with bipolar I who experienced a manic episode, 13.0% reported legal involvement (being arrested or jailed) during the most severe manic episode [148]. Legal involvement was associated with symptoms of increased self-esteem and libido, high-risk pleasurable activities, more manic symptoms, and social and occupational impairment [148].

Prevalence of aggressive behavior was compared in a sample of 255 individuals with bipolar I and bipolar II disorder, 85 individuals with other psychopathology, and 84 healthy controls [149]. Lifetime aggression was assessed using a questionnaire that was administered by interviewers in the subjects' homes. Bipolar patients showed significantly higher scores on an aggression questionnaire than the other groups. Subjects who were currently psychotic showed significantly higher total aggression scores, hostility, and anger than those who were not. Patients experiencing a current mood episode showed significantly higher aggression scores than those not in a mood episode. This effect was independent of the severity of bipolar disorder and polarity of the episode [149].

In summary, the prevalence of violent behavior in bipolar disorder is comparable to the prevalence in schizophrenia; it may be even higher. The risk is increased during manic episodes. Similar to schizophrenia, comorbidity of bipolar disorder with substance use disorders further increases the risk. Although the problems caused by violent behavior of bipolar patients are not less important than those caused by similar behavior in schizophrenia, violence in bipolars has received considerably less research attention [150–152].

5.2. Risk Factors for Violence in Bipolar Disorder

5.2.1. Static Factors. Risk factors for aggression were examined in a sample of 100 consecutively evaluated patients with bipolar disorder [153]. The 32-item Brown-Goodwin Aggression scale (BGA) [154] was used to assess lifetime history of aggression. Age was significantly related to BGA scores ($r = -0.236$ and $P = 0.020$), indicating that younger patients were more aggressive. Gender had no significant relation to aggression.

History of *childhood trauma* was retrieved using the childhood trauma questionnaire which examines 5 types of maltreatment (physical abuse, physical neglect, emotional abuse, emotional neglect, and sexual abuse) [155]. The

bivariate correlation coefficient between the BGA and the total score on the childhood trauma questionnaire was 0.325 ($P = 0.001$). When specific subtypes of childhood trauma were explored, physical abuse and emotional abuse were found to be significantly correlated with BGA.

Biological and psychological links between suicide and outward aggression have been intensively studied. Patients with bipolar disorder who had a *history of suicide attempt* scored higher on scales assessing hostility and lifetime history of aggression than those without such a history [156]. In a similar study of bipolar patients, suicide attempters scored significantly higher than nonattempters on a hostility scale [157], particularly on the subscale measuring overt physical aggression [158]. The attempters also showed higher level of impulsiveness. Furthermore, impulsiveness and hostility were correlated in the attempter subset.

5.2.2. Dynamic Factors. *Comorbidities* of bipolar disorder with other disorders are frequent, and some of them substantially elevate the risk of violence. A study of 983 bipolar patients showed that the prevalence of comorbidity between bipolar disorder and alcohol abuse/dependence ranged between 31.9% and 47.3%; drug abuse/dependence abuse range was 15.1%–34.2%, depending on age of onset [159]. Early onset was associated with higher risk of comorbidity. Other studies yield a range of 17%–64% for substance abuse comorbidity with bipolar disorder [160].

The impact of alcohol abuse on symptoms was assessed in patients with bipolar mania with and without current alcohol abuse [161]. 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 robust [91, 147], even though much of the aggression in this population is attributable to other factors as well [162].

As mentioned in the preceding section on prevalence, comorbidity of bipolar disorder with antisocial personality disorder was demonstrated in the NESARC sample [145]. It was also observed in forensic facilities and prisons [163] and described in case reports [164]. This comorbidity would be expected to elevate the risk of aggression since the diagnosis of antisocial personality disorder is partly defined by it.

Bipolar disorder and borderline personality disorder share several clinical features, such as affective lability, impulsiveness, and aggressiveness. These and other shared features have led to discussions debating whether borderline personality disorder should belong to the bipolar spectrum. These disorders co-occur, and there are overlaps as well as important differences in phenomenology and in medication response. A detailed discussion of the relationship between these two disorders and its impact on the risk of violence in psychotic patients can be found elsewhere [114].

Comorbidity with borderline personality disorder elevates risk of aggression while it is also associated with higher impulsiveness in patients with bipolar disorder [165]. This is consistent with the fact that impulsive aggression is a core component of borderline personality disorder [166].

In the study of 100 bipolar patients reviewed above [153], comorbid substance use disorder, posttraumatic stress

disorder, borderline personality disorder, and antisocial personality disorder were all found to be associated with elevated BGA scores in bivariate analyses.

In a stepwise multiple regression, after iterative entries it was found that the combination of three variables provided the best-fit model for the data: diagnosis of borderline personality disorder, total score on the Hamilton depression rating scale [167], and total score on the Young mania rating scale [168]. The model significantly predicted the BGA scores [$F(3, 91) 1/4 21.763, P < 0.001$]. The sample multiple correlation coefficient (r) was 0.646, indicating that approximately 41.8% of the variance of the aggression score in the sample could be accounted for by the linear combination of these three predictors.

Similar to schizophrenia, bipolar disorder is associated with *poor insight* [169]. The predictive effect of insight on clinical outcomes was investigated in a 2-year prospective study of 65 remitted bipolar I disorder patients [170] who were administered the schedule of assessment of insight [171] to assess baseline insight and then received follow-up assessments during subsequent 2 years. Impaired insight into treatment significantly increased the risk of adverse clinical outcomes with bipolar disorder in the 2-year period. The most frequent adverse outcome observed was occurrence of violent behavior. This observation is consistent with the literature on aggression in bipolar disorder. This finding is consistent with the literature on aggression in bipolar disorder [150]. Thus, impaired insight may be one of the mechanisms that raise the risk of violence in bipolar disorder.

Finally, *executive dysfunction* predicted aggressive behavior among psychiatric inpatients with various diagnoses, including bipolar disorder [172]. Stable and euthymic bipolar patients performed significantly worse than controls on neuropsychological tests of executive function and showed an impairment of inhibition [173]. Thus, stable and remitted euthymic bipolar patients have distinct impairments of executive function, verbal memory, psychomotor speed, and sustained attention [174]. It is possible that some of these dysfunctions, perhaps present as traits, predispose bipolar patients to aggressive behavior. These neuropsychological impairments, plus the elevated trait hostility and impulsivity mentioned before, may form a diathesis that predisposes some bipolar patients to respond by aggression to the experience of stress. A manic episode would be a typical stressful experience of these patients, but other stresses that may occur during remissions can have a similar effect.

5.3. Treatment of Violent Behavior in Bipolar Disorder

5.3.1. Treatment of Agitation in Acute Manic Episode. Acute agitation is common in manic episodes. Staff training in the management of agitated patients is important, since their intervention may prevent an escalation of agitation into violence. The first interventions include removing the nonagitated patients from the room, having several staff members available to assist, and encouraging the patient to talk about his\her needs and concerns. Prompt use of sedating or calming agents is important [108].

Benzodiazepines are frequently administered. They are particularly useful in patients who are in withdrawal from alcohol or sedatives. *Lorazepam* is a benzodiazepine that is typically used as injections for nonspecific treatment of agitation since it is reliably absorbed intramuscularly. Its half-life ranges between 10 and 20 hours; usual dose is 0.5–2.0 mg every 1–6 hours. It has no active metabolites. Respiratory depression is a potential adverse effect. Similar to other benzodiazepines, lorazepam has a potential for developing tolerance and dependence. It is therefore not recommended for long-term use.

