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REVIEW ARTICLE

Pharmacological treatment of violence in schizophrenia

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Chronic aggression and violence in schizophrenia are rare, but receive disproportionate negative media coverage. This contributes to the stigma of mental illness and reduces accessibility to mental health services. Substance Use Disorders (SUD), antisocial behavior, non-adherence and recidivism are known risk factors for violence. Treatment with antipsychotic medication can reduce violence. Aside from clozapine, long-acting injectable antipsychotics (LAI) appear to be superior to oral antipsychotics for preventing violence, addressing adherence and recidivism. LAI also facilitate the implementation of functional skills training. For the high-risk recidivist target population with schizophrenia, better life skills have the potential to also reduce the risk for contact with the legal system, including an improved ability to live independently in supported environments and interact appropriately with others. High-risk patients who are resistant to treatment with other antipsychotics should receive treatment with clozapine due to its direct positive effects on impulsive violence, along with a reduction in comorbid risk factors such as SUDs.

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Clinical Implications

- Most patients with schizophrenia, save for a small minority, are not chronically aggressive or violent.
- Known predictors of violence include patients with comorbid substance use disorders (SUDs) and non-adherence with prescribed treatments, those with comorbid personality disorders, and those with frequent relapses/arrests/civil commitments.
- Among the few modifiable risk factors for violent behavior in patients with schizophrenia is treatment with antipsychotics.
- Aside from Clozapine, it appears that treatment with Long-acting Injectable Medications (LAI) is superior to oral antipsychotic in terms of violence prevention. Moreover, LAI facilitate the successful implementation of functional skills training in people with schizophrenia. For the high-risk recidivist target population, better life skills have the potential to also reduce risk for contact with the legal system, including an improved ability to live independently in supported environments and interact appropriately with others.
- High-risk patients who are resistant to treatment with other antipsychotics should receive treatment with clozapine due to its direct positive effects on impulsive violence, along with a reduction in comorbid risk factors such as SUDs.

Acute treatment of schizophrenia patients is often triggered by attempting to thwart aggression or violence in an inpatient hospital setting. Administration of oral or injectable antipsychotics to acutely agitated patients, perhaps in conjunction with a benzodiazepine, can lead to rapid de-escalation. Short-acting intramuscular formulations of atypical antipsychotics are now available, perhaps with better tolerability compared to the short-acting intramuscular formulation of haloperidol. New alternative formulations that avoid injections include inhalation and sublingual administration have also become available, further adding to the therapeutic options for calming down acutely agitated patients.[1] In contrast, the treatment of chronic aggression and violence can be a more vexing problem in clinical and community settings, including successful transitioning to an outpatient setting and successful residence in the community.[2]

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Most patients with schizophrenia are not chronically aggressive or violent; among patients with schizophrenia, there is a small increase in violence and violent offending on average compared to general population standards in the USA and Europe.[3,4] However, much of the excess risk appears to be mediated by substance abuse comorbidity. Unfortunately, the small subgroup of patients who commit violent acts under certain circumstances are frequently the focus of intense media scrutiny, negatively affecting the public perception of the entire population of schizophrenia patients.[5] This contributes to the stigma associated with mental illness, which is considered to be the most significant obstacle to the development of mental health services.[6] In fact, patients with psychosis are more likely to be victims rather than perpetrators of violence.[7]

Aggression and violence are often used interchangeably although in a strict sense, they are two slightly different concepts albeit located along the same continuum: aggression usually involves threatening behavior, whereas violence goes a step further, and adds an act of furtherance, involving physical harm to others. For the purpose of our review, we will include both aggression and violence towards others, while also acknowledging that aggression and violence are multifactorially and dynamically determined. Moreover, there is often a systematic bias in studying violence in schizophrenia, with many samples examining patients who are involuntarily committed to inpatient facilities or who are undomiciled and receive no mental health treatment, while also abusing substances. Because involuntary commitment criteria often require that the patient has already engaged in threatening or otherwise dangerous behaviors, only the patients already likely to commit violent acts or those who have expressed such an intent are being studied in most inpatient samples. Similarly, outpatient studies are often either retrospective studies of violent acts or include only patients civilly committed in outpatient settings, with the same selection bias applicable.

