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Schizophrenia and Other Psychotic Disorders (J Csemansky, Section Editor)

Preventing Violence in Patients with Schizophrenia

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Opinion statement

Violence in patients with schizophrenia has garnered substantial public attention in the lay press. Although schizophrenia is associated with a modestly elevated risk for violent behavior, which is further increased by comorbid substance use disorders, most patients with schizophrenia are not violent and most violent individuals do not have schizophrenia. At present, primary prevention efforts are of theoretical interest and include attention being placed on childhood maltreatment. Research into secondary prevention, defined as the prevention of occurrence of violent behavior in persons already diagnosed with schizophrenia, has identified several risk factors including substance use and nonadherence to medication treatment. A specific antiaggressive effect of clozapine has been identified and should be considered as a treatment option for persons with schizophrenia and persistent aggressive behavior. A potential alternative to clozapine is olanzapine, based on a randomized controlled trial where although olanzapine was less efficacious than clozapine in aggression outcomes, olanzapine was more efficacious than haloperidol, and the choice of olanzapine is further supported by evidence from two large effectiveness studies, the Clinical Antipsychotic Trials of Intervention Effectiveness and the European First-Episode Schizophrenia study. Tertiary prevention, defined as the acute management of agitated and aggressive behavior, is accomplished with the use of psychological and behavioral interventions such as verbal de-escalation techniques, in combination with pharmacological agents. For persons with schizophrenia, antipsychotics are preferred. Although rapidly acting intramuscular formulations have been the mainstay for this type of treatment, oral agents such as inhaled loxapine and sublingual asenapine can be considered.

Introduction

Although most patients with schizophrenia are not violent and most violent individuals do not have schizophrenia, violence in persons with schizophrenia is considered highly newsworthy by the lay media [1–3]. This has led to continued stigmatization of schizophrenia in general. In a retrospective analysis of Canadian newspaper coverage from 2005 to 2010, danger, violence, and criminality were direct themes in 40 % of newspaper articles [1]. Treatment for a mental illness was discussed in only 19 % of newspaper articles, and in only 18 % was recovery or rehabilitation a significant theme [1].

However, recent epidemiological studies in the USA [4•] and Sweden [5] indicate that schizophrenia is associated with a modestly elevated risk for violent behavior, which is further increased by comorbid substance use disorders. In reality, violence in patients with schizophrenia is a frequent reason for hospitalization; it may delay hospital discharge and increases the illness burden carried by patients' families [6]. The severity of violent behavior in patients with schizophrenia is variable, and homicide may rarely occur [7, 8]. For all these reasons, efforts to prevent or reduce violence in patients with schizophrenia are worthwhile. The origins of violence in patients with schizophrenia are heterogeneous, with different pathways leading to the same phenotype of violent behavior [6, 9, 10]. This heterogeneity of origin will be reflected in preventative efforts.

Prevention in medicine is divided into three components—primary, secondary, and tertiary. The goal of primary prevention is protecting healthy people from developing a disease. Interventions for secondary prevention occur after an illness has already been diagnosed, and the goal is to halt or slow the progress of disease. In schizophrenia research, the focus for secondary prevention has been on the management of the prodrome or first episode [11]; however, for our purposes, we will include all persons with schizophrenia who have exhibited aggressive behavior, with the goal of secondary prevention in this instance being the decrease in frequency and intensity of future episodes of aggressive behavior. Tertiary prevention focuses on the management of often complex and long-term health problems and disabilities; in this review, tertiary prevention will include a discussion of the acute management of agitation.

Primary prevention

Primary prevention of violence in schizophrenia would focus on the improvement of rearing environment. In persons without schizophrenia, there is a relationship between childhood maltreatment and violent behavior in adulthood [12–14], and this relationship may be moderated by genomic factors [12, 15].

A similar relationship between childhood maltreatment and violent behavior may be present in persons with schizophrenia. A meta-analysis of 110 studies involving 45,533 individuals with psychosis, of whom 8439 were violent, revealed a moderate relationship between adult violence and childhood physical (OR=2.2, 95 % CI=1.5–3.1) or sexual (OR=1.9, 95 % CI=1.5–2.4) abuse [16•]. History of severe physical abuse in childhood was more prevalent among violent than nonviolent adult schizophrenia patients. Furthermore, violent schizophrenia patients exhibited a significant volume loss of anterior cingulate, and this deficit was explained, at least in part, by their histories of stressful childhood experiences [17]. A cross-sectional, noninterventional study of 195 adolescent nonpregnant girls assessed the potential for child abuse using an inventory [18]. That potential was increased in girls who had conduct disorder, depressive disorder, and anxiety disorder and who had been exposed to maltreatment. Pre-pregnancy counseling of high-risk adolescent girls about healthy mothering behaviors has been suggested as a

prevention of child abuse [18]. A multimodal approach to the prevention of recurrent child maltreatment has been proposed [19].