Antipsychotics. First-generation antipsychotics, mostly haloperidol, have been used to treat agitated behavior in acute mania. These agents are associated with extrapyramidal adverse effects, including acute dystonia and akathisia. These extrapyramidal symptoms are difficult to tolerate. Akathisia can be confused by the staff with underlying agitation; if that happens, it may be erroneously concluded that the dose of haloperidol is too low to be effective. Raising the dose under these conditions is a major error; it will make akathisia worse. Adverse effects of haloperidol can be mitigated by the administration of promethazine [175].

Short-acting intramuscular formulations of atypical antipsychotics aripiprazole, olanzapine, and ziprasidone are available to treat acute agitation. The effects for the reduction of agitation are similar to that observed for haloperidol or lorazepam [176]. These atypical antipsychotics have lower propensity for extrapyramidal adverse effects, which is an advantage in comparison with haloperidol. A recent unpublished randomized double-blind placebo-controlled trial suggests that sublingual tablets of another atypical antipsychotic, asenapine, can be used for treatment of acutely agitated patients [177].

Loxapine, a typical antipsychotic, has recently become available in an inhalation form. The drug is delivered using a device that produces an aerosol, resulting in rapid delivery into the lung and then into the systemic circulation [178, 179]. Inhaled loxapine was demonstrated to be a rapid, well-tolerated treatment for agitation in patients with bipolar I disorder [180].

5.3.2. Long-Term Treatment of Violent Behavior in Bipolar Disorder. Typical symptoms of mania include aggression and irritability. Thus, the treatment of the underlying manic episode should reduce or eliminate the concurrent aggressive behavior. Long-term antiaggressive pharmacological treatment of manic patients is therefore implied in the general management of bipolar disorder. Such general information is not in the scope of this review. General guidelines for the pharmacological treatment of bipolar disorder are available [181–183].

Nonpharmacological management of bipolar disorder frequently uses cognitive behavioral therapy (CBT) that can address many aspects of bipolar disorder elevating 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 addressed treatment adherence [184]. The patients who

received six CBT sessions showed better adherence to medication, better insight, and fewer hospitalizations than a control group. The use of CBT in bipolar disorder has been manualized [185]. Parts of the manuals are directed at treatment adherence and substance use.

Family members are the most likely victims of assaults by psychotic patients. Psychoeducational programs for the patients' families focus on information about the illness, lack of skills in conflict resolution, and communication problems in the family [186].

6. Conclusions

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 represents a major public health problem and contributes to the stigma of mental illness. The risk of violence is further increased if schizophrenia or bipolar disorder patients concurrently suffer with substance use disorders and personality disorders, but it exists even without such comorbidities. Pharmacological treatments, particularly clozapine, are the principal tools for the long-term management of violence in schizophrenia. However, the effectiveness of pharmacotherapy is limited due to treatment resistance, treatment nonadherence, adverse effects, 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 the detection and treatment of comorbidities, particularly substance abuse, are therefore of primary importance. Psychosocial treatments are necessary components of the management of violence in psychosis.

Conflict of Interests

The author declares that there is no conflict of interests regarding the publication of this paper.

References

- [1] J. Volavka, *Neurobiology of Violence*, American Psychiatric Publishing, Washington, DC, USA, 2nd edition, 2002.
- [2] S. C. Yudofsky, J. M. Silver, W. Jackson, J. Endicott, and D. Williams, "The overt aggression scale for the objective rating of verbal and physical aggression," *The American Journal of Psychiatry*, vol. 143, no. 1, pp. 35–39, 1986.
- [3] S. R. Kay, F. Wolkenfeld, and L. M. Murrill, "Profiles of aggression among psychiatric patients—I. Nature and prevalence," *The Journal of Nervous and Mental Disease*, vol. 176, no. 9, pp. 539–546, 1988.
- [4] D. W. Knodler, "The modified overt aggression scale," *The American Journal of Psychiatry*, vol. 146, no. 8, pp. 1081–1082, 1989.
- [5] H. J. Steadman, E. P. Mulvey, J. Monahan et al., "Violence by people discharged from acute psychiatric inpatient facilities and by others in the same neighborhoods," *Archives of General Psychiatry*, vol. 55, no. 5, pp. 393–401, 1998.
- [6] J. W. Swanson, M. S. Swartz, and E. B. Elbogen, "Effectiveness of atypical antipsychotic medications in reducing violent behavior among persons with schizophrenia in community-based treatment," *Schizophrenia Bulletin*, vol. 30, no. 1, pp. 3–20, 2004.
- [7] J. W. Swanson, M. S. Swartz, E. B. Elbogen, and R. A. van Dorn, "Reducing violence risk in persons with schizophrenia: olanzapine versus risperidone," *The Journal of Clinical Psychiatry*, vol. 65, no. 12, pp. 1666–1673, 2004.
- [8] J. W. Swanson, M. S. Swartz, R. A. van Dorn et al., "A national study of violent behavior in persons with schizophrenia," *Archives of General Psychiatry*, vol. 63, no. 5, pp. 490–499, 2006.
- [9] S. R. Kay, L. A. Opler, and J.-P. Lindenmayer, "The positive and negative syndrome scale (PANSS): rationale and standardisation," *The British Journal of Psychiatry*, vol. 155, no. 7, pp. 59–65, 1989.
- [10] W. Guy, *ECDEU Assessment Manual for Psychopharmacology*, National Institute of Mental Health, Rockville, Md, USA, 1986.
- [11] J.-P. Lindenmayer, H. Liu-Seifert, P. M. Kulkarni et al., "Medication nonadherence and treatment outcome in patients with schizophrenia or schizoaffective disorder with suboptimal prior response," *The Journal of Clinical Psychiatry*, vol. 70, no. 7, pp. 990–996, 2009.
- [12] R. D. Hare, *The Hare Psychopathy Checklist-Revised (PCL-R)*, Multi-Health Systems, Toronto, Canada, 2003.
- [13] A. Tengström, M. Grann, N. Långström, and G. Kullgren, "Psychopathy (PCL-R) as a predictor of violent recidivism among criminal offenders with schizophrenia," *Law and Human Behavior*, vol. 24, no. 1, pp. 45–58, 2000.
- [14] S. D. Hart, R. D. Hare, and A. E. Forth, "Psychopathy as a risk marker for violence: development and validation of a screening version of the revised psychopathy checklist," in *Violence and Mental Disorder: Developments in Risk Assessment*, J. Monahan and H. J. Steadman, Eds., pp. 81–98, The University of Chicago Press, Chicago, Ill, USA, 1994.
- [15] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, American Psychiatric Association, Arlington, Va, USA, 5th edition, 2013.
- [16] D. A. Regier, J. H. Boyd, J. D. Burke Jr. et al., "One-month prevalence of mental disorders in the United States, based on five epidemiologic catchment area sites," *Archives of General Psychiatry*, vol. 45, no. 11, pp. 977–986, 1988.
- [17] D. A. Regier, J. K. Myers, M. Kramer et al., "The NIMH epidemiologic catchment area program. Historical context, major objectives, and study population characteristics," *Archives of General Psychiatry*, vol. 41, pp. 934–941, 1984.
- [18] J. W. Swanson, C. E. Holzer III, V. K. Ganju, and R. T. Jono, "Violence and psychiatric disorder in the community: evidence from the epidemiologic catchment area surveys," *Hospital and Community Psychiatry*, vol. 41, no. 7, pp. 761–770, 1990.
- [19] J. W. Swanson, "Mental disorder, substance abuse, and community violence: an epidemiological approach," in *Violence and Mental Disorder: Developments in Risk Assessment*, J. Monahan and H. J. Steadman, Eds., pp. 101–136, The University of Chicago Press, Chicago, Ill, USA, 1994.
- [20] S. Fazel, N. Langström, A. Hjern, M. Grann, and P. Lichtenstein, "Schizophrenia, substance abuse, and violent crime," *The Journal of the American Medical Association*, vol. 301, no. 19, pp. 2016–2023, 2009.
- [21] S. Fazel, G. Gulati, L. Linsell, J. R. Geddes, and M. Grann, "Schizophrenia and violence: systematic review and meta-analysis," *PLoS Medicine*, vol. 6, no. 8, Article ID e1000120, 2009.