Known predictors of violence include patients with comorbid substance use disorders (SUDs) and non-adherence with prescribed treatments, those with comorbid personality disorders, and those with a history of violence, frequent relapses/hospitalizations/arrests/and/or commitments.[8] Lifelong antisocial behavior often predated by childhood conduct disorder is a risk factor as well.[4] Comprehensive earlier studies from the New York State Mental Health System, and later the California State Hospital System have delineated three types of violence that are common among patients with schizophrenia: psychosis-driven, impulsive (for example, due to fear, anger, provocation), and predatory.[9,10] Viewed from a caregiver perspective, the burden of dealing with aggression and violence falls on family members, clinical care staff, roommates, law enforcement, and staffs of emergency rooms and jails, adding a dynamic element that can be either helpful or detrimental, depending on how the interaction is perceived by the aggressor. Effective management of violence thus requires consideration of these risk factors and circumstances as they interact with the type of violence encountered, in addition to pharmacological treatment, as reviewed below.

Because a large proportion of violent patients end up in jail, a variety of jail diversion programs has been implemented in the USA and Europe, among other countries, to reduce their presence in the criminal justice system. Although they vary in their structure and procedures and operate from different juncture points within the criminal justice process, all jail diversion programs have at their core the idea that persons with severe mental illness should be redirected to mental health services rather than the penal system.[11] Moreover, linking the mentally ill accused and offenders to community-based treatment services shifts the locus of intervention to community-based mental health treatment, reducing jail time while better serving the mental health needs of these patients. However, patients in these programs do not typically receive court-ordered medications and many of the comorbidities associated with violence risk (e.g. substance use, antisocial PD, violence history) associated with future violence risk limit their effectiveness for future violence prevention.

Antipsychotics, Impulsive Aggression and Violence in Schizophrenia

Among the few modifiable risk factors for violent behavior in patients with schizophrenia is the success of treatment with antipsychotic medication.[2,12] Psychosis-driven aggression and violence can be addressed with treatment of the underlying psychosis. As such, standard treatment algorithms apply including those recommended for otherwise treatment-resistant patients.[13] Clozapine is the preferred treatment for resistant psychosis, but remains largely underutilized. Impulsive aggression, the most common form of aggression in schizophrenia patients, does appear to respond well to clozapine also. For example, Clozapine has been shown to reduce aggression, hostility, and violent behavior,[14] coinciding with empirical observations that patients with schizophrenia who take clozapine are less likely to engage in physical and verbal aggression[15,16] and are less likely to require restraints and seclusion in hospital settings.[17] In other words, along with its effects on otherwise treatment-resistant
psychotic symptoms, clozapine may have direct anti-violence effects, such as its demonstrated effects on suicidal behaviors,[18] and moreover, possible direct effects on smoking and substance abuse as well,

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addressing key independent risk factors for violence, further reducing risk.[19] If so, clozapine may effectively address several domains involved in the generation of violence including psychosis-driven and impulsive violence while reducing a major comorbid risk factor (SUDs), a possibility we aim to examine in our review as well.

Finally, in a subset of recidivist offenders, lasting treatment adherence is oftentimes difficult to achieve. In these patients, there have been efforts to augment adherence, including through the use of long-acting injectable (LAI) antipsychotics and other, non-pharmacological interventions that aim to reduce other, dynamic risk factors for violence. Since there is little evidence that LAI medications are effective in patients who are treatment resistant to oral medications, we will review the databases separately as most people with schizophrenia treated with clozapine are in fact treatment resistant regardless of their level of violence, substance abuse or smoking status.

Treatment Adherence and the use of LAI Antipsychotics for Violence Prevention

Poor treatment adherence is common in the schizophrenia population; rates of non-adherence have been found to be as high as 50–75%.[20] Although non-adherence to medical treatment is often this common in general medical conditions, the consequences of non-adherence in schizophrenia are more immediate than, say, the consequence of non-adherence to blood pressure or lipid-lowering medications. Factors associated with poor adherence to antipsychotic medication include the patient's insight into illness, homelessness, family support, and the efficacy, side effects, and cost of medication.[21] Poor treatment adherence is of particular concern in patients with comorbid substance use and those with prior involvement with the legal system, which are also risk factors for violence. Non-adherence often becomes a precursor to frequent symptom exacerbations, including increased propensity for violent behaviors. Certain predictors of violence are found in higher rates among patients with schizophrenia compared to the general population; these predictors include low socioeconomic status, unemployment, alcohol abuse, and antisocial personality disorder.[22] The relationship between poor adherence and violence in patients with schizophrenia has been demonstrated. Proper treatment with antipsychotics reduces violence by decreasing positive symptoms of schizophrenia, whereas non-adherence to antipsychotics is associated with higher rates among violence.