Thus, child abuse appears to moderately increase the risk of violence in schizophrenia. Research is beginning to explore the mechanisms of this effect. Risk factors of child abuse and corresponding preventative measures are under study.

Secondary prevention

Pharmacological prevention of violence in schizophrenia

Here, we review pharmacological interventions to prevent repeated violent incidents and violent crimes. This includes, for some patients, prevention of relapses. We do not review here the treatment of violence occurring in the context of acute agitation that may for example be seen immediately after hospital admission and that subside after several days of treatment. This type of violent behavior is discussed below under the heading of "Tertiary prevention".

Pharmacological treatment is the mainstay of secondary prevention of violence in schizophrenia. A study aimed to establish the effect of antipsychotics and mood stabilizers on the rate of violent crime committed by 82,647 psychiatric patients in Sweden [20••]. The primary outcome was the occurrence of violent crime. Within-individual analyses were conducted to compare the rate of violent criminality during the time that patients were prescribed these medications versus the rate for the same patients while they were not receiving the drugs. In the subset of patients diagnosed with schizophrenia (N=9125), antipsychotics significantly reduced the risk for violent crime (HR=0.65, 95 % CI 0.45–0.93). However, no reduction of risk was observed with mood stabilizers in schizophrenia patients. Thus, antipsychotics appear to be an effective preventative measure to reduce violent crime in schizophrenia [20••]. This result is consistent with a meta-analysis comparing antipsychotics with placebo in schizophrenia [21•]. In that meta-analysis of 65 trials and 6493 patients, aggressive acts occurred in 2 % of patients on an antipsychotic drug versus 12 % of patients on placebo (RR=0.27, 95 % CI 0.15–0.52).

In an observational nationwide study, 10,757 Danish schizophrenia patients were followed up for a median of 428 days after discharge from a psychiatric ward [22]. During that period, 1282 committed a violent crime. Various features of inpatient care were studied as possible predictors of violent criminality. Among those features, two were associated with lower criminality: antipsychotic treatment (HR=0.79, 95 % CI 0.68–0.91, p<0.001) and contact between staff and patients' relatives during hospitalization (HR=0.80, 95 % CI=0.71–0.91, p<0.001) [16•].

Pharmacological treatments vary in their antiaggressive effectiveness. We reviewed the within-individual analyses conducted in the study by Fazel et al. [20••] mentioned above. Additionally, between-individual analyses were also implemented in that study, and separate results for mood stabilizers, antipsychotics, and clozapine are available for the entire cohort (N=82,647). The between-individual analyses were adjusted by age, sex, and concomitant use of other psychotropic medications. These analyses showed a remarkable reduction of violent crime associated with the use of clozapine (HR=0.10, 95 % CI 0.05–0.19)—a considerably greater effect than that of mood stabilizers or non-clozapine antipsychotics.

Specific antiaggressive effect of clozapine was noted in two reviews [23, 24], although questions and problems with this effective treatment should not be underestimated [25]. The risk of agranulocytosis and metabolic adverse effects needs to be considered when prescribing this medication. It should be noted that the superior antiaggressive effect of clozapine appears only after the patient has been exposed to an adequate dose regimen [26]. Given the slow escalation rate necessitated by clozapine's cardiovascular adverse effects, reaching adequate dose may take 3 weeks [26].

Olanzapine was shown to have a lower antiaggressive effect than clozapine but higher than haloperidol [27]. The superiority of olanzapine over several other antipsychotics in its effects against hostility was shown in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) [28] and the European First-Episode Schizophrenia (EUFEST) [29] data.

Adjunctive lithium and anticonvulsants are sometimes used in an attempt to control persistent violent behavior in schizophrenia, but the support for this treatment is scant at best [30, 31]. We note again that no effect of mood stabilizers on violent crime rate in schizophrenia patients was observed in the large Swedish epidemiological study we described above [20••].

