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Pathways to Aggression in Schizophrenia Affect Results of Treatment

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Schizophrenia elevates the risk for aggressive behavior and violent crime, and different approaches have been used to manage this problem. The results of such treatments vary. One reason for this variation is that aggressive behavior in schizophrenia is heterogeneous in origin. This heterogeneity has usually not been accounted for in treatment trials nor is it adequately appreciated in routine clinical treatment planning. Here, we review pathways that may lead to the development of aggressive behavior in patients with schizophrenia and discuss their impact on treatment. Elements in these pathways include predisposing factors such as genotype and prenatal toxic effects, development of psychotic symptoms and neurocognitive impairments, substance abuse, nonadherence to treatment, childhood maltreatment, conduct disorder, comorbid antisocial personality disorder/psychopathy, and stressful experiences in adult life. Clinicians' knowledge of the patient's historical trajectory along these pathways may inform the choice of optimal treatment of aggressive behavior. Clozapine has superior antiaggressive activity in comparison with other antipsychotics and with all other pharmacological treatments. It is usually effective when aggressive behavior is related to psychotic symptoms. However, in many patients, aggression is at least partly based on other factors such as comorbid substance use disorder, comorbid antisocial personality disorder/psychopathy, or current stress. These conditions which are sometimes underdiagnosed in clinical practice must be addressed by appropriate adjunctive psychosocial approaches or other treatments. Treatment adherence has a crucial role in the prevention of aggressive behavior in schizophrenia patients.

Key words: violence/antipsychotics/substance use/antisocial personality disorder/psychopathy/adherence

Introduction

There is a general agreement that schizophrenia is associated with elevated risk for aggressive behavior and violent crime.[1,2] There is also relatively robust evidence indicating that clozapine is the most effective pharmacological treatment for hostility[3] and persistent overt aggression in schizophrenia.[4–7] Other clozapine studies are reviewed elsewhere[8(pp273–277)].

However, some doubts remain. The effect sizes reported for the clozapine antiaggressive action[3] as well as for the differences between clozapine and other medications[5] are modest. Furthermore, clozapine did not show the expected antiaggressive superiority in all studies.

Other pharmacological treatments used for persistent aggression in schizophrenia patients include typical and atypical antipsychotics, mood stabilizers,[9] beta blockers, and various other medications. There seems to be no general agreement about their antiaggressive effectiveness, although the evidence for beta blockers appears somewhat encouraging.[7]

Thus, there are many uncertainties in the field of treatment for aggression in schizophrenia. We argue that some of these uncertainties are due to the fact that aggressive behavior in schizophrenia is heterogeneous in origin, and this etiological heterogeneity results in variations in response to treatment. Etiological factors can interact with each other, creating a set of pathways that eventually lead to aggressive behavior in some patients with schizophrenia. Etiological heterogeneity has not been accounted for in typical experimental design of treatment trials. The results of the trials have therefore been at least to some degree confounded. Understanding the pathways to aggression is a prerequisite for designing more effective treatment trials in the future.

Pathways to Violence in Schizophrenia Patients

Figure 1 outlines the complex causal pathways that can result to aggressive and violent behavior. There is considerable overlap among predisposing risk factors and psychiatric symptoms for several psychiatric disorders that can result in risk interactions and precipitating factors. The key elements in this schematic are discussed below.

