Psychopharmacology of Aggression in Schizophrenia

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The management of aggression in patients with schizophrenia is a complex and challenging clinical dilemma. It also is greatly influenced by prevailing societal and medicolegal considerations regarding the perceived associations between violence and mental illness. This article provides a succinct account of a complex area and offers evidence for available treatments to reduce the occurrence of violent behavior among patients with schizophrenia.

Key words: schizophrenia/violence/treatment

Introduction

The treatment of patients with schizophrenia who are aggressive is particularly challenging. Our capacity for accurate prediction of violent behavior—itself a daunting task—juxtaposes our responsibilities for societal risk alongside our responsibility to provide and safe care to the psychotic patient who is/could become violent. Moreover, the choice of the treatment methods varies depending on the possible cause of aggression: is the aggression stemming directly from psychosis or due to some other comorbidity, eg, traumatic brain injury or mental retardation or due to the personality disorder? For a long time, the clinicians had available only the typical (first generation) antipsychotics to reduce aggression, and often "megadoses" were used and/or potentially coercive use when noncompliance involved long-acting injectable.[1]

Complicating medication choice is the multifactorial etiology for the agitated behavior. This requires the assessment of the patient for possible comorbidities, such as somatic conditions or other psychiatric conditions, or adverse effects of medications, such as akathisia. In particular, special consideration needs to be made for patients who may be in acute alcohol or sedative withdrawal where reduction of the seizure threshold with the use of antipsychotics can be problematic. In these instances, medications that are cross-tolerant with alcohol, such as lorazepam (well absorbed intramuscularly), are preferred because they will treat the potential withdrawal state as well as exert a calming effect. However, these agents do not address the underlying core psychotic illness, and long-term use of a benzodiazepine can also result in physiological tolerance, leading to potential rebound anxiety or agitation in between doses or when doses are missed. Moreover, the underlying causes for the propensity toward aggression are themselves complex.[1,2] Herein, we briefly illuminate core principles—both legal and clinical—and practices that currently guide our management of this complicated clinical scenario.

Study Methodologies and Inconsistencies Complicate Interpretation of Risk of Violence and Required Interventions

The assessment and prediction of violent behavior in individuals with schizophrenia is inherently difficult and is made more complex by discrepant results across studies secondary to variations in methodology used to assess and predict violence,[2] types of study samples (eg, forensic patients vs civil psychiatric patients vs community-based samples[3,4]), and inevitably informed consent for conducting violence research studies.[5] There initially was an overreliance on clinical judgment as the primary source of violence prediction.[6] Unfortunately, clinical judgment is incorrect more often than correct.[6] Indeed, in a Texas death penalty Supreme Court appeal, Barefoot contended.[7] "The use of psychiatrists at the punishment hearing to make predictions about petitioner's future conduct was unconstitutional because psychiatrists, individually and as a class, are not competent to predict future dangerousness. Hence, their predictions are so likely to produce erroneous sentences that their use violated the 8th and 14th Amendments (p. 884–885)."

Improving on clinical judgment, actuarial and structured professional guidance measures of risk assessment

are used to determine risk based upon type of violence and specific symptoms.[8] Examples include the Violence Risk Assessment Guide and the Historical Clinical Risk-20. Most studies of violence and schizophrenia do not specify type of violence. Violence is a heterogeneous construct inclusive of type, frequency, function, seriousness and lethality, as well as whom the violence is directed against. Likewise, symptom pattern in schizophrenia is not diverse—many individuals experience fearful hallucinations and manifest threat-control override symptoms, which have been linked to violent behavior.[9] Others have symptoms that are easier to manage and which are not linked to violent behavior. Another way to evaluate violence potential is through a process known as anamnestic assessment. Anamnestic assessments are an individualistic approach to understanding violence risk and are frequently embedded within comprehensive risk evaluations.[10] The individual is questioned about each violent incident in order to identify antecedents in order to develop a comprehensive risk assessment plan. Antecedents include thoughts, emotions, and symptoms that have been linked to violent behavior. Although effective in understanding individual factors associated with violence, by definition this approach is difficult to quantify.