Patients with schizophrenia who are non-adherent are faced with multiple repercussions outside of recidivism. Risk of relapse is 3.7 times greater in patients with schizophrenia who are non-adherent in comparison to patients who are adherent. Moreover, non-adherence predisposes patients to a higher risk of psychiatric rehospitalization, emergency room visits, substance abuse or relapse to substance use, attempted suicide,[21] and being the victim of a crime.[23] With every psychotic episode, patients with schizophrenia suffer from a worsened disease state and further deterioration of social functioning, including evidence of structural brain changes associated with relapse and re-treatment.[24] Consequently, it is imperative to consider relapse prevention as a treatment target in the management of schizophrenia.

Long-Acting Injectable (LAI) Antipsychotics

LAI antipsychotics assure delivery of therapeutic levels of medications over several weeks, and with more recent LAI formulations for up to 3 months, essentially eliminating the need for daily oral medication administration. Although the primary indication for LAI use is poor treatment adherence, less than one-fifth of patients with schizophrenia receive their medication in the form of an LAI.[23] Despite the persistent stigma that follows LAIs and the unsubstantiated and antiquated notion that LAIs cause more adverse effects than oral antipsychotic medications (OAPs), it has been found that LAIs and OAPs do not differ significantly regarding adverse effects.[20] Additionally, adherence remains a barrier to efficacious treatment in patients with schizophrenia who are treated with OAPs. One-third of patients on OAPs are poorly adherent to their medication.[23]

There is a limited number of retrospective studies and prospective trials that suggest LAI may have clinical benefit in schizophrenia patients with high risk of violent behavior. One study by Arango et al reported that patients with schizophrenia who were considered violent had significantly fewer violent episodes after treatment with LAI medications compared to those treated with OAPs.[22] Moreover, LAIs can effectively reduce the severity of hostility, aggression, and frequency of violent incidents. When patients are adherent to their treatment, LAIs reduce both violent and nonviolent offending behaviors.[25]

Additionally, LAI have been found to be superior to oral antipsychotics in reducing violent behavior in patients with schizophrenia both with and without comorbid substance abuse.[25] Substance abuse is highly prevalent among patients with schizophrenia. Studies show that 47% of patients with schizophrenia have lifetime comorbid substance abuse and 27% have current substance abuse.[26] Nearly 50% of patients with schizophrenia report substance abuse prior to their first episode of schizophrenia.[27] While schizophrenia is a risk factor for violence, substance abuse, regardless if accompanied by a comorbid diagnosis or not, is known to increase the

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risk of violence.[26] Therefore, the ability of LAI to treat patients with comorbid substance abuse makes it an even more desirable treatment option. LAIs may also benefit patients in early-phase or first-episode schizophrenia,[23] possibly improving long-term outcome.

Although systematic bias is often present in studies examining violence in schizophrenia, the Paliperidone Palmitate Research in Demonstrating Effectiveness (PRIDE) study was designed to reflect real-world management of patients with schizophrenia and is therefore worth discussing.[28] The PRIDE study was a 15-month, randomized, prospective, study of adult patients with a history of incarceration in addition to a DSM-IV diagnosis of schizophrenia conducted between May 2010 and December 2013. The authors hypothesized that existing clinical trials comparing LAI and oral antipsychotics generated inconclusive results due to failure to enroll individuals representative of patients with schizophrenia in real-world settings. The authors of the PRIDE study note that by failing to enroll patients with complex comorbidities and histories, the factors which complicate management of schizophrenia such as comorbid substance abuse, unemployment, and unstable living conditions remain unaccounted for. By creating broader criteria for PRIDE study participants, the authors hoped to produce study results with greater generalizability in comparison to previous studies. Efforts were made to recruit participants who would normally be excluded from trials, such as patients from homeless shelters, soup kitchens, and jail-release or diversion programs. Furthermore, participants were not excluded for a history of substance abuse, although individuals with history of intravenous drug abuse within 3 months of screening or with an opiate dependence disorder were excluded. Additionally, the study allowed for substantial flexibility in terms of treatment decisions and analyzed clinically relevant endpoints with an explanatory approach, which resulted in an overall pragmatic study design.