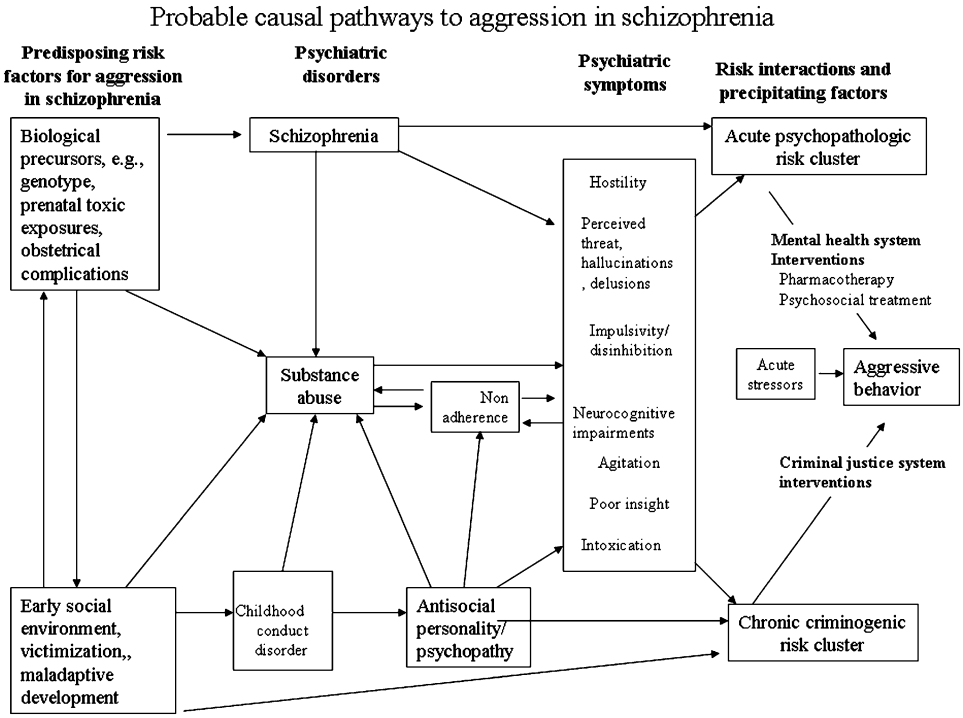

Fig. 1. Probable causal pathways to aggression in schizophrenia. Adapted, with permission, from Figure 12.3 In: Volavka J, Swanson JW, Citrome L. Managing violence and aggression in schizophrenia. In: Lieberman JA, Murray RM, eds. *Comprehensive Care of Schizophrenia: A Textbook of Clinical Management*. 2nd ed.. New York, NY: Oxford University Press; 2011

Factors Predisposing to Aggression in Schizophrenia - Phase I of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)[10] was designed to study comparative effectiveness of perphenazine, olanzapine, risperidone, quetiapine, and ziprasidone in schizophrenia. Aggression was one of the many outcomes evaluated in that study. Prevalence of aggressive behavior during the first 6 months of the study was determined by interview conducted at the end of that period.[11] Baseline risk factors predicting aggressive behavior during the 6 months included "economic deprivation, substance use disorders, violent victimization, childhood conduct problems, and perhaps childhood sexual abuse." Aggressive behavior declined in all treatment groups, with no substantial group differences.[11] Interestingly, nonadherence to treatment reduced the treatment effects only in the subjects without history of childhood conduct problems. Thus, it is possible that if psychosis is not the main cause of violence in these patients, then even successful treatment for psychosis may not substantially reduce aggressive behavior because it cannot affect the underlying (eg, developmental or environmental) causes of violence. The prevalence of aggression was higher among patients with a history of childhood conduct problems than among those without this history. Positive psychotic symptoms were linked to aggression only in the group without conduct problems. Thus, aggression in schizophrenia may follow at least 2 distinct pathways—one associated with premorbid conditions, including antisocial conduct (pathway depicted in bottom part of figure 1), and another associated with the acute psychopathology of schizophrenia (pathway in top part of figure 1).[12]

Following the premorbid conditions pathway in figure 1, we now turn to "antisocial personality disorder/ psychopathy." Unlike the current Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision (DSM-IV-TR) criteria for antisocial personality disorder which focus largely on criminal behavior, psychopathy in the modern sense emphasizes personality traits and psychological processes.[13] Relationship between the DSM-IV-TR concept of antisocial personality disorder and Hare's concept of psychopathy is discussed elsewhere.[8(p185–189)] A compromise "Antisocial/psychopathic type" of personality disorder has been proposed for Diagnostic and Statistical Manual of Mental Disorders V.