Key differences in research results focusing on schizophrenia and violence have occurred as a function of sample. The Epidemiological Catchment Area project[11] evaluated over 17 000 individuals in the community and another 1379 individuals from various inpatient settings (eg, mental health hospitals) and followed over 3 years. Although controversial, the results found that mental illness (independent from other criminological factors) was related to increases in violent behavior. This study did identify that failing to account for antisociality in the forms of released prisoners miscalculates the links between mental illness and violence. Swanson and colleagues[12] evaluated violence in 1410 individuals diagnosed with Schizophrenia across 56 sites located throughout the United States. Overall, 19.1% of the study participants engaged in violence behavior; however, 3.6% of the individuals engaged in serious violence over the 6-month follow-up. Beyond prevalence rates, the results of this study were highly informative in identifying specific patterns of symptoms related to violent behavior. Variables such as dysfunctional childhood, positive symptoms of psychosis, and depression were linked to serious violence in this community sample.

The MacArthur Study of Mental Disorder and Violence,[13] which employed an innovative strategy for assessing violent behavior among 1100 patients through the use of collateral interviews (McArthur risk assessment), demonstrated how variables other than schizophrenia are stronger predictors of violent behavior, wherein substance abuse and psychopathy were the most prominent predictors of violent behavior in discharged civil psychiatric patients. Other factors in forensic patients that make them more likely to engage in violent behavior include victimization,[14]

higher levels of psychopathy, which is a risk factor even in civil psychiatric patients[15] leading to a higher propensity to engage in violent behavior.

Patients with schizophrenia who engage in violent behavior often lack insight into their legal situation[16] have impairments in decisional competence[13] leading to problems providing consent for research participation. In some cases, like evaluating violence on an inpatient forensic unit, informed consent is not needed for data collection. Likewise, observational measures like the Overt Aggression Scale do not require informed consent to complete. Complex methodologies where collateral contacts are interviewed, like the methodology utilized in the MacArthur study, require a high degree of understanding and information. As a result of these complexities, research on schizophrenia and violence is often not able to be generalized much beyond the study sample.

Acute Aggression/Agitation Clinical Trials

Psychopharmacological interventions are routinely used to manage acute agitation in patients with schizophrenia. Optimally, this is done early enough to forestall actual aggressive behavior toward self or others and avoid or minimize the use of physical restraints. The successful use of these medications is further enhanced by using verbal de-escalation techniques and simple environmental interventions such as clearing the room of other patients and having ample staff available.[17] The ultimate goal is to reduce the patient's level of agitation so that they are calm but not in a deep sleep. Medications that are most useful in this regard also require a rapid onset of action, thus usually favoring parenteral preparations that result in a rapid increase in plasma level of the agent at a high concentration.

Clinicians have many years of experience using first-generation antipsychotics to treat agitation in patients with schizophrenia. Despite their propensity for causing extrapyramidal side effects, including akathisia which can be confused for the underlying agitation, and acute dystonia, which will lead to substantial problems in terms of convincing the patient to continue with medication, first-generation antipsychotics remain commonly used. The combination of haloperidol and lorazepam is supported by a double-blind randomized clinical trial that compared 5 mg intramuscular haloperidol, 2 mg intramuscular lorazepam, or both in combination in 98 psychotic, agitated, and aggressive patients (47 with schizophrenia) treated in emergency departments.[18] Patients in each treatment group received 1–6 injections of the same study drug within 12 hours based on clinical need. Symptoms were assessed hourly using a 14-item observational scale, and effective symptom reduction was achieved in each treatment group with significant mean decreases from baseline. Patients assigned to combination treatment experienced more rapid tranquilization. Side effects did not

differ significantly between treatment groups, although patients receiving haloperidol alone tended to have more extrapyramidal system symptoms.

Droperidol, a neuroleptic not Food and Drug Administration (FDA) approved as an antipsychotic but indicated for tranquilization and antiemesis in surgical and diagnostic procedures, as well as premedication, induction, and as adjunct in maintenance of general and regional anesthesia and neuroleptanalgesia with opioid analgesics, has also been used to manage agitation in emergency department patients.[19] Concerns over electrocardiogram (ECG) QT interval prolongation have emerged, but although FDA guidelines recommend continuous cardiac monitoring for patients receiving droperidol, others suggest that low-risk patients receiving small doses may not require this.[20] A prospective, randomized, double-blind trial of 144 agitated emergency department patients with acute alcohol intoxication, acute drug intoxication, or closed head injury, requiring emergent sedation, was performed that tested the efficacy of sedation, need for rescue sedation, rates of respiratory depression, and complications of 5 mg droperidol, 20 mg ziprasidone, and 5 mg midazolam administered intramuscularly.[21] Unknown are the number of patients, if any, that also had a diagnosis of schizophrenia. The onset of adequate sedation was delayed with ziprasidone, relative to the other agents. Patients sedated with droperidol or ziprasidone required rescue medications to achieve adequate sedation less frequently than those sedated with midazolam. No cardiac dysrhythmias were identified in any treatment group. Respiratory depression that clinically required treatment with supplemental oxygen occurred in 21 of 144 patients (8% for droperidol, 15% for ziprasidone, and 21% for midazolam). No patients required endotracheal intubation. Older controlled studies of droperidol among psychiatric populations are also available. A double-blind study compared 10 mg intravenous droperidol with intravenous placebo in 41 acutely agitated patients (20 with schizophrenia).[22] Patients receiving intravenous droperidol were significantly less likely to need additional haloperidol intramuscular injections within the first few minutes than those given intravenous placebo. In another double-blind study, 5 mg intramuscular droperidol was directly compared with 5 mg intramuscular haloperidol in 27 acutely agitated patients involuntarily hospitalized for mental illness (actual diagnosis not reported, but all patients assumed to be psychotic and intoxicated patients specifically excluded).[23] At 30 minutes after treatment, 81% of the patients receiving haloperidol required a second injection vs 36% for those patients randomized to droperidol.