Participants were randomly assigned to treatment with one of the seven reviewed oral antipsychotics or with a monthly long-acting injection of paliperidone palmitate. The primary end point was time to first treatment failure, defined as either arrest/incarceration, psychiatric hospitalization, suicidal behavior, discontinuation of antipsychotic treatment or supplementation with an additional antipsychotic due to inadequate efficacy, or a necessary increase in psychiatric services to prevent impending psychiatric hospitalization.

The results of the PRIDE study demonstrated that once-monthly treatment with paliperidone palmitate was more effective in delaying treatment failure than treatment with daily oral antipsychotics. In terms of adherence, 95.2% of patients in the paliperidone palmitate group has a medication possession ratio (MPR) greater than 80%, whereas merely 24.3% of patients in the oral antipsychotic group were found to have an MPR greater than 80%. In summary, the PRIDE study results indicate that medication choice may improve outcomes for patients with schizophrenia who are at risk for treatment failure.

In the PRIDE study, 40% of the paliperidone palmitate patients and 54% of the oral antipsychotic patients had a treatment failure event. However, the time to first failure was 416 days in the Paliperidone group and 226 in the oral medication group. 21% of the Paliperidone group and 29% of the oral treatment group had an arrest, with the time to the first arrest being found to be considerably different: Median time to arrest in the Paliperidone group was over 450 days, with the time to arrest for the oral medication group being 274 days. Thus, there is considerable evidence that LAI treatment provides extensive protection against hospitalization and arrest even in cases with lengthy histories of multiple arrests and hospitalizations. This head-to-head randomized trial provides quite convincing evidence of efficacy for relapse and arrest reduction.

Additional Benefits of LAI Medications

Many people with schizophrenia who have a history of recidivist violence have other schizophrenia-related co-morbidities. These include deficits in the abilities to everyday functioning skills. While functional skills deficits are most strongly related to negative symptoms and cognitive deficits,[29] there is emerging evidence that clinical stability induced by LAI treatment is also correlated with improvements in everyday functioning. In the most recent example, Fu et al.[30] reported that long-term treatment with LAI medications led to persistent benefits in everyday functioning indexed with a targeted clinical rating scale, particularly when compared to patients receiving placebo treatment. These results are similar to results of previous studies that have suggested gains in everyday functioning with successful LAI treatment,[31] reductions in risk for homelessness,[32] and improvement in outcomes in first- episode samples.[33] Thus, treatment with LAI medications seems to facilitate other interventions aimed at improving functional outcomes in people with schizophrenia. For the high-risk recidivist population, improvement in life skills might also reduce risk of contact with the legal system, due to increases in the ability to live independently in supported environments and interact more proficiently with others.

Who Should not Receive LAI Treatment?

Although there are very few indications that LAI actually lead to more side effects than oral medications, there is also no evidence that patients who are treatment resistant to oral medication in trials with adequate adherence

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would receive any additional benefits from LAI. Thus, a prequalification for using LAI treatment is demonstrated adequate response to oral formulations of the same medications. For patients who are treatment resistant to antipsychotic medication and by extension, to LAI, there is only one effective treatment for treatment resistance, and that is clozapine. In the sections below, we will describe the use of clozapine as a violence reduction treatment and evaluate which subset of patients would benefit the most from clozapine.

Clozapine for Violence

Clozapine is among the most unique pharmacological treatments for severe mental illness. It is the only treatment approved for treatment resistance and suicidal behavior in schizophrenia, and has also been extensively researched for its effects on comorbid smoking and SUDs, the latter being a major risk factor for violence. As noted above, psychotic symptoms, either due to nonresponse or treatment discontinuation in otherwise treatment responsive patients, can be drivers of violence. Clozapine may have a direct effect on violence reduction, in line with its known suicide risk reduction, or indirectly, due to a reduction in psychotic symptoms and SUDs in otherwise nonresponsive patients.

In our literature review, we examined prospective studies and other evidence (case series, and retrospective studies). We divided the prospective studies we reviewed into randomized and nonrandomized trials.

Randomized Controlled Trials

A randomized double-blind controlled trial involving 101 patients, with aggression as the target symptom, was performed with participants who were inpatients of the research ward at a hospital.[34] Compared to olanzapine and haloperidol, clozapine had the best anti-aggressive effect in the trial, as indexed by reductions in the primary outcomes scale, the Barratt Impulsiveness Scale. The researchers in the study stated their belief that reduced aggressiveness was a direct result of effects of clozapine on impulsivity and depression, with clozapine's serotonergic action likely playing a role.