- [22] E. B. Elbogen and S. C. Johnson, "The intricate link between violence and mental disorder: results from the national epidemiologic survey on alcohol and related conditions," *Archives of General Psychiatry*, vol. 66, no. 2, pp. 152–161, 2009.
- [23] R. van Dorn, J. Volavka, and N. Johnson, "Mental disorder and violence: is there a relationship beyond substance use?" *Social Psychiatry and Psychiatric Epidemiology*, vol. 47, no. 3, pp. 487–503, 2011.
- [24] P. Czobor, J. Volavka, H. J. Steadman et al., "Violence in the mentally ill: questions remain," *Archives of General Psychiatry*, vol. 56, no. 2, pp. 193–194, 1999.
- [25] J. A. Lieberman, S. T. Stroup, J. P. McEvoy et al., "Effectiveness of antipsychotic drugs in patients with chronic schizophrenia," *The New England Journal of Medicine*, vol. 353, no. 12, pp. 1209–1223, 2005.
- [26] M. Eronen, P. Hakola, and J. Tiihonen, "Mental disorders and homicidal behavior in Finland," *Archives of General Psychiatry*, vol. 53, no. 6, pp. 497–501, 1996.
- [27] H. Schanda, G. Knecht, D. Schreinze, T. Stompe, G. Ortwein-Swoboda, and T. Waldhoer, "Homicide and major mental disorders: a 25-year study," *Acta Psychiatrica Scandinavica*, vol. 110, no. 2, pp. 98–107, 2004.
- [28] S. Fazel and M. Grann, "Psychiatric morbidity among homicide offenders: a Swedish population study," *The American Journal of Psychiatry*, vol. 161, no. 11, pp. 2129–2131, 2004.
- [29] O. Nielssen and M. Large, "Rates of homicide during the first episode of psychosis and after treatment: a systematic review and meta-analysis," *Schizophrenia Bulletin*, vol. 36, no. 4, pp. 702–712, 2010.
- [30] M. J. Hoptman, K. F. Yates, M. B. Patalinjug, R. C. Wack, and A. Convit, "Clinical prediction of assaultive behavior among male psychiatric patients at a maximum-security forensic facility," *Psychiatric Services*, vol. 50, no. 11, pp. 1461–1466, 1999.
- [31] R. B. Flannery, A. Staffieri, S. Hildum, and A. P. Walker, "The violence triad and common single precipitants to psychiatric patient assaults on staff: 16-Year analysis of the assaulted staff action program," *Psychiatric Quarterly*, vol. 82, no. 2, pp. 85–93, 2011.
- [32] R. D. Hare and L. M. McPherson, "Violent and aggressive behavior by criminal psychopaths," *International Journal of Law and Psychiatry*, vol. 7, no. 1, pp. 35–50, 1984.
- [33] A.-M. R. Leistico, R. T. Salekin, J. DeCoster, and R. Rogers, "A large-scale meta-analysis relating the hare measures of psychopathy to antisocial conduct," *Law and Human Behavior*, vol. 32, no. 1, pp. 28–45, 2008.
- [34] G. D. Walters, R. A. Knight, M. Grann, and K.-P. Dahle, "Incremental validity of the psychopathy checklist facet scores: predicting release outcome in six samples," *Journal of Abnormal Psychology*, vol. 117, no. 2, pp. 396–405, 2008.
- [35] K. A. Nolan, J. Volavka, P. Mohr, and P. Czobor, "Psychopathy and violent behavior among patients with schizophrenia or schizoaffective disorder," *Psychiatric Services*, vol. 50, no. 6, pp. 787–792, 1999.
- [36] T. Laajasalo, S. Salenius, N. Lindberg, E. Repo-Tiihonen, and H. Häkkänen-Nyholm, "Psychopathic traits in Finnish homicide offenders with schizophrenia," *International Journal of Law and Psychiatry*, vol. 34, no. 5, pp. 324–330, 2011.
- [37] K. McGregor, D. Castle, and M. Dolan, "Schizophrenia spectrum disorders, substance misuse, and the four-facet model of psychopathy: the relationship to violence," *Schizophrenia Research*, vol. 136, no. 1–3, pp. 116–121, 2012.
- [38] K. A. Nolan, P. Czobor, B. B. Roy et al., "Characteristics of assaultive behavior among psychiatric inpatients," *Psychiatric Services*, vol. 54, no. 7, pp. 1012–1016, 2003.
- [39] R. S. Fullam and M. C. Dolan, "Executive function and inpatient violence in forensic patients with schizophrenia," *The British Journal of Psychiatry*, vol. 193, no. 3, pp. 247–253, 2008.
- [40] P. Moran and S. Hodgins, "The correlates of comorbid antisocial personality disorder in schizophrenia," *Schizophrenia Bulletin*, vol. 30, no. 4, pp. 791–802, 2004.
- [41] B. Schiffer, N. Leygraf, B. W. Muller et al., "Structural brain alterations associated with schizophrenia preceded by conduct disorder: a common and distinct subtype of schizophrenia?" *Schizophrenia Bulletin*, vol. 39, no. 5, pp. 1115–1128, 2012.
- [42] J. W. Coid, S. Ullrich, C. Kallis et al., "The relationship between delusions and violence: findings from the east London first episode psychosis study," *Journal of the American Medical Association Psychiatry*, vol. 70, no. 5, pp. 465–471, 2013.
- [43] K. Witt, R. van Dorn, and S. Fazel, "Risk factors for violence in psychosis: systematic review and meta-regression analysis of 110 studies," *PLoS ONE*, vol. 8, no. 2, Article ID e55942, 2013.
- [44] E. F. Coccaro, C. S. Bergeman, R. J. Kavoussi, and A. D. Seroczynski, "Heritability of aggression and irritability: a twin study of the Buss-Durkee aggression scales in adult male subjects," *Biological Psychiatry*, vol. 41, no. 3, pp. 273–284, 1997.
- [45] S. Comai, M. Tau, and G. Gobbi, "The psychopharmacology of aggressive behavior: a translational approach—part I: neurobiology," *Journal of Clinical Psychopharmacology*, vol. 32, no. 1, pp. 83–94, 2012.
- [46] E. R. Allan, M. Alpert, C. E. Sison, L. Citrome, G. Laury, and I. Berman, "Adjunctive nadolol in the treatment of acutely aggressive schizophrenic patients," *The Journal of Clinical Psychiatry*, vol. 57, no. 10, pp. 455–459, 1996.
- [47] J. M. Silver, S. C. Yudofsky, J. A. Slater et al., "Propranolol treatment of chronically hospitalized aggressive patients," *The Journal of Neuropsychiatry & Clinical Neurosciences*, vol. 11, no. 3, pp. 328–335, 1999.
- [48] J. A. Gogos, M. Morgan, V. Luine et al., "Catechol-O-methyltransferase-deficient mice exhibit sexually dimorphic changes in catecholamine levels and behavior," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 95, no. 17, pp. 9991–9996, 1998.
- [49] C. Fernandes, J. L. Paya-Cano, F. Sluyter, U. D'Souza, R. Plomin, and L. C. Schalkwyk, "Hippocampal gene expression profiling across eight mouse inbred strains: towards understanding the molecular basis for behaviour," *European Journal of Neuroscience*, vol. 19, no. 9, pp. 2576–2582, 2004.
- [50] H. M. Lachman, K. A. Nolan, P. Mohr, T. Saito, and J. Volavka, "Association between catechol O-methyltransferase genotype and violence in schizophrenia and schizoaffective disorder," *The American Journal of Psychiatry*, vol. 155, no. 6, pp. 835–837, 1998.
- [51] R. D. Strous, N. Bark, S. S. Parsia, J. Volavka, and H. M. Lachman, "Analysis of a functional catechol-O-methyltransferase gene polymorphism in schizophrenia: evidence for association with aggressive and antisocial behavior," *Psychiatry Research*, vol. 69, no. 2–3, pp. 71–77, 1997.
- [52] J. P. Singh, J. Volavka, P. Czobor, and R. A. van Dorn, "A meta-analysis of the Val158Met COMT polymorphism and violent behavior in schizophrenia," *PLoS ONE*, vol. 7, no. 8, Article ID e43423, 2012.
- [53] S. G. Bhakta, J. P. Zhang, and A. K. Malhotra, "The COMT Met158 allele and violence in schizophrenia: a meta-analysis," *Schizophrenia Research*, vol. 140, no. 1–3, pp. 192–197, 2012.