Thus, epidemiological evidence indicates that antipsychotic treatment is effective for the prevention of violent behavior in schizophrenia. However, epidemiological studies are not particularly well suited to shed light on obstacles of pharmacological treatment. The chief obstacle is that most patients with schizophrenia do not take their prescribed medication [32, 33]. Nonadherence to medication elevates the risk for violent behavior [16•, 34]. The assessment of adherence begins with the acknowledgment that partial or nonadherence is a common obstacle to treatment [35]. Management of partial or nonadherence includes identifying the specific barriers to adherence present for an individual patient and ongoing monitoring and providing alternatives and assistive tools [35]. Long-acting injectable antipsychotics can be helpful [36].

Low insight and hostility can be predictive of nonadherence, as demonstrated in a post hoc analysis of EUFEST data [37]. The use of illicit substances and alcohol is also related to worse adherence [38]. Thus, a strategy to prevent violence in schizophrenia patients should include steps to assess [39, 40] and improve [41] patients' insight, to develop therapeutic alliance [42], and to treat comorbid substance use disorders.

In summary, antipsychotics are effective in preventing or reducing persistent violent behavior in schizophrenia patients. In spite of its limitations, clozapine is the gold standard of antiaggressive treatment. Olanzapine appears to be the second choice for this indication. The effectiveness of pharmacological treatments is limited by nonadherence, which is in turn associated with poor insight, hostility, and comorbid substance use.

Comorbid substance use disorders

Patients with schizophrenia and other psychoses frequently use alcohol and illicit drugs. Relative to the general population, individuals with severe psychotic disorders have increased risk for heavy alcohol use (OR=4.0, 95 % CI 3.6–4.4) and recreational drug use (OR=4.6, 95 % CI 4.3–5.0) [43•]. Comorbid substance use disorders robustly elevate the risk of violence in schizophrenia. Acute intoxication with alcohol or other abused substances such as cocaine is well

known to elevate the risk of violence in nonpsychotic or psychotic individuals. In a large meta-analysis of violence in psychosis that was described above [16•], violence was very strongly associated with a history of polysubstance abuse (OR=10.3, 95 % CI 2.5–41.5) and associated with a diagnosis of comorbid substance use disorder (OR=3.1, 95 % CI 1.9–5.0). Substance use disorders may mediate the relationship between schizophrenia and violence [44]. As reviewed above, substance use is associated with nonadherence to pharmacological treatment and therefore is a candidate for a mediating factor in that relationship. For these reasons, detection and treatment of comorbid substance use disorders is an important strategy to prevent violence in schizophrenia.

Although the high prevalence and clinical importance of the comorbidity are known, substance use disorders in patients with schizophrenia frequently remain undetected. Screening for alcohol and substance use should be a part of routine unstructured clinical interviews. Screening instruments are such as the Drug Disorders Identification Test (DUDIT) are available [45].

Psychopharmacological approaches to the treatment of patients with comorbid schizophrenia and substance use disorders rely on antipsychotics and medications for substance use disorders. Uncontrolled older reports indicate that clozapine may reduce drug use and craving [46], but evidence based on randomized controlled trials is lacking. Nevertheless, since clozapine's antiaggressive effects are well supported, this compound is a good choice of treatment in schizophrenia patients who are at risk for violence because of comorbid substance use disorders. Medications for alcohol or opioid dependence have been used safely in patients with schizophrenia. There are numerous psychosocial approaches to the treatment of schizophrenia patients with substance use but are beyond the scope of this review.

Psychological and behavioral interventions to prevent violence in schizophrenia

Some patients with schizophrenia routinely discontinue their antipsychotic medication after discharge and then may engage in violent behavior, which results in their rehospitalization or arrest. After they are stabilized on medication and discharged again, the cycle repeats.

An inpatient cognitive-behavioral program tailored to this "revolving door" population was shown to prevent or reduce rehospitalization and rearrest [47]. Furthermore, various types of outpatient commitment statutes enacted by many jurisdictions in the USA authorize assisted outpatient treatment for persons with serious mental illness who are deemed at risk of failing to live safely in the community. There is evidence that these programs are effective in terms of reducing violence risk by improving adherence and reducing substance use [48], preventing repeated illness episodes, switching care from hospitals to outpatient facilities, and reducing costs [49].

Tertiary prevention

Agitation is defined as excessive motor or verbal activity and can escalate into aggressive or violent behavior. Fortunately, acute treatment options for the management of agitation are plentiful and generally efficacious [50]. Published are a set of guidelines created by the American Association for Emergency Psychiatry titled "Best practices in Evaluation and Treatment of Agitation" (BETA) [51].