Unlike the categorical classification on which the concept of antisocial personality is based, psychopathy can also be assessed dimensionally, using various versions of Psychopathy Checklist. One of these versions, Psychopathy Checklist: Screening Version (PCL:SV), was developed for use in patients with various psychiatric disorders, including schizophrenia.[14] Analyses of PCL:SV yielded 2 factors: factor 1 reflects interpersonal and affective characteristics and factor 2 describes a socially deviant lifestyle. Enduring personality features

are less amenable to pharmacological treatment than disturbances in mood and impulse control.

DSM-IV-TR diagnostic criteria for antisocial personality disorder include aggressive behavior. Association between psychopathy and aggressive behavior is well established.[8(p187)] Several studies investigated aggressive behavior in schizophrenia patients with comorbid psychopathy symptoms. PCL:SV scores were significantly higher in persistently aggressive schizophrenia patients than in those who were not aggressive.[15] Interestingly, in a small, all male schizophrenia sample, symptoms of hostility, suspiciousness, and uncooperativeness were driving aggressive behavior only in patients showing low levels of psychopathy scores.[16] Patients with high scores had high probability of aggressive behavior independent of symptoms. These findings are consistent with the CATIE results cited above.[11] The authors conclude that "The evaluation of … medications as antiaggression agents can be enhanced when taking into consideration both the patients' psychopathic and symptom profiles."[16(p210)] We agree with that assessment.

In addition to direct link between antisocial personality disorder/psychopathy and aggression in schizophrenia, there are indirect links mediated by substance abuse, impulsiveness, and nonadherence to medication (see figure 1). Antisocial personality disorder is more prevalent in patients with schizophrenia than in members of general population, and this comorbidity is associated with elevated risk for substance abuse. The same applies to history of conduct disorder.[17] Antisocial personality disorder/psychopathy is associated with impulsivity by definition, and it is probably also affecting adherence to medication treatment. This is suggested by the fact that history of aggressive behavior, arrest, or incarceration was strongly related to nonadherence to treatment in a large prospective naturalistic study of schizophrenia patients.[18]

We now turn to the pathway depicting the effects of schizophrenia symptoms on aggression (top part of figure 1). Genotype is a potential predisposing factor to aggression in schizophrenia. A common functional polymorphism in the catechol *O*-methyltransferase (COMT) gene results in a substitution of methionine for valine (Val 158 Met), and the methionine allele has been associated with aggressive behavior in patients diagnosed with schizophrenia or schizoaffective disorder in some studies[19–23] but not in other studies.[24]

Numerous other genes and their polymorphisms were explored in relation to therapeutic effects of antipsychotics. The results were interesting but not sufficiently robust for clinical applications at this time.

Recent evidence suggests potential importance of familial (genetic or early environmental) factors in the development of violence in patients with schizophrenia. Parental violent crime was moderately associated with convictions for violent crime in Swedish patients with schizophrenia.[25]

A recent study was designed to determine the risk of violent crime in schizophrenia and the role of substance abuse in mediating that risk.[26] The results showed a substantial increase of risk for violence in patients with comorbid substance abuse compared with general population controls, supporting the mediating role of this comorbidity. The study also explored the role of familial confounding by investigating the risk of violence among unaffected siblings of schizophrenia patients.[26] The violence risk increase conferred by comorbid substance abuse was much less pronounced when unaffected siblings were used as controls instead of general population. This finding, apparently related to an elevated rate of substance abuse among the unaffected siblings, was interpreted to indicate a familial confounding: The increased risk of violence in schizophrenia in comparison with general population may be due to genetic or early environmental factors.