- [54] C. S. Widom, "The cycle of violence," *Science*, vol. 244, no. 4901, pp. 160–166, 1989.
- [55] A. Caspi, J. McCray, T. E. Moffitt et al., "Role of genotype in the cycle of violence in maltreated children," *Science*, vol. 297, no. 5582, pp. 851–854, 2002.
- [56] C. S. Widom and L. M. Brzustowicz, "MAOA and the "cycle of violence": childhood abuse and neglect, MAOA genotype, and risk for violent and antisocial behavior," *Biological Psychiatry*, vol. 60, no. 7, pp. 684–689, 2006.
- [57] T. C. Silva, P. Larm, F. Vitaro, R. E. Tremblay, and S. Hodgins, "The association between maltreatment in childhood and criminal convictions to age 24: a prospective study of a community sample of males from disadvantaged neighbourhoods," *European Child & Adolescent Psychiatry*, vol. 21, no. 7, pp. 403–413, 2012.
- [58] N. J. Kolla, C. Malcolm, S. Attard, T. Arenovich, N. Blackwood, and S. Hodgins, "Childhood maltreatment and aggressive behaviour in violent offenders with psychopathy," *Canadian Journal of Psychiatry*, vol. 58, no. 8, pp. 487–494, 2013.
- [59] K. L. McCabe, E. A. Maloney, H. J. Stain, C. M. Loughland, and V. J. Carr, "Relationship between childhood adversity and clinical and cognitive features in schizophrenia," *Journal of Psychiatric Research*, vol. 46, no. 5, pp. 600–607, 2012.
- [60] N. Alia-Klein, T. M. O'Rourke, R. Z. Goldstein, and D. Malaspina, "Insight into illness and adherence to psychotropic medications are separately associated with violence severity in a forensic sample," *Aggressive Behavior*, vol. 33, no. 1, pp. 86–96, 2007.
- [61] M. Bennouna-Greene, V. Bennouna-Greene, F. Berna, and L. Defranoux, "History of abuse and neglect in patients with schizophrenia who have a history of violence," *Child Abuse & Neglect*, vol. 35, no. 5, pp. 329–332, 2011.
- [62] S. Hodgins, J. Tiihonen, and D. Ross, "The consequences of conduct disorder for males who develop schizophrenia: associations with criminality, aggressive behavior, substance use, and psychiatric services," *Schizophrenia Research*, vol. 78, no. 2–3, pp. 323–335, 2005.
- [63] S. Hodgins, "Parental violent crime, previous violence and substance abuse predict future violence in people with schizophrenia," *Evidence-Based Mental Health*, vol. 12, no. 4, article 127, 2009.
- [64] J. W. Swanson, R. A. van Dorn, M. S. Swartz, A. Smith, E. B. Elbogen, and J. Monahan, "Alternative pathways to violence in persons with schizophrenia: the role of childhood antisocial behavior problems," *Law and Human Behavior*, vol. 32, no. 3, pp. 228–240, 2008.
- [65] C. Wallace, P. E. Mullen, and P. Burgess, "Criminal offending in schizophrenia over a 25-year period marked by deinstitutionalization and increasing prevalence of comorbid substance use disorders," *The American Journal of Psychiatry*, vol. 161, no. 4, pp. 716–727, 2004.
- [66] S. Hodgins, M. Calem, R. Shimel et al., "Criminal offending and distinguishing features of offenders among persons experiencing a first episode of psychosis," *Early Intervention in Psychiatry*, vol. 5, no. 1, pp. 15–23, 2011.
- [67] J. A. Lam and R. Rosenheck, "The effect of victimization on clinical outcomes of homeless persons with serious mental illness," *Psychiatric Services*, vol. 49, no. 5, pp. 678–683, 1998.
- [68] V. A. Hiday, J. W. Swanson, M. S. Swartz, R. Borum, and H. R. Wagner, "Victimization: a link between mental illness and violence?" *International Journal of Law and Psychiatry*, vol. 24, no. 6, pp. 559–572, 2001.
- [69] E. Silver, "Mental disorder and violent victimization: the mediating role of involvement in conflicted social relationships," *Criminology*, vol. 40, no. 1, pp. 191–212, 2002.
- [70] T. B. Short, S. Thomas, S. Luebbers, P. Mullen, and J. R. Ogloff, "A case-linkage study of crime victimisation in schizophrenia-spectrum disorders over a period of deinstitutionalisation," *BMC Psychiatry*, vol. 13, article 66, 2013.
- [71] M. L. Crowner, G. Peric, F. Stepic, and S. Lee, "Assailant and victim behaviors immediately preceding inpatient assault," *Psychiatric Quarterly*, vol. 76, no. 3, pp. 243–256, 2005.
- [72] G. T. Harris and G. W. Varney, "A ten-year study of assaults and assaulters on a maximum security psychiatric unit," *Journal of Interpersonal Violence*, vol. 1, no. 2, pp. 173–191, 1986.
- [73] J. A. Yesavage and V. Zarcone, "History of drug abuse and dangerous behavior in inpatient schizophrenics," *The Journal of Clinical Psychiatry*, vol. 44, no. 7, pp. 259–261, 1983.
- [74] D. A. Regier, M. E. Farmer, D. S. Rae et al., "Comorbidity of mental disorders with alcohol and other drug abuse. Results from the epidemiologic catchment area (ECA) study," *The Journal of the American Medical Association*, vol. 264, no. 19, pp. 2511–2518, 1990.
- [75] J. Junginger, "Command hallucinations and the prediction of dangerousness," *Psychiatric Services*, vol. 46, no. 9, pp. 911–914, 1995.
- [76] J. Junginger, L. McGuire, D. E. McNiel, J. P. Eisner, and R. L. Binder, "The paradox of command hallucinations," *Psychiatric Services*, vol. 52, no. 3, article 385, 2001.
- [77] L. J. Warren, P. E. Mullen, S. D. M. Thomas, J. R. P. Ogloff, and P. M. Burgess, "Threats to kill: a follow-up study," *Psychological Medicine*, vol. 38, no. 4, pp. 599–605, 2008.
- [78] B. G. Link and A. Stueve, "Psychotic symptoms and the violent/illegal behavior of mental patients compared to community controls," in *Violence and Mental Disorder: Developments in Risk Assessment*, J. Monahan and H. J. Steadman, Eds., pp. 137–159, The University of Chicago Press, Chicago, Ill, USA, 1994.
- [79] B. G. Link, A. Stueve, and J. Phelan, "Psychotic symptoms and violent behaviors: probing the components of "threat/control-override" symptoms," *Social Psychiatry and Psychiatric Epidemiology*, vol. 33, no. 1, supplement, pp. S55–S60, 1998.
- [80] P. S. Appelbaum, P. C. Robbins, and J. Monahan, "Violence and delusions: data from the MacArthur violence risk assessment study," *The American Journal of Psychiatry*, vol. 157, no. 4, pp. 566–572, 2000.
- [81] S. Ullrich, R. Keers, and J. W. Coid, "Delusions, anger, and serious violence: new findings from the MacArthur violence risk assessment study," *Schizophrenia Bulletin*, 2013.
- [82] C. Arango, A. C. Barba, T. González-Salvador, and A. C. Ordóñez, "Violence in inpatients with schizophrenia: a prospective study," *Schizophrenia Bulletin*, vol. 25, no. 3, pp. 493–503, 1999.
- [83] P. F. Buckley, D. R. Hrouda, L. Friedman, S. G. Noffsinger, P. J. Resnick, and K. Camlin-Shingler, "Insight and its relationship to violent behavior in patients with schizophrenia," *The American Journal of Psychiatry*, vol. 161, no. 9, pp. 1712–1714, 2004.
- [84] M. Soyka, C. Graz, R. Bottlender, P. Dirschedl, and H. Schoech, "Clinical correlates of later violence and criminal offences in schizophrenia," *Schizophrenia Research*, vol. 94, no. 1–3, pp. 89–98, 2007.
- [85] O. Ekinici and A. Ekinici, "Association between insight, cognitive insight, positive symptoms and violence in patients with schizophrenia," *Nordic Journal of Psychiatry*, vol. 67, no. 2, pp. 116–123, 2013.

