Psychopharmacology of Aggression and Violence in Mental Illness

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Several studies have been undertaken to test the efficacy of drugs in the management of aggression and hostility in patients with schizophrenia and other mood disorders.

Most patients with mental illness are not violent, and when violent behavior does occur, it is usually transient. Nevertheless, violent behavior is a challenging problem. Swanson and colleagues provided evidence that demonstrated that schizophrenia and major mood disorders confer an elevated risk of violent behavior, and that risk is augmented by comorbid substance use disorders and by comorbid personality disorders. Comorbid substance use disorders play a particularly important role in the development of violent behavior in schizophrenia. This was studied in a meta-analysis of violent criminality using data from 18,423 individuals with schizophrenia and other psychoses. The odds ratio for violent crime was 2.1 (95% confidence interval [CI], 1.7 - 2.7) without comorbidity, but it increased to 8.9 (95% CI, 5.4 - 14.7) with comorbidity. The difference between odds ratios indicated a marked effect of substance abuse on violent crime. The clinical importance of this effect is underlined by the fact that risk for substance use disorders in schizophrenia is very high; lifetime prevalence of this comorbidity in schizophrenia is estimated at 47%. For these reasons, evaluation of comorbid substance use disorders is an important component of the clinical assessment of patients with schizophrenia. Management of comorbid substance use disorders must be an inherent part of the treatment plan. Violent behavior is heterogeneous in origin, and its development is not limited to the context of mental illness. Therefore, management approaches that rely exclusively on psychopharmacology are frequently unsuccessful—not only because of incorrect societal context, but also because violent behavior in mental illness frequently results from nonadherence to treatment.

**Acute management of agitation and violent behavior**

Agitation is a common reason for presentation to an emergency department (ED); it can tip the decision for in-patient care and can be an obstacle to hospital discharge. Agitation can easily escalate to aggression and violent behavior, and thus acute agitation is considered a behavioral emergency that requires immediate action. In addition to nonpharmacological interventions related to managing crisis situations, medication approaches are vital.
Although oral medications can be effective, rapidity of onset of action is enhanced with the use of short-acting parenteral formulations that allow for maximal plasma levels to be reached more quickly. Lorazepam can be useful when the cause of the disturbed behavior is unclear and perhaps due to withdrawal from alcohol. It is reliably absorbed intramuscularly, has no active metabolites, and has a half-life of 10 to 20 hours; the usual dosage is 0.5 to 2 mg every 1 to 6 hours.\(^7\) Caution is required with lorazepam when respiratory depression is a possibility. In addition, lorazepam should not be used for long-term daily use because of the problems that are associated with benzodiazepine use—tolerance, dependence, and withdrawal.

What is already known about treating aggression?

Schizophrenia and major mood disorders confer an elevated risk of violent behavior, which is further raised by comorbid substance use disorders and by comorbid personality disorders. Intramuscular short-acting formulations of lorazepam, haloperidol, aripiprazole, olanzapine, and ziprasidone are available for the management of acute agitation and aggression. All available antipsychotics as well as mood stabilizers and other drugs have been used for the long-term management of violent behavior in mental illness. Clozapine has demonstrated superiority over other treatments.

What new information does this article provide?

We update information on efficacy and safety of medications used for acute agitation and aggression, particularly intramuscular formulations.

What are the implications for psychiatric practice?

Clozapine is the first-choice treatment for persistently violent patients with schizophrenia. It is not likely to be fully effective before an adequate dose (approximately 400 mg/d) is reached—often several weeks. Clozapine should not be prematurely discontinued during this escalation period. If necessary, another medication may be temporarily added to control violent behavior. If clozapine cannot be used, olanzapine may be a second choice. Other antipsychotics do not show any systematic differences in their antiaggressive effects.