Further research focusing on molecular genetic studies and interactions between genes and early environment may clarify the familial mechanisms involved in the risks for violence in schizophrenia. The COMT Val 158 Met polymorphism mentioned in the preceding section may be a suitable candidate for such molecular studies. Such studies may have impact beyond schizophrenia. Familial risk factors for violent crime are not limited to patients with schizophrenia; they were shown to exert strong effects in general population.[27]

Among the schizophrenia symptoms shown in figure 1, "hostility" has the most direct relationship to overt physical aggression. In most current studies, hostility is assessed as one of the items on the Positive and Negative Syndrome Scale (PANSS).[28] The rating of hostility assesses verbal and nonverbal expressions of anger and resentment. The hostility item is scored on a scale ranging from 1, indicating no hostility, to 7, indicating extreme hostility that includes marked anger resulting in extreme uncooperativeness that precludes other interactions or in one or more episodes of physical assault against others. A score of 3 is assigned when the patient presents a guarded or even openly distrustful attitude, but his or her thoughts, interactions, and behavior are minimally affected. The hostility ratings are linked to overt aggression: in the CATIE study, for each unit increase on the 7-point rating of hostility, the odds of serious aggression increased by a factor of 1.65 ($P < .001$).[29] The linkage of the hostility item ratings with overt aggression is slightly tautological because the rating of 7 is partly defined by it (see above). However, subjects may nonetheless have hostility ratings that are considered clinically relevant even though they did not exhibit physically aggressive behaviors during the rating periods.

This item has been routinely used as a proxy measure for overt aggression in studies of schizophrenia patients.[3,30] These studies were not originally designed to study aggression, and therefore, the subjects were

not selected because they exhibited aggressive behavior. Under such conditions, the prevalence of overt physically aggressive behavior is usually too low to provide useful information. However, the PANSS was administered to all patients in these studies, and thus, the hostility item was conveniently available for post hoc analyses. Theoretically, hostility can be seen as a mediating variable between schizophrenia and overt aggression. An association between aggression in patients with mental illness and a certain constellation of symptoms referred to as "threat-control override" has been observed.[31] These symptoms are "dominated by forces beyond you," "thoughts put into your head," and "people who wished you harm."

"Command hallucinations" may lead to aggressive behavior, although the risk may be small.[32]

"Impulsive aggression" occurs in schizophrenia as well as in psychopathy. Factor analysis of interview data probing reasons for assaults occurring on an inpatient ward specializing in violence research yielded a factor differentiating impulsive from psychopathic assaults; another factor showed high loading on positive symptoms of schizophrenia, such as delusions and hallucinations.[33] Event-related potentials in the Go/No Go paradigm showed that the neural processes underlying response inhibition were abnormal in both schizophrenia and psychopathy, but there were differences between the 2 conditions. Assessing impulsiveness in research into aggression is important because patients whose assaults are impulsive may require different treatments from those whose assaults are based on psychotic symptoms. Impulsiveness may be assessed using the Barratt impulsiveness scale.[34]

"Neurocognitive impairments" in aggressive schizophrenia patients have been recognized for some time.[8] More recently, it has been shown that neurocognitive function may be an important treatment target in aggressive schizophrenia patients. A study of antiaggressive efficacy of clozapine, olanzapine, and haloperidol in aggressive schizophrenia patients[5] included a neurocognitive component. A battery of tests assessing psychomotor function, general executive function, visual and verbal memory, and visuospatial ability was administered before and after treatment with these 3 antipsychotics.[35] Olanzapine treatment was associated with better improvement of cognitive functioning than haloperidol and clozapine, and this improvement was associated with a decrease in aggressive behavior. Clozapine treatment was associated with a (nonsignificant) deterioration of cognitive function. Nevertheless, clozapine antiaggressive effect was significantly superior to that of olanzapine. A similar pattern of clozapine effects was observed in a different study: superior improvement of hostility[3] combined with a slight deterioration of the neurocognitive global score in the same trial.[36] Thus, clozapine effects against aggression and hostility are not mediated through an improvement of cognitive symptoms.