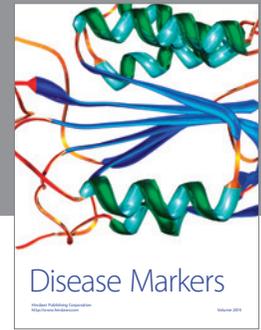
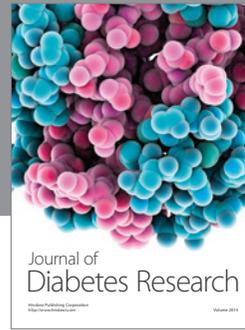
- [86] G. L. Calatayud, N. H. Sebastián, E. A. García-Iturrospe, J. C. G. Piqueras, J. S. Arias, and C. L. Cercós, "Relationship between insight, violence and diagnoses in psychotic patients," *Revista de Psiquiatria y Salud Mental*, vol. 5, no. 1, pp. 43–47, 2012.
- [87] T. M. Lincoln and S. Hodgins, "Is lack of insight associated with physically aggressive behavior among people with schizophrenia living in the community?" *The Journal of Nervous and Mental Disease*, vol. 196, no. 1, pp. 62–66, 2008.
- [88] D. I. Velligan, P. J. Weiden, M. Sajatovic et al., "The expert consensus guideline series: adherence problems in patients with serious and persistent mental illness," *The Journal of Clinical Psychiatry*, vol. 70, supplement 4, pp. 1–46, 2009.
- [89] A. Berger, J. Edelsberg, K. N. Sanders, J. M. Alvir, M. A. Mychaskiw, and G. Oster, "Medication adherence and utilization in patients with schizophrenia or bipolar disorder receiving aripiprazole, quetiapine, or ziprasidone at hospital discharge: a retrospective cohort study," *BMC Psychiatry*, vol. 12, no. 1, article 99, 2012.
- [90] H. Ascher-Svanum, D. E. Faries, B. Zhu, F. R. Ernst, M. S. Swartz, and J. W. Swanson, "Medication adherence and long-term functional outcomes in the treatment of schizophrenia in usual care," *The Journal of Clinical Psychiatry*, vol. 67, no. 3, pp. 453–460, 2006.
- [91] M. S. Swartz, J. W. Swanson, V. A. Hiday, R. Borum, H. Ryan Wagner, and B. J. Burns, "Violence and severe mental illness: the effects of substance abuse and nonadherence to medication," *The American Journal of Psychiatry*, vol. 155, no. 2, pp. 226–231, 1998.
- [92] E. L. Coldham, J. Addington, and D. Addington, "Medication adherence of individuals with a first episode of psychosis," *Acta Psychiatrica Scandinavica*, vol. 106, no. 4, pp. 286–290, 2002.
- [93] H. Ascher-Svanum, B. Zhu, D. Faries, J. P. Lacro, and C. R. Dolder, "A prospective study of risk factors for nonadherence with antipsychotic medication in the treatment of schizophrenia," *The Journal of Clinical Psychiatry*, vol. 67, no. 7, pp. 1114–1123, 2006.
- [94] S. Mohamed, R. Rosenheck, J. McEvoy, M. Swartz, S. Stroup, and J. A. Lieberman, "Cross-sectional and longitudinal relationships between insight and attitudes toward medication and clinical outcomes in chronic schizophrenia," *Schizophrenia Bulletin*, vol. 35, no. 2, pp. 336–346, 2009.
- [95] R. S. Kahn, W. W. Fleischhacker, H. Boter et al., "Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial," *The Lancet*, vol. 371, no. 9618, pp. 1085–1097, 2008.
- [96] R. Kemp, P. Hayward, G. Applewhaite, B. Everitt, and A. David, "Compliance therapy in psychotic patients: randomised controlled trial," *British Medical Journal*, vol. 312, no. 7027, pp. 345–349, 1996.
- [97] P. Czobor, J. Volavka, E. M. Derks et al., "Insight and hostility as predictors and correlates of nonadherence in the European first episode schizophrenia trial," *Journal of Clinical Psychopharmacology*, vol. 33, no. 2, pp. 258–261, 2013.
- [98] J. Volavka, P. Czobor, L. Citrome et al., "Efficacy of aripiprazole against hostility in schizophrenia and schizoaffective disorder: data from 5 double-blind studies," *The Journal of Clinical Psychiatry*, vol. 66, no. 11, pp. 1362–1366, 2005.
- [99] J. Volavka, P. Czobor, B. Sheitman et al., "Clozapine, olanzapine, risperidone, and haloperidol in the treatment of patients with chronic schizophrenia and schizoaffective disorder," *The American Journal of Psychiatry*, vol. 159, no. 2, pp. 255–262, 2002.
- [100] L. Citrome, J. Volavka, P. Czobor et al., "Effects of clozapine, olanzapine, risperidone, and haloperidol on hostility among patients with schizophrenia," *Psychiatric Services*, vol. 52, no. 11, pp. 1510–1514, 2001.
- [101] J. Volavka, P. Czobor, K. Nolan et al., "Overt aggression and psychotic symptoms in patients with schizophrenia treated with clozapine, olanzapine, risperidone, or haloperidol," *Journal of Clinical Psychopharmacology*, vol. 24, no. 2, pp. 225–228, 2004.
- [102] M. I. Krakowski, P. Czobor, L. Citrome, N. Bark, and T. B. Cooper, "Atypical antipsychotic agents in the treatment of violent patients with schizophrenia and schizoaffective disorder," *Archives of General Psychiatry*, vol. 63, no. 6, pp. 622–629, 2006.
- [103] W. H. Wilson, "Clinical review of clozapine treatment in a state hospital," *Hospital and Community Psychiatry*, vol. 43, no. 7, pp. 700–703, 1992.
- [104] J. Volavka, J. M. Zito, J. Vitrai, and P. Czobor, "Clozapine effects on hostility and aggression in schizophrenia," *Journal of Clinical Psychopharmacology*, vol. 13, no. 4, pp. 287–289, 1993.
- [105] T.-P. Su, J. Tuskan, L. Tsao, and D. Pickar, "Aggression during drug-free and antipsychotic treatment in inpatients with chronic schizophrenia, using the overt aggression scale," in *Proceedings of the 33rd Annual Meeting of the American College of Neuropsychopharmacology*, vol. 229, San Juan, Puerto Rico, December 1994.
- [106] P. Buckley, J. Bartell, K. Donenwirth, S. Lee, F. Torigoe, and S. C. Schulz, "Violence and schizophrenia: clozapine as a specific antiaggressive agent," *Bulletin of the American Academy of Psychiatry and the Law*, vol. 23, no. 4, pp. 607–611, 1995.
- [107] W. H. Wilson and A. M. Claussen, "18-month outcome of clozapine treatment for 100 patients in a state psychiatric hospital," *Psychiatric Services*, vol. 46, no. 4, pp. 386–389, 1995.
- [108] J. Volavka, J. W. Swanson, and L. L. Citrome, "Understanding and managing violence in schizophrenia," in *Comprehensive Care of Schizophrenia: A Textbook of Clinical Management*, J. A. Lieberman and R. M. Murray, Eds., pp. 262–290, Oxford University Press, New York, NY, USA, 2012.
- [109] S. Comai, M. Tau, Z. Pavlovic, and G. Gobbi, "The psychopharmacology of aggressive behavior: a translational approach—part 2: clinical studies using atypical antipsychotics, anticonvulsants, and lithium," *Journal of Clinical Psychopharmacology*, vol. 32, no. 2, pp. 237–260, 2012.
- [110] A. Topiwala and S. Fazel, "The pharmacological management of violence in schizophrenia: a structured review," *Expert Review of Neurotherapeutics*, vol. 11, no. 1, pp. 53–63, 2011.
- [111] C. Frogley, D. Taylor, G. Dickens, and M. Picchioni, "A systematic review of the evidence of clozapine's antiaggressive effects," *The International Journal of Neuropsychopharmacology*, vol. 15, no. 9, pp. 1351–1371, 2012.
- [112] J. Volavka, "Clozapine is gold standard, but questions remain," *The International Journal of Neuropsychopharmacology*, vol. 15, no. 9, pp. 1201–1204, 2012.
- [113] J. A. Lieberman, A. Z. Safferman, S. Pollack et al., "Clinical effects of clozapine in chronic schizophrenia: response to treatment and predictors of outcome," *The American Journal of Psychiatry*, vol. 151, no. 12, pp. 1744–1752, 1994.
- [114] J. Volavka, "Comorbid personality disorders and violent behavior in psychotic patients," *Psychiatric Quarterly*, 2013.
- [115] J. M. J. Alvir, J. A. Lieberman, A. Z. Safferman, J. L. Schwimmer, and J. A. Schaaf, "Clozapine-induced agranulocytosis: incidence and risk factors in the United States," *The New England Journal of Medicine*, vol. 329, no. 3, pp. 162–167, 1993.