Second-generation antipsychotics are now available in short-acting intramuscular formulations, including ziprasidone, olanzapine, and aripiprazole[24] (for a bibliography of the registration trials, see supplementary material). All have a lower propensity for extrapyramidal adverse effects compared with the older antipsychotics. First to receive FDA approval was ziprasidone mesylate in 2002. Two pivotal registration studies established superiority of 20 or 10 vs 2 mg intramuscular ziprasidone, the later dose representing a "pseudoplacebo." All participants were agitated hospitalized subjects, and approximately 80% of the subjects had schizophrenia or schizoaffective disorder. Although product labeling recommends the range of 10–20 mg per injection, the 20-mg dose yielded a higher percentage of responders and a greater degree of response in terms of reduction of agitation than the 10-mg dose. Safety concerns noted in product labeling include caution in patients with impaired renal function because the cyclodextrin excipient is cleared by renal filtration and ziprasidone's potential to prolong the ECG QT interval.[25] However, a decade's clinical availability has not resulted in evidence that ziprasidone by itself poses a substantial clinical obstacle regarding QTc prolongation. Naturalistic studies of intramuscular ziprasidone that enrolled somewhat more severely agitated patients than those in the registration program are now available and support the use of this option.[26]

A short-acting intramuscular formulation of olanzapine was approved by the FDA in 2004. Two, 1-day, placebo-controlled inpatient trials with haloperidol as the active comparator specifically enrolled patients with schizophrenia. In the trial examining a fixed dose of 10 mg olanzapine, olanzapine was superior to 7.5 mg haloperidol at 15, 30, and 45 minutes after injection. In the study comparing multiple fixed doses of intramuscular olanzapine with 7.5 mg intramuscular haloperidol, patients treated with 5, 7.5, or 10 mg of olanzapine had greater mean improvement in agitation than those given placebo at all time points. Subjects randomized to 2.5 mg olanzapine or to haloperidol did not show greater mean improvement compared with those given placebo until 60 minutes after the first injection. The recommended dose in product labeling is 10 mg (with lower doses of 2.5–5 mg for vulnerable patients such as the elderly or medically infirm).[27] Safety concerns noted in product labeling include hypotension, bradycardia with or without hypotension, tachycardia, and syncope as reported during the clinical trials. As per the product label, patients should remain recumbent if drowsy or dizzy after injection until examination has indicated that they are not experiencing postural hypotension, bradycardia, and/or hypoventilation. Simultaneous intramuscular injection of olanzapine and parenteral benzodiazepines is not recommended, as also outlined in a report of a case series where comorbid medical conditions were noted to increase risk.[28] Others have reported that this combination may be safe in patients who have not ingested alcohol.[29] Similar to ziprasidone, naturalistic studies of intramuscular olanzapine that enrolled somewhat more severely agitated patients than those in the registration program are now available and support the use of this option.[30]

Intramuscular aripiprazole for agitation was approved by the FDA in late 2006. Two, 1-day, placebo-controlled trials with haloperidol as the active comparator specifically enrolled patients with schizophrenia. In the study comparing 9.75 mg intramuscular aripiprazole with 6.5 mg intramuscular haloperidol, aripiprazole was noninferior to haloperidol. However, for the aripiprazole group, decrease in agitation differed significantly from placebo at 1 hour after the first injection, in contrast to a significant difference achieved at 45 minutes in the haloperidol group. There was no significant difference in the improvement in the agitation scores between the aripiprazole and haloperidol groups at these time points, nor at 30 minutes or 2 hours, but the difference at 90 minutes was significant in favor of haloperidol. In the second study, changes in agitation scores were statistically significant as early as 45 minutes for the 9.75-mg aripiprazole group, whereas a significant difference between haloperidol and placebo was first seen at 105 minutes. In product labeling, the usual recommended dose is 9.75 mg.[31] Safety concerns noted in product labeling include greater sedation and orthostatic hypotension with the combination of lorazepam and aripiprazole as compared with that observed with aripiprazole alone.

In development is inhaled loxapine, where the drug is delivered using a handheld device that produces a thermally generated condensation aerosol free of excipients or propellants, resulting in rapid delivery into the lung and then into the systemic circulation. Two studies in patients with schizophrenia have been published; the reader is referred to[32] for a comprehensive review.

Other alternatives to parenteral administration are oral formulations, with the proviso that achieving a peak increase in plasma levels will be delayed compared with what has been discussed so far. In addition to capsules or tablets, currently available are liquid preparations of risperidone and aripiprazole and orally disintegrating tablets for olanzapine, risperidone, aripiprazole, and asenapine (the latter administered and absorbed sublingually). In a rater-blinded trial of risperidone liquid that enrolled patients with schizophrenia, schizoaffective disorder, mania with psychotic features, acute paranoid reaction, or delusional disorder, a single oral dose of risperidone plus lorazepam was as effective as intramuscular haloperidol plus lorazepam.[33] In a double-blinded trial of olanzapine that enrolled patients with schizophrenia, schizoaffective disorder, schizophreniform disorder, or bipolar I disorder, manic or mixed episode (not necessarily with psychotic features), subjects receiving oral olanzapine at doses of 20–40 mg/day were compared with those randomized to 10 mg/day oral olanzapine combined with oral lorazepam up to 4 mg/day.[34] Although agitation improved for both groups over the 4-day observation period, the high-dose olanzapine group was superior to the low-dose olanzapine plus lorazepam group on the primary efficacy measure of agitation assessed 24 hours after initiation of study medication. In a rater-blinded trial of agitated inpatients with schizophrenia, bipolar disorder, or schizoaffective disorder, 10 mg intramuscular olanzapine, 10 mg orally disintegrating olanzapine tablets, and 3 mg oral risperidone solution were as effective as 7.5 mg intramuscular haloperidol and intramuscular olanzapine and disintegrating olanzapine tablets were more effective than intramuscular haloperidol in the early phase of the intervention.[35] There were no significant differences in effectiveness among intramuscular olanzapine, orally disintegrating olanzapine tablets, and risperidone liquid.

A special case can be made for nicotine replacement therapy for smokers with schizophrenia who present with agitation, as evidenced in a double-blind randomized clinical trial.[36] Agitation scale scores for the nicotine replacement group were 33% lower at 4 hours and 23% lower at 24 hours than for the placebo group. However, subjects with lower levels of nicotine dependence responded better than those with higher levels of dependence.

The Treatment of Persistent Aggression

The management of patients with schizophrenia who are aggressive has been a major challenge for caregivers for years. In the schizophrenia Comparative Antipsychotic Trial Interventions Effectiveness (CATIE) study, approximately 19% of patients had exhibited violent behavior at some point prior to the study.[37] The rate of volume declined to 14%. Violence was associated with conduct disorders, comorbid substance abuse, victimization, and socially adverse situations. There has been a growing body of literature to support the use of clozapine in the treatment of persistent aggression in patients diagnosed with schizophrenia and other psychotic disorders. Early observational studies suggested that clozapine was helpful in treating aggression in patients with schizophrenia and that the antiaggression effect may be unrelated to the antipsychotic effect.[38] Krakowski and colleagues[38] found that clozapine was most efficacious in reducing the aggressive acts, followed by olanzapine and haloperidol, while all 3 medications were equally efficacious in reducing antipsychotic symptoms.

It appears that all atypical antipsychotics (clozapine, risperidone, olanzapine, quetiapine, and ziprasidone) have at least some capacity to reduce hostility, depression, and suicidality in patients with schizophrenia. However, the direct effect and selectivity is hard to determine, and so selection of medication, other than for clozapine, is also unclear. The Expert Consensus Guideline[39] suggested that clozapine and risperidone would be a good first line choice for chronic aggression, followed by olanzapine or long-acting injectable atypical antipsychotic or quetiapine, ziprasidone, aripiprazole, as well

as long-acting conventional antipsychotics. Augmentation with