Clozapine has demonstrated superior antipsychotic efficacy and effectiveness in many studies, particularly those targeting treatment-resistant schizophrenia patients. It would therefore seem reasonable to hypothesize that the antiaggressive effect of clozapine is nonspecific: Clozapine may simply improve all symptoms of psychosis, including hostility and aggression, more or less equally. However, although clozapine treats the positive symptoms such as delusions and hallucinations that are sometimes underlying aggressive behavior, it has specific antiaggressive activity that is (at least statistically) independent of the improvement of positive symptoms.[3,5] The underlying mechanisms of the antiaggressive action of clozapine are not understood.

Thus, antiaggressive effects of some medications (other than clozapine) may be mediated by their influence on cognitive functions. These functions should therefore be assessed at baseline and then at various time points during trials of antiaggressive treatments in schizophrenia patients. The apparent difference between clozapine and olanzapine in the mechanism of antiaggressive action is intriguing and merits further investigation.

As indicated in figure 1, "substance use disorders" have a central role in the etiology of violence in patients with schizophrenia. (By the way, this is also true in persons without mental illness[8]).

There is no question that the use of alcohol and illicit drugs by schizophrenia patients elevates the risk of aggressive behavior.[1,2,8] Furthermore, schizophrenia elevates the risk for substance use disorders. The lifetime prevalence of a substance abuse diagnosis in persons with schizophrenia or schizophreniform disorder in the United States was 47.0%, the OR was 4.6 vs the rest of the population.[8(p239)]

There are several mechanisms by which co-occurring substance abuse may be implicated in violence risk in schizophrenia.[37] Acute pharmacological effects of alcohol and certain drugs may exacerbate psychiatric symptoms. Violence risk increases when substance abuse is added to the combinations of impaired impulse control and symptoms such as hostility, threat perception, grandiosity, and dysphoria. Substance use disorders are also associated with treatment nonadherence, which increases the risk for violence in patients with schizophrenia.

The question is "does schizophrenia without comorbid substance use disorder elevate the risk for aggressive behavior?" The answer to that question has implications for treatment, policy, and stigma. If there is no important contribution of schizophrenia to aggressive behavior unless the patient also uses alcohol or illicit drugs, then the prevention and treatment of aggression could be refocused on the management of substance use disorders. Scarce resources could be reassigned accordingly. Furthermore, because fear of patient violence 7contributes to the stigma of schizophrenia, a finding that schizophrenia per se does not cause violence may sound reassuring. It would remove part of the stigma

from schizophrenia and transfer it to substance use disorders.

To answer the question of relationship between schizophrenia, substance abuse, and aggression using epidemiologic methods, large numbers of schizophrenia patients showing aggressive behaviors need to be studied. Two such studies were conducted in Scandinavia.

The rate of arrest for violent crime in a Danish birth cohort (n = 358 180) was 2.7%. There was a total of 1143 male schizophrenia patients, 11.2% of whom were arrested for violent crime. OR for arrest was 4.6 (CI 3.8–5.6). Of the 1143 schizophrenia patients, a total of 846 did not have comorbid substance abuse diagnosis and only 7.1% had a history of arrest for violent crime (OR 2.8, CI 2.1–3.6). The prevalence of arrest for violent crime was considerably higher in patients with comorbid substance abuse. The numbers for females showed a similar trend, with lower proportions of violent patients overall.[38]

A study using Swedish registers compared risk of conviction for violent crime in 8003 schizophrenia patients with 80 025 general population controls. In patients with schizophrenia, 1054 (13.2%) had at least 1 violent offense compared with 4276 (5.3%) of general population controls (OR 2.0; CI 1.8–2.2). The risk was mostly confined to patients with substance abuse comorbidity (of whom 27.6% committed an offense), yielding an increased risk of violent crime among such patients (OR 4.4, CI 3.9–5.0), whereas the risk increase was small in schizophrenia patients without substance abuse comorbidity, 8.5% of whom had at least 1 violent offense (OR 1.2; CI 1.1–1.4).[2]