- [116] J. W. Swanson, M. S. Swartz, R. A. van Dorn et al., "Comparison of antipsychotic medication effects on reducing violence in people with schizophrenia," *The British Journal of Psychiatry*, vol. 193, no. 1, pp. 37–43, 2008.
- [117] J. Volavka, P. Czobor, L. Citrome, and R. A. van Dorn, "Effectiveness of antipsychotic drugs against hostility in patients with schizophrenia in the clinical antipsychotic trials of intervention effectiveness (CATIE) study," *CNS Spectrums*, 2013.
- [118] J. Volavka, P. Czobor, E. M. Derks et al., "Efficacy of antipsychotic drugs against hostility in the European first-episode schizophrenia trial (EUFEST)," *The Journal of Clinical Psychiatry*, vol. 72, no. 7, pp. 955–961, 2011.
- [119] L. Citrome, M. Krakowski, W. M. Greenberg, E. Andrade, and J. Volavka, "Antiaggressive effect of quetiapine in a patient with schizoaffective disorder," *The Journal of Clinical Psychiatry*, vol. 62, no. 11, p. 901, 2001.
- [120] V. Villari, P. Rocca, V. Fonzo, C. Montemagni, P. Pandullo, and F. Bogetto, "Oral risperidone, olanzapine and quetiapine versus haloperidol in psychotic agitation," *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, vol. 32, no. 2, pp. 405–413, 2008.
- [121] C. Arango and M. Bernardo, "The effect of quetiapine on aggression and hostility in patients with schizophrenia," *Human Psychopharmacology*, vol. 20, no. 4, pp. 237–241, 2005.
- [122] P. Czobor, J. Volavka, and R. C. Meibach, "Effect of risperidone on hostility in schizophrenia," *Journal of Clinical Psychopharmacology*, vol. 15, no. 4, pp. 243–249, 1995.
- [123] K. N. R. Chengappa, J. Levine, R. Ulrich et al., "Impact of risperidone on seclusion and restraint at a state psychiatric hospital," *Canadian Journal of Psychiatry*, vol. 45, no. 9, pp. 827–832, 2000.
- [124] I. Bitter, P. Czobor, M. Dossenbach, and J. Volavka, "Effectiveness of clozapine, olanzapine, quetiapine, risperidone, and haloperidol monotherapy in reducing hostile and aggressive behavior in outpatients treated for schizophrenia: a prospective naturalistic study (IC-SOHO)," *European Psychiatry*, vol. 20, no. 5–6, pp. 403–408, 2005.
- [125] S. Brook, J. Walden, I. Benattia, C. O. Siu, and S. J. Romano, "Ziprasidone and haloperidol in the treatment of acute exacerbation of schizophrenia and schizoaffective disorder: comparison of intramuscular and oral formulations in a 6-week, randomized, blinded-assessment study," *Psychopharmacology*, vol. 178, no. 4, pp. 514–523, 2005.
- [126] L. Citrome, J. Volavka, P. Czobor, S. Brook, A. Loebel, and F. S. Mandel, "Efficacy of ziprasidone against hostility in schizophrenia: post hoc analysis of randomized, open-label study data," *The Journal of Clinical Psychiatry*, vol. 67, no. 4, pp. 638–642, 2006.
- [127] N. J. Yorkston, J. H. Gruzelier, and S. A. Zaki, "Propranolol as an adjunct to the treatment of schizophrenia," *The Lancet*, vol. 2, no. 8038, pp. 575–578, 1977.
- [128] G. P. Sheppard, "High-dose propranolol in schizophrenia," *The British Journal of Psychiatry*, vol. 134, no. 5, pp. 470–476, 1979.
- [129] J. R. Whitman, G. J. Maier, and B. Eichelman, "Beta-adrenergic blockers for aggressive behavior in schizophrenia," *The American Journal of Psychiatry*, vol. 144, no. 4, pp. 538–539, 1987.
- [130] N. Caspi, I. Modai, P. Barak et al., "Pindolol augmentation in aggressive schizophrenic patients: a double-blind crossover randomized study," *International Clinical Psychopharmacology*, vol. 16, no. 2, pp. 111–115, 2001.
- [131] W. J. Newman and B. E. McDermott, "Beta blockers for violence prophylaxis: case reports," *Journal of Clinical Psychopharmacology*, vol. 31, no. 6, pp. 785–787, 2011.
- [132] L. Citrome, "Adjunctive lithium and anticonvulsants for the treatment of schizophrenia: what is the evidence?" *Expert Review of Neurotherapeutics*, vol. 9, no. 1, pp. 55–71, 2009.
- [133] J. Volavka and L. Citrome, "Heterogeneity of violence in schizophrenia and implications for long-term treatment," *The International Journal of Clinical Practice*, vol. 62, no. 8, pp. 1237–1245, 2008.
- [134] J. Volavka and L. Citrome, "Pathways to aggression in schizophrenia affect results of treatment," *Schizophrenia Bulletin*, vol. 37, no. 5, pp. 921–929, 2011.
- [135] M. S. Swartz, J. W. Swanson, V. A. Hiday, R. Borum, R. Wagner, and B. J. Burns, "Taking the wrong drugs: the role of substance abuse and medication noncompliance in violence among severely mentally ill individuals," *Social Psychiatry and Psychiatric Epidemiology*, vol. 33, no. 1, pp. S75–S80, 1998.
- [136] J. W. Swanson, M. S. Swartz, R. Borum, V. A. Hiday, H. R. Wagner, and B. J. Burns, "Involuntary out-patient commitment and reduction of violent behaviour in persons with severe mental illness," *The British Journal of Psychiatry*, vol. 176, pp. 324–331, 2000.
- [137] K. F. Yates, M. Kunz, A. Khan, J. Volavka, and S. Rabinowitz, "Psychiatric patients with histories of aggression and crime five years after discharge from a cognitive-behavioral program," *Journal of Forensic Psychiatry & Psychology*, vol. 21, no. 2, pp. 167–188, 2010.
- [138] G. Haddock, C. Barrowclough, J. J. Shaw, G. Dunn, R. W. Novaco, and N. Tarrier, "Cognitive-behavioural therapy v. social activity therapy for people with psychosis and a history of violence: randomised controlled trial," *The British Journal of Psychiatry*, vol. 194, no. 2, pp. 152–157, 2009.
- [139] A. E. Cullen, A. Y. Clarke, E. Kuipers, S. Hodgins, K. Dean, and T. Fahy, "A multi-site randomized controlled trial of a cognitive skills programme for male mentally disordered offenders: violence and antisocial behavior outcomes," *Journal of Consulting and Clinical Psychology*, vol. 80, no. 6, pp. 1114–1120, 2012.
- [140] K. T. Mueser, F. Deavers, D. L. Penn, and J. E. Cassisi, "Psychosocial treatments for schizophrenia," *Annual Review of Clinical Psychology*, vol. 9, pp. 465–497, 2013.
- [141] R. L. Binder and D. E. McNiel, "Effects of diagnosis and context on dangerousness," *The American Journal of Psychiatry*, vol. 145, no. 6, pp. 728–732, 1988.
- [142] K. Barlow, B. Grenyer, and O. Ilkiw-Lavalle, "Prevalence and precipitants of aggression in psychiatric inpatient units," *Australian & New Zealand Journal of Psychiatry*, vol. 34, no. 6, pp. 967–974, 2000.
- [143] P. W. Corrigan and A. C. Watson, "Findings from the national comorbidity survey on the frequency of violent behavior in individuals with psychiatric disorders," *Psychiatry Research*, vol. 136, no. 2–3, pp. 153–162, 2005.
- [144] A. J. Pulay, D. A. Dawson, D. S. Hasin et al., "Violent behavior and DSM-IV psychiatric disorders: results from the national epidemiologic survey on alcohol and related conditions," *The Journal of Clinical Psychiatry*, vol. 69, no. 1, pp. 12–22, 2008.
- [145] B. F. Grant, F. S. Stinson, D. S. Hasin et al., "Prevalence, correlates, and comorbidity of bipolar I disorder and axis I and II disorders: results from the national epidemiologic survey on alcohol and related conditions," *The Journal of Clinical Psychiatry*, vol. 66, no. 10, pp. 1205–1215, 2005.