A 12-week prospective, randomized, double-blind trial involving 100 inpatients diagnosed with schizophrenia targeted aggression measured with the Modified Overt Aggression Scale (MOAS).[35] Inpatients were randomized to either haloperidol, olanzapine, or clozapine in equal numbers. The study found that there was no significant difference in the response to psychotic symptoms across the three medications, although both olanzapine and clozapine were more effective than haloperidol at reducing aggressiveness. Similar results were found in a randomized, double-blind trial focusing on 110 inpatients with either schizophrenia or schizoaffective disorder.[36] The study compared clozapine, olanzapine, and haloperidol in their anti-violence effect on these patients, and also used the MOAS as the outcomes. This study found that clozapine was superior to haloperidol and olanzapine in its anti-aggressive effect, while the antipsychotic effect of the three drugs was equal. These findings again suggest an anti-impulsive aggression effect of clozapine that is independent of its antipsychotic effect.

A prospective, double-blinded, and randomized trial looked at the effectiveness of clozapine, olanzapine, haloperidol, and risperidone on treating hostility in 157 patients with schizophrenia or schizoaffective disorder.[37] The study participants were inpatients at state psychiatric hospitals either in New York or North Carolina. The patients were intended to receive a target daily dose of 500 mg of clozapine. The study determined that clozapine decreased aggressiveness in patients compared to the other treatments with minimal differences in antipsychotic efficacy.

In a secondary analysis from the first phase of the CATIE schizophrenia trial, patients were randomized to one of the four atypical antipsychotics, other than clozapine, or a typical agent.[38] Although violence was reduced for the entire sample, there were no differences between the groups in rates of reduction, with rates of violence being minimal at baseline (19%) compared to other studies. This study highlights the fact that most randomized trials do not suggest that atypical medications other than clozapine have significant potential to reduce violence.

Overall, the results from these studies suggest there may be a direct anti-aggressive effect of clozapine operative when compared to other typical and atypical antipsychotic medications, independent of symptom reductions.

Other Evidence (Nonrandomized Trials and Case Series)

Three nonrandomized, prospective studies examined the effect of clozapine on violence reduction and clozapine treatments were suggested to be protective against future aggressive behavior[39,40] and fewer restraint episodes in the hospital.[41] One large, nonrandomized observational study in 675 participants with either schizophrenia or bipolar disorder, with patients recruited from homeless shelters, jails, hospitals, and the streets, did not find enough evidence to determine if clozapine decreased violence in this population, but it asserted that not enough patients with schizophrenia are prescribed clozapine in order to make an accurate conclusion.[42]

A nonrandomized, prospective study of 20 children examined clozapine's impact on aggression in adolescents. The study participants were treatment-resistant

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schizophrenia inpatients at a child psychiatric center, and all were treated with clozapine.[43] The number and frequency of emergency injectable medication events, emergency oral medication events, and/or seclusions were assessed for each of the patients both before and after clozapine treatment, with the incidence of these events drastically decreasing after the administration of clozapine. In addition, administration of clozapine also allowed patients to be discharged to less restrictive environments more expediently.

Several case series were similar in that they all produced results that demonstrated clozapine's effectiveness for violence reduction.[44–46]

We also identified a number of large-scale retrospective studies relevant to this review. All of these studies concluded that treatment with clozapine resulted in a measurable decrease in aggressiveness, violence, and/or hostility in the study participants.[16,47–51]

In summary, clozapine appears to be beneficial in reducing aggressiveness in patients suffering from schizophrenia and schizoaffective disorder. Compared to other antipsychotics, several studies demonstrate that clozapine's anti-aggressive effects are superior to those of haloperidol, olanzapine, and risperidone and both dependent and independent of its antipsychotic effects. Finally, even in the presence of comorbidities such as intellectual disability and antisocial tendencies, clozapine was effective. These data indicate that clozapine should be considered as a treatment for violence in any patient who manifests continued violence, hostility, or aggression after other treatments, regardless of psychosis.

Outpatient Civil Commitment

A fundamental conflict exists between individual autonomy and the need for treatment of people suffering from severe mental illness, inclusive of potentially violent patients.[52] This challenge is magnified when aggression and violence are involved. Given that the common consequence of violence to patient perpetrators is incarceration, often for lengthy terms, there is a clear argument that outpatient commitment (OPC), applied fairly, has benefits to both patients and society as a whole.