The combination of intramuscular haloperidol with intramuscular lorazepam is also commonly used and is supported by a double-blind randomized clinical trial that compared intramuscular haloperidol 5 mg, intramuscular lorazepam 2 mg, or a combination of both in psychotic, agitated, and aggressive patients treated in EDs.\(^8\) However, continued use of haloperidol as a foundational antipsychotic would be suboptimal in schizophrenia or bipolar disorder. Consequently, there has been increased interest in intramuscular formulations of second-generation antipsychotics, of which 3 are available in the US: ziprasidone, olanzapine, and aripiprazole.\(^9\)

Intramuscular ziprasidone’s efficacy in reducing agitation was evidenced in 2 pivotal clinical trials that enrolled patients with schizophrenia, schizoaffective disorder, bipolar disorder with psychotic features, or another psychotic disorder.\(^10,11\) Although the product label recommends a dose of 10 or 20 mg, the best dose appears to be 20 mg; this conclusion is based on the proportion of patients with a clinically relevant reduction in agitation-rating-scale scores. A naturalistic study of intramuscular ziprasidone in patients who can have more severe levels of agitation than those participating in a randomized controlled study also supports the use of intramuscular ziprasidone as an effective treatment.\(^12\) Product labeling cautions prescribers regarding ziprasidone’s potential to prolong the QT interval and that the cyclodextrin excipient used in the formulation is cleared by renal filtration, which may be an issue in patients who have impaired
Intramuscular olanzapine was found to be effective in reducing agitation in patients with schizophrenia and in patients with bipolar disorder, manic or mixed.\textsuperscript{14-16} The recommended dose of olanzapine is 10 mg, but lower doses of 2.5 to 5 mg can be considered for medically vulnerable patients.\textsuperscript{17} Naturalistic studies of intramuscular olanzapine are also supportive of its effectiveness.\textsuperscript{18} The product label is cautionary regarding hypotension, bradycardia with or without hypotension, tachycardia, and syncope as reported during the clinical trials. Simultaneous injection of olanzapine and benzodiazepines is not recommended, and this advice is reinforced in a report of a case series in which comorbid medical conditions were noted to increase risk.\textsuperscript{19}

Study findings indicate that intramuscular aripiprazole reduces agitation in patients with schizophrenia and in patients with bipolar disorder, manic or mixed.\textsuperscript{20-22} The recommended dose is 9.75 mg.\textsuperscript{23} The product label cautions clinicians regarding greater sedation and orthostatic hypotension with the combination of lorazepam and aripiprazole compared with aripiprazole alone. Once past the acute phase, patients who are receiving intramuscular ziprasidone, olanzapine, or aripiprazole can be successfully transitioned to the oral counterpart of the medication.\textsuperscript{24-27}

**Long-term management of violent behavior**

Most of the evidence on long-term treatment of aggression in mental illness has been collected in patients with schizophrenia. There are very few controlled trials that were a priori designed to test antiaggressive treatments. Most of the data available were obtained in the form of clinical observations, uncontrolled chart reviews, and post hoc retrospective analyses of databases collected primarily for purposes other than the study of aggression. Antipsychotics are the mainstay of the long-term pharmacological treatment of aggression in schizophrenia.

### Antipsychotics

Randomized controlled trials of antipsychotics are summarized in the Table. Two randomized, controlled, double-blind trials were designed a priori to study aggression in schizophrenia. The first trial compared clozapine, olanzapine, risperidone, and haloperidol in 157 patients with schizophrenia or schizoaffective disorder.\textsuperscript{28} The hostility item of the PANSS (Positive and Negative Syndrome Scale) was used as a proxy measure for aggression in the analyses. Clozapine was superior to risperidone and haloperidol (but not to olanzapine) in reducing hostility.\textsuperscript{29} Neither risperidone nor olanzapine showed superiority to haloperidol.

In the same randomized controlled trial, incidents of overt physical aggression were also recorded and analyzed.\textsuperscript{28,30} The results showed clozapine (and, in some analyses, all 3 atypicals) to be superior to haloperidol in antiaggressive efficacy, particularly after the first 24 days in the trial, when scheduled dose escalation of clozapine was completed. Thus, an important clinical take-home lesson from this study is that full effectiveness of clozapine cannot be expected until the patient has been exposed to an adequate-dose regimen. If aggressive behavior is a problem during the escalation period of clozapine, other medications need to be temporarily coadministered. Discontinuation of clozapine for lack of effectiveness during this period would be premature.

The second randomized double-blind trial compared clozapine, olanzapine, and risperidone in 110 patients with schizophrenia or schizo-affective disorder who were selected for being violent.\textsuperscript{31} For reducing overt physical aggression, clozapine was more efficacious than olanzapine, which was, in turn, more efficacious than haloperidol.