Comparing these 2 large studies, we observe that the proportions of schizophrenia patients arrested or convicted for violent crime are similar (11.2 and 13.2%, respectively). Regarding the subset of schizophrenia patients without history of violent crime, the proportions are also similar (7.1 and 8.5%, respectively). The ORs, however, are substantially lower in the Swedish sample. This difference seems to be related to the fact that the general population rate for conviction for violent crime in Sweden (5.3%) was twice as high as the analogous number for arrest in Denmark (2.7%).

All the ORs abstracted here from the 2 Scandinavian studies are statistically significant, although the effect sizes are not large. Does schizophrenia without comorbid substance use disorder elevate the risk for aggressive behavior? These studies indicate that this effect can be reliably detected but leave open the question of its importance. However, small effect sizes do become important when the outcomes of interest include serious bodily harm or death.

In a large US epidemiological study, data on mental disorder and violence were collected as part of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), a 2-wave face-to-face survey conducted by the National Institute on Alcohol Abuse and Alcoholism. A total of 34 653 subjects completed NESARC waves 1 (2001–2003) and 2 (2004–2005) interviews. Wave 1 data on severe mental illness (such as schizophrenia, bipolar disorder, and major depression) and risk factors for violence were analyzed to predict wave 2 data on violent behavior.[39]

Statistical analyses revealed that severe mental illness alone did not predict future violence. Instead, violence was associated with historical (past violence, juvenile detention, physical abuse, and parental arrest record), clinical (substance abuse and perceived threats), dispositional (age, sex, and income), and contextual (recent divorce, unemployment, and victimization) factors. Most of these factors were present more often in subjects with severe mental illness, but severe mental illness did not independently predict future violent behavior.[39]

Thus, these authors have confirmed the importance of various well-known risk factors for violence jn mental illness (including substance abuse); some of these factors are depicted in figure 1 of the present article. However, they were unable coconfirm an independent role of mental illness per se in the causation of violence. From this failure, they infer that "… it is simplistic as well as inaccurate to say the cause of violence among mentally ill individuals is the mental illness itself …"[39(p159)]

This conclusion is obviously inconsistent with the current consensus view which posits a direct causal relationship between severe mental illness and violence. This article[39] elicited critical comments focusing particularly on the role of comorbid substance abuse in violence.[37]

Furthermore, a recent reanalysis of the same NESARC data came to different conclusions than those reached by Elbogen and Johnson.[40] Those reanalyses, focused on causal relationships rather than statistical predictions, have confirmed a statistically significant, yet modest relationship between serious mental illness and violence, which was independent of substance abuse status. This finding is in agreement with the view that assigns direct causal role to serious mental illness in the development of violence.

Epidemiological studies usually have limited information on clinical factors, particularly on treatment. Clinical observations and considerations may complement their results. If aggressive behavior in schizophrenia patients is caused, for all practical purposes, by comorbid substance use disorder, what would be its mechanism of action? Acute pharmacological effects of alcohol, cocaine, and other drugs may exacerbate psychiatric symptoms such as hostility and further impair inhibitory control of patients' behavior. Furthermore, illicit drug abuse is associated with aggression related to conducting illicit transactions, need to obtain funds for drug purchases, and similar criminogenic factors.