Under US Civil Law, OPC orders, issued by a judge, mandate people with serious mental illness (SMI) to adhere to outpatient treatment in order to prevent recidivism and improve outcomes. According to recent data, at least 46 states and the District of Columbia had commitment statutes permitting some form of OPC,[53] with inconsistent implementation, evaluation, and funding across states. The first such program was implemented in North Carolina in 1983, a "preventive" form of OPC used as model for OPC laws implemented in other states, often named for murder victims who were killed by people with severe mental illness, such as "Kendra's Law" in New York or "Laura's Law" in California. Involuntary administration of medication is usually explicitly prohibited under the authority of OPC and, if indicated, requires separate legal authority and procedures for administration of involuntary medication. The patient may be sent to a hospital for evaluation if needed, depending on state law.

The ethics and effectiveness of OPC orders continue to be debated.[54] Major limitations that have led to unclear evidence include difficulties in conducting and interpreting trials, the definition and measurement of violence, comparing outcomes across different health systems nationally, working with a frequently uncooperative and risky population, small sample sizes, and selection bias. What is often missing in the debate, however, is the above-mentioned restriction on administering compulsory medication. This appears to be a major limitation to programs designed to facilitate treatment in people whose reason for placement under involuntary treatment orders is often triggered by non-adherence to medication.

Among the United States' civil commitment programs, the program in New York had the most solid funding and implementation, allowing for adequate outcome evaluation, compared to other States. NY patients under OPC orders did appear to have improved outcomes, in contrast to results from a recent meta-analysis utilizing international data: 58 among the noted results were reduced hospitalization and length of stay, higher rates of receiving psychotropic medication prescriptions and intensive case management services, and greater engagement in outpatient treatment with resultant decreased safety-risk, a 17% reduction in offenses, 11% in initial-victimizations, and 22% for repeat-perpetrations.[55] Another, similar study pointed out that CTO-initiated-re-hospitalization was associated with a 13% reduced-initial-perpetration-risk, a 17% reduced-initial-victimization-risk, and a 22% reduced-repeat-victimization-risk.[56]

Recommendations

The treatment of chronic aggression and violence in schizophrenia involves assessment of interdependent risk factors including the type of aggression (psychosis-driven, impulsive, or predatory), comorbidities (SUDs), antisocial behavior, and environmental factors. Antipsychotics are not effective for predatory violence. Psychosis-driven violence is likely the most easily accessible type of violence encountered, and follows the same treatment algorithm as for partially/unresponsive patients, eventually oftentimes involving LAIs or clozapine. Aside from Clozapine, it appears that treatment with LAI medications is superior to oral antipsychotic in terms of violence prevention.

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Moreover, LAI facilitate the successful implementation of functional skills training in people with schizophrenia. For the high-risk recidivist target population, better life skills have the potential to also reduce risk for contact with the legal system, including an improved ability to live independently in supported environments and interact appropriately with others. High-risk patients who are resistant to treatment with other antipsychotics should receive treatment with clozapine.

Impulsive violence appears to respond well to clozapine also, due to its direct positive effects on impulsive violence, along with a reduction in comorbid risk factors such as SUDs. Moreover, the direct antiviolence effect of clozapine lends itself particularly well to treating violent offenders. Community treatment orders (CTOs) should be stringently implemented and if needed, hospitalization is initiated so that these treatments can be safely introduced, or restarted.

Treatment Algorithm

In patients with a history of non-adherence and a history of violent acts during relapses, a trial of LAI seems to be a reasonable first step. As treatment nonresponse and the need for clozapine is determined on the basis of 12 weeks of treatment or less, a rapid decision regarding treatment response, within 3 one-month injection cycles, can be made. For individuals who are involuntarily committed, LAI treatment also reduces the need for monitoring for surreptitious non-adherence to medication. In cases where adherence to oral medication can be ascertained, the benefits of LAI to oral medications of the same type/class is not proven.

In cases with history of treatment resistance, clozapine treatment appears indicated in any cases and certain for any cases with a history of violence. As noted above, violence may be reduced even in the presence of clozapine nonresponse for psychotic symptoms. Thus, for individuals who do manifest clear treatment response but are not intolerant, clozapine as an antiviolence treatment seems viable.

Finally, as noted elsewhere in this issue (Jones & Harvey), cognitive, social cognitive, and functional skills training appears to have violence reduction potential on its own. As these interventions have optimal efficacy in patients with greater clinical stability, concurrent optimized antipsychotic treatment would seem critical, regardless of whether the treatment was LAI or clozapine.

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