- [146] S. Fazel, P. Lichtenstein, M. Grann, G. M. Goodwin, and N. Långström, "Bipolar disorder and violent crime: new evidence from population-based longitudinal studies and systematic review," *Archives of General Psychiatry*, vol. 67, no. 9, pp. 931–938, 2010.
- [147] S. Fazel, P. Lichtenstein, T. Frisell, M. Grann, G. Goodwin, and N. Långström, "Bipolar disorder and violent crime: time at risk reanalysis," *Archives of General Psychiatry*, vol. 67, no. 12, pp. 1325–1326, 2010.
- [148] P. P. Christopher, P. J. McCabe, and W. H. Fisher, "Prevalence of involvement in the criminal justice system during severe mania and associated symptomatology," *Psychiatric Services*, vol. 63, no. 1, pp. 33–39, 2012.
- [149] J. Ballester, T. Goldstein, B. Goldstein et al., "Is bipolar disorder specifically associated with aggression?" *Bipolar Disorders*, vol. 14, no. 3, pp. 283–290, 2012.
- [150] K. Latalova, "Bipolar disorder and aggression," *The International Journal of Clinical Practice*, vol. 63, no. 6, pp. 889–899, 2009.
- [151] K. Latalova, *Aggression in Psychiatry*, Grada, Prague, Czech Republic, 2013, (Czech).
- [152] K. Latalova, *Bipolar Affective Disorder*, Grada, Prague, Czech Republic, 2011, (Czech).
- [153] J. L. Garno, N. Gunawardane, and J. F. Goldberg, "Predictors of trait aggression in bipolar disorder," *Bipolar Disorders*, vol. 10, no. 2, pp. 285–292, 2008.
- [154] G. L. Brown, F. K. Goodwin, J. C. Ballenger, P. F. Goyer, and L. F. Major, "Aggression in humans correlates with cerebrospinal fluid amine metabolites," *Psychiatry Research*, vol. 1, no. 2, pp. 131–139, 1979.
- [155] D. P. Bernstein, L. Fink, L. Handelsman et al., "Initial reliability and validity of a new retrospective measure of child abuse and neglect," *The American Journal of Psychiatry*, vol. 151, no. 8, pp. 1132–1136, 1994.
- [156] M. A. Oquendo, C. Waternaux, B. Brodsky et al., "Suicidal behavior in bipolar mood disorder: clinical characteristics of attempters and nonattempters," *Journal of Affective Disorders*, vol. 59, no. 2, pp. 107–117, 2000.
- [157] A. H. Buss and A. Durkee, "An inventory for assessing different kinds of hostility," *Journal of Consulting Psychology*, vol. 21, no. 4, pp. 343–349, 1957.
- [158] B. H. Michaelis, J. F. Goldberg, G. P. Davis, T. M. Singer, J. L. Garno, and S. J. Wenzel, "Dimensions of impulsivity and aggression associated with suicide attempts among bipolar patients: a preliminary study," *Suicide and Life-Threatening Behavior*, vol. 34, no. 2, pp. 172–176, 2004.
- [159] R. H. Perlis, S. Miyahara, L. B. Marangell et al., "Long-term implications of early onset in bipolar disorder: data from the first 1000 participants in the systematic treatment enhancement program for bipolar disorder (STEP-BD)," *Biological Psychiatry*, vol. 55, no. 9, pp. 875–881, 2004.
- [160] C. F. Baldassano, "Illness course, comorbidity, gender, and suicidality in patients with bipolar disorder," *The Journal of Clinical Psychiatry*, vol. 67, supplement 11, pp. 8–11, 2006.
- [161] I. M. Salloum, J. R. Cornelius, J. E. Mezzich, and L. Kirisci, "Impact of concurrent alcohol misuse on symptom presentation of acute mania at initial evaluation," *Bipolar Disorders*, vol. 4, no. 6, pp. 418–421, 2002.
- [162] J. Volavka and J. Swanson, "Violent behavior in mental illness: the role of substance abuse," *The Journal of the American Medical Association*, vol. 304, no. 5, pp. 563–564, 2010.
- [163] M. I. Good, "Primary affective disorder, aggression, and criminality. A review and clinical study," *Archives of General Psychiatry*, vol. 35, no. 8, pp. 954–960, 1978.
- [164] W. F. Thorneloe and E. L. Crews, "Manic depressive illness concomitant with antisocial personality disorder: six case reports and review of the literature," *The Journal of Clinical Psychiatry*, vol. 42, no. 1, pp. 5–9, 1981.
- [165] B. Carpiniello, L. Lai, S. Pirarba, C. Sardu, and F. Pinna, "Impulsivity and aggressiveness in bipolar disorder with comorbid borderline personality disorder," *Psychiatry Research*, vol. 188, no. 1, pp. 40–44, 2011.
- [166] K. Látalová and J. Praško, "Aggression in borderline personality disorder," *Psychiatric Quarterly*, vol. 81, no. 3, pp. 239–251, 2010.
- [167] M. Hamilton, "Development of a rating scale for primary depressive illness," *British Journal of Social and Clinical Psychology*, vol. 6, no. 4, pp. 278–296, 1967.
- [168] R. C. Young, J. T. Biggs, V. E. Ziegler, and D. A. Meyer, "A rating scale for mania: reliability, validity and sensitivity," *The British Journal of Psychiatry*, vol. 133, no. 11, pp. 429–435, 1978.
- [169] K. Latalova, "Insight in bipolar disorder," *Psychiatric Quarterly*, vol. 83, no. 3, pp. 293–310, 2012.
- [170] C.-F. Yen, C.-S. Chen, J.-Y. Yen, and C.-H. Ko, "The predictive effect of insight on adverse clinical outcomes in bipolar I disorder: a two-year prospective study," *Journal of Affective Disorders*, vol. 108, no. 1–2, pp. 121–127, 2008.
- [171] A. S. David, "Insight and psychosis," *The British Journal of Psychiatry*, vol. 156, pp. 798–808, 1990.
- [172] M. Serper, D. R. Beech, P. D. Harvey, and C. Dill, "Neuropsychological and symptom predictors of aggression on the psychiatric inpatient service," *Journal of Clinical and Experimental Neuropsychology*, vol. 30, no. 6, pp. 700–709, 2008.
- [173] M. Mur, M. J. Portella, A. Martínez-Arán, J. Pifarré, and E. Vieta, "Persistent neuropsychological deficit in euthymic bipolar patients: executive function as a core deficit," *The Journal of Clinical Psychiatry*, vol. 68, no. 7, pp. 1078–1086, 2007.
- [174] K. Latalova, J. Prasko, T. Diveky, and H. Velartova, "Cognitive impairment in bipolar disorder," *Biomedical Papers*, vol. 155, no. 1, pp. 19–26, 2011.
- [175] G. Huf, J. Alexander, M. H. Allen, and N. S. Raveendran, "Haloperidol plus promethazine for psychosis-induced aggression," *Cochrane Database of Systematic Reviews*, no. 3, Article ID CD005146, 2009.
- [176] L. Citrome, "Comparison of intramuscular ziprasidone, olanzapine, or aripiprazole for agitation: a quantitative review of efficacy and safety," *The Journal of Clinical Psychiatry*, vol. 68, no. 12, pp. 1876–1885, 2007.
- [177] M. Pratts, W. Grant, L. A. Opler et al., "Treating acutely agitated patients with asenapine sublingual tablets: a single-dose, randomized, double-blind placebo controlled trial," in *Proceedings of the 53rd Annual NCDEU Meeting*, pp. 28–31, Hollywood, Calif, USA, May 2013.
- [178] L. Citrome, "Inhaled loxapine for agitation revisited: focus on effect sizes from 2 phase III randomised controlled trials in persons with schizophrenia or bipolar disorder," *The International Journal of Clinical Practice*, vol. 66, no. 3, pp. 318–325, 2012.
- [179] L. Citrome, "Addressing the need for rapid treatment of agitation in schizophrenia and bipolar disorder: focus on inhaled loxapine as an alternative to injectable agents," *Therapeutics and Clinical Risk Management*, vol. 2013, article 9, pp. 235–245, 2013.
- [180] J. Kwentus, R. A. Riesenberger, M. Marandi et al., "Rapid acute treatment of agitation in patients with bipolar I disorder: a