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) has yielded important information about antiaggressive effects of antipsychotics.\textsuperscript{32} In the double-blind phase 1 trial, 1445 patients with chronic schizophrenia were randomly assigned to receive 1 of 5 antipsychotics: risperidone, olanzapine, quetiapine, ziprasidone, or perphenazine. They were then followed up for 6 months for violent behavior.\textsuperscript{33} Violence declined with all medications. The only difference between medications was that perphenazine showed greater violence reduction than quetiapine in some analyses.
Data acquired in the context of the European First Episode Schizophrenia Trial (EUFEST) were used to compare in post hoc analyses the effects of haloperidol, amisulpride, olanzapine, quetiapine, and ziprasidone on hostility (assessed as a PANSS item).\(^{34,35}\) The results showed that at months 1 and 3, olanzapine was significantly superior to haloperidol, quetiapine, and amisulpride in reducing hostility. Smaller studies, also summarized in the Table, have shown the superiority of risperidone, quetiapine, and aripiprazole in comparison with placebo in terms of antiaggressive efficacy.\(^{36-38}\) The effects of ziprasidone could not be distinguished from those of other antipsychotics.\(^{33}\) Thus, randomized controlled trials as well as uncontrolled studies strongly support the superiority of clozapine over other antipsychotics in reducing violent behavior. Emerging evidence suggests that olanzapine may be a good second choice if clozapine cannot be used. However, metabolic adverse effects of these medications must be taken into account when making individual clinical decisions.

**Mood stabilizers (anticonvulsants and lithium)**

Although not approved by the FDA for impulsive aggression, valproate is frequently prescribed as an adjunctive medication for patients with schizophrenia, perhaps with the expectation that impulse control will be improved.\(^{39}\) Satisfactory efficacy of adjunctive valproate in schizophrenia has been reported, and post hoc analysis of the hostility item of the PANSS has demonstrated valproate efficacy during the first week of treatment.\(^{40,41}\) However, these results could not be replicated; thus, the empirical data available do not support the efficacy of valproate as adjunctive treatment for violent patients with schizophrenia.

Lamotrigine has been tested as adjunctive treatment in schizophrenia, with contradictory results.\(^{42,43}\) Findings from a recent meta-analysis suggest that lamotrigine may be useful in the most severely ill patients who are clozapine-resistant.\(^{44}\) A recent meta-analysis examined the effects of valproate, carbamazepine, and phenytoin in the treatment of aggression with associated impulsivity in various psychiatric disorders. The researchers found that the evidence is insufficient to allow any firm conclusion to be drawn about the use of antiepileptic medication in the treatment of aggression and associated impulsivity.\(^{45}\) Another meta-analysis excluded patients with psychosis, organic brain disorder, and mental retardation and, thus, focused mainly on personality disorders.\(^{46}\) The effects of valproate, carbamazepine, phenytoin, levetiracetam, and lithium on aggression were analyzed. Some evidence of antiaggressive efficacy was found for carbamazepine, phenytoin, and lithium. Lithium has been found to reduce aggressive behavior in mood disorders, particularly in bipolar disorder.\(^{47}\) There is some evidence of antiaggressive effects of mood stabilizers in personality disorders.

Although mood stabilizer treatment of aggression in schizophrenia is not supported by adequate empirical evidence and is not approved by the FDA, it is possible that it may be effective in some patients. Such use must be weighed against potential adverse effects. The effectiveness of adjunctive treatment must be closely monitored, and the treatment must be promptly discontinued if it fails to show clear benefits.\(^{39}\) SSRIs were reported to reduce aggressive behavior in patients with personality disorders and in the intellectually disabled.\(^{48,49}\) Adjunctive citalopram showed antiaggressive efficacy in persistently violent schizophrenia inpatients in a study that awaits replication.\(^{50}\)

**Summary**

Several studies have been undertaken to test the efficacy of drugs in the management of aggression and hostility in patients with schizophrenia and other mood disorders. Clozapine was found to be most efficacious in reducing violent behavior in agitated patients with schizophrenia. However, clozapine is not likely to be fully effective against aggression before an optimal dose (approximately 400 mg/d) is reached, and dose titration may take several weeks. During the initial escalation period, clozapine should not be prematurely discontinued for apparent lack of effectiveness; if necessary, other medications can be added to clozapine temporarily to reduce aggressive behavior. If clozapine is contraindicated, olanzapine may be the second choice. Other antipsychotics do not show any systematic differences in their antiaggressive effects.

**References:**

2. Swanson JW, Holzer CE 3rd, Ganju VK, Jono RT. Violence and psychiatric disorder in the


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