Remarkably, there are many schizophrenia patients exhibiting aggression while hospitalized on locked wards

of inpatient facilities.[8] Aggressive behavior may persist for months or even years, while these patients generally have no access to alcohol or illicit drugs. Although some of these patients have a history of substance abuse, it is not clear how that could cause aggressive behavior long after the last ingestion of any alcohol or illicit drug. This is discussed in some detail elsewhere.[37]

Approximately 20% of assaults on inpatients wards appear to be caused by positive psychotic symptoms such as delusions or hallucinations; the balance is associated with confusion, impulsiveness, or psychopathic features.[33] Thus, although there is a robust statistical association between substance use disorder and aggression in schizophrenia, it is possible that the association is not causative. There may be a third persistent factor that may cause both substance abuse and aggressive behavior in schizophrenia; that factor operates relatively independently of the current level of alcohol or drug ingestion.

One such factor may reside in a patient's earlier development. Conduct disorder history was associated with aggressive behavior and alcohol and drug abuse in adult schizophrenia men; the relationship with aggressive behavior remained significant after controlling for lifetime diagnosis of substance abuse. History of conduct disorder was also associated with earlier onset of schizophrenia.[17]

Evidence of conduct disorder with onset before 15 years is of course a DSM-IV-TR diagnostic criterion for antisocial personality disorder. The prevalence of a substance abuse diagnosis in persons with antisocial personality disorder is very high.[8] Thus, there appears to be a considerable overlap between these 2 constructs.

Taken together, this evidence suggests that the association between substance use disorder and aggressive behavior in schizophrenia is complex. It could be partly direct causative effect that depends on the acute pharmacological activity of the substances and the associated criminogenic factors, partly an epiphenomenon that is independent of the pharmacological effects: It is the antisocial personality/psychopathy that causes aggression, while covarying with substance use disorder. Statistical analyses that do not account for personality disorder then show a strong association of substance use disorder on aggression, but a major part of that association is not causative.[37]

This perspective has implications for the management of aggressive behavior in schizophrenia. First, prevention and treatment of comorbid substance use disorders should be an integral part of care for schizophrenia patients. However, we should not expect that this will be adequate for all cases of aggressive behavior in schizophrenia. Early treatment with clozapine or perhaps another antipsychotic with proven antiaggressive action is indicated for persistent aggression in schizophrenia.[5] The results of the Krakowski study[5] as well as emerging evidence[30] suggest that olanzapine might be a candidate for such indication. Finally, a substantial proportion of schizophrenia patients will continue with their aggressive behavior in spite of treatments for substance abuse and psychosis. Many of these treatment resistant patients will have a history of conduct disorder and exhibit current features of psychopathy. Until recently, there was little, we could offer these patients. However, recently developed long-term psychosocial interventions using cognitive behavioral approaches are surprisingly effective in reducing persistent aggressive behavior in psychotic patients.[41] These programs are expensive to administer. We suggest that these approaches should receive more support.

Nonadherence

Nonadherence to antipsychotic medication treatment has been associated with symptom worsening, including aggressive behavior.[42] The combination of alcohol or other drug abuse problems with poor adherence to medication can confer an even higher risk of violent behavior among persons with severe mental illness.[43] Disentangling the effects of substance use and nonadherence on relapse (and aggressive behavior secondary to subsequent psychotic symptoms) can be challenging because both substance use and nonadherence are robust risk factors for hospitalization.[44]

Inadequate insight into mental illness is a strong predictor of nonadherence,[44] and this is a potential mechanism through which it may increase the risk of violence in schizophrenia. However, in a forensic sample of individuals with psychotic disorders, poor insight into illness and nonadherence to medications had independent associations with severity of violence.[45] Medication adverse effects such as parkinsonism, weight gain, and loss of libido are well known to reduce adherence.[44]

While it is clear that nonadherence to medication elevates the risk for violence, emerging evidence suggests that rising hostility predicts the development of nonadherence in patients with schizophrenia or schizoaffective disorder.[46] However, rising hostility in itself may be the result of inadequate treatment for symptoms in general or lack of sufficient antipsychotic response, consequently rendering adherence a less compelling choice for the patient. The effects of comorbid personality disorder on adherence to treatment in schizophrenia were discussed above in the section on antisocial personality disorder/psychopathy, and to reiterate, may be due to impulsivity.