multicenter, randomized, placebo-controlled clinical trial with inhaled loxapine," *Bipolar Disorders*, vol. 14, no. 1, pp. 31–40, 2012.

- [181] N. Collins, T. R. E. Barnes, A. Shingleton-Smith, D. Gerrett, and C. Paton, "Standards of lithium monitoring in mental health trusts in the UK," *BMC Psychiatry*, vol. 10, article 80, 2010.
- [182] A. Podawiltz, "A review of current bipolar disorder treatment guidelines," *The Journal of Clinical Psychiatry*, vol. 73, no. 3, article e12, 2012.
- [183] K. N. Fountoulakis, S. Kasper, O. Andreassen et al., "Efficacy of pharmacotherapy in bipolar disorder: a report by the WPA section on pharmacopsychiatry," *European Archives of Psychiatry and Clinical Neuroscience*, vol. 262, no. 1, supplement, pp. 1–48, 2012.
- [184] S. D. Cochran, "Preventing medical noncompliance in the outpatient treatment of bipolar affective disorders," *Journal of Consulting and Clinical Psychology*, vol. 52, no. 5, pp. 873–878, 1984.
- [185] M. R. Basco and A. J. Rush, *Cognitive-Behavioral Therapy for Bipolar Disorder*, Guilford Press, New York, NY, USA, 2nd edition, 2007.
- [186] E. Herman, P. Grof, J. Hovorka, J. Prasko, and P. Doubek, "Bipolar disorder," in *Postupy v Lecbe Psychickyh Poruch*, D. Seifertova, J. Prasko, and C. Hoschl, Eds., pp. 93–120, Academia Medica Pragensis, Prague, Czech Republic, 2004, (Czech).



Hindawi
Submit your manuscripts at
<http://www.hindawi.com>