Included in these guidelines are sections regarding medical evaluation and triage, psychiatric evaluation, verbal de-escalation, psychopharmacologic approaches, and the use and avoidance of seclusion and restraint [52, 53, 54••, 55, 56].

Although pharmacological interventions for agitation are commonly used, environmental and behavioral approaches are important in order to calm the agitated patient as rapidly as possible, decrease the likelihood of harm to self or others, and decrease the need for seclusion or restraint (a time where staff and patient injury can occur) [54••, 56]. Simultaneously, diagnostic considerations include ruling out somatic causes of the change in mental status [52, 53].

Verbal de-escalation has been successfully employed in order to avoid seclusion and restraint and enhance the ability to use less-invasive pharmacological interventions such as oral medications rather than injections [54••]. Environmental and behavioral approaches to decrease seclusion and restraint were tested in a randomized controlled trial at a secured national psychiatric hospital in Finland [57]. In that study, the proportion of patient days with seclusion, restraint, or room observation declined from 30 to 15 % for intervention wards versus from 25 to 19 % for control wards. Seclusion-restraint time decreased from 110 to 56 h per 100 patient days for intervention wards but increased from 133 to 150 h for control wards. Although between-group differences were significant for seclusion-restraint-observation days (p=0.001) and seclusion-restraint time (p=0.001), this was not the case for violence (p=0.91), where the incidence of violence decreased from 1.1 to 0.4 % for the intervention wards and from 0.1 to 0.0 % for control wards.

Intramuscular formulations of antipsychotics and benzodiazepines remain foundational for the management of acute agitation because of their rapid onset of action [50]. These include intramuscular formulations of first-generation antipsychotics (e.g., haloperidol), benzodiazepines (e.g., lorazepam), and several second-generation antipsychotics (ziprasidone, olanzapine, and aripiprazole). The intramuscular second-generation antipsychotics used to treat agitation have effect sizes similar to those for the older agents, but with a lower propensity for extrapyramidal side effects [58].

Up to very recently, there have not been oral formulations that have demonstrated rapidity of onset of anti-agitation effect. One alternative that is now approved by regulatory authorities in the USA and in the EU for the treatment of agitation is inhaled loxapine, based on double-blind, placebo-controlled, randomized trials in patients with schizophrenia [59, 60•] and bipolar mania [61]. The optimal dose is 10 mg. Efficacy was noted as early as 10 min post-administration, which was the earliest time point measured. Effect sizes were similar to those observed with intramuscular alternatives [62, 63]. In the USA, because of the risk of bronchospasm, a Risk Evaluation and Mitigation Strategies (REMS) program is in place, and prior to administering inhaled loxapine, patients must be screened for a history of pulmonary disease and examined by chest auscultation for respiratory abnormalities such as wheezing. After administration, patients are required to be monitored for signs and symptoms of bronchospasm at least every 15 min for at least 1 h [64, 65].

Although sublingual asenapine is not approved by regulatory authorities for the treatment of acute agitation, it appears to have a rapid onset of action for this purpose, with an effect size similar to that for intramuscular agents or inhaled loxapine [66•]. In contrast to the orally disintegrating tablets of olanzapine, risperidone, and aripiprazole, asenapine is administered sublingually and is absorbed in the oral mucosa, bypassing first-pass metabolism [67].

The BETA guidelines recommend that for schizophrenia-driven agitation, antipsychotics be used instead of benzodiazepines because antipsychotics address the underlying psychosis [55]. In addition, second-generation antipsychotics with data supporting their use in acute treatment of agitation are preferred over haloperidol and other standard neuroleptics administered either alone or with an adjunctive medication.

Conclusions

Violence in patients with schizophrenia has garnered substantial public attention in the lay press. Although schizophrenia is associated with a modestly elevated risk for violent behavior, which is further increased by comorbid substance use disorders, most patients with schizophrenia are not violent, and most violent individuals do not have schizophrenia. At present, primary prevention efforts are of theoretical interest; however, research into secondary and tertiary prevention strategies have yielded specific recommendations that include the consideration of clozapine (or perhaps olanzapine) to reduce the recurrence of violent behavior and the use of antipsychotics (in tandem with psychological and behavioral interventions) to manage acute agitation.

Compliance with Ethics Guidelines

Conflict of Interest

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Human and Animal Rights and Informed Consent

Among cited articles where one of the authors of the current report was an author, local Institutional Review Board approval was obtained and maintained for studies where human (or animal) subjects research was performed.

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