Thus, in summary, nonadherence to treatment is of central importance among pathways to violence in schizophrenia. As depicted in figure 1, 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 nonadherence.

Stress

Stress is a pathophysiological factor in aggression in schizophrenia patients, although its role has not been fully investigated. Most animals and humans are more likely to develop aggressive behavior under stressful conditions.[8] Thus, as depicted in figure 1, stress may directly cause or at least facilitate aggressive behavior. Schizophrenia patients are disadvantaged in their ability to cope with stress in a nonaggressive way by many mechanisms, including misunderstandings of social situations and lower ability to control their impulses. Evidence supporting this includes experiments regarding the misidentification of facial stimuli.[47]

The reduction of stress and active attention to a patient's needs can result in a decrease of overt physical aggression. We have encountered this when transferring patients from their regular psychiatric hospital wards to our research unit specializing in aggression research.[48] These patients were selected for their persistent aggressive behavior on their regular ward. However, it was not unusual for patients to no longer exhibit the same intensity and frequency of their aggressive behaviors once they arrived on the unit. Our research unit was less crowded, quieter, and our personnel were trained to deal with aggressive psychotic patients in a nonconfrontational way. We attributed the rapid reduction of aggressive behavior to a reduction of the level of stress to which the patients were subjected. In addition, when we implemented a new clinical process for routine active monitoring, the incidents of physical aggression were further decreased.[49]

Factors-Modifying Treatment Response: Clinical Implications

Strong evidence and general agreement support the key role of clozapine in the treatment of aggression in schizophrenia. However, as mentioned above, many incidents of aggressive behavior appear to be driven primarily by other factors than psychosis.[33] The response of these other factors to clozapine is questionable.

The central role of *comorbid substance use* disorders in the pathogenesis of aggression in schizophrenia patients is clear in group studies. However, it has not yet become a routine part of clinical practice to diagnose and treat these comorbid disorders.

Taking a detailed history of substance use is particularly important in aggressive patients with schizophrenia. Information that emerges in a patient's history is frequently useful and sometimes intriguing. For example, aggressive schizophrenia patients reporting a history of improved subjective well-being with prior cannabis use can experience amelioration of aggressive behavior with dronabinol, a schedule III controlled substance that contains delta-9-tetrahydrocannabinol, a major active ingredient found in marijuana.[50]

Comorbid personality disorders usually do not receive much attention in the diagnostic evaluation or treatment plan for patients with schizophrenia. This is regrettable because the illness interacts with each individual's personality and such interactions modify behavior. Effects on aggressive behavior are depicted in the premorbid conditions pathway (figure 1).

Schizophrenia patients exhibiting persistent aggressive behavior should receive a detailed diagnostic evaluation for Axis II disorders, including the Psychopathy Checklist (PCL:SV).[14] Aggression in patients with comorbid psychopathy may not respond adequately to pharmacotherapy alone; it may require adjunctive psychosocial treatments.

Stressful environment may play a role in the pathophysiology of aggression. Thus, social interactions and, more generally, the patient's environment should be explored in schizophrenia patients showing persistent aggression. It is possible that modifications of such interactions may improve response to pharmacological treatment. Working closely with the patient, the family, and caregivers is of paramount importance. The approach must be tailored to the particular environment at hand.

Finally, individualized approach must be taken in relation to adherence with treatment. Explaining the purpose, benefits, and side effects of the treatment to each patient and family, if available, is necessary. Patients' feelings and reports of adverse effects must be respected and taken into account for treatment planning in order to enhance the potential for treatment adherence.

Long-acting (depot) antipsychotics may improve treatment adherence and should be considered as an option in aggressive patients with schizophrenia. Based on evidence gathered using their oral formulations, second-generation depot antipsychotics may be more helpful than the older agents for this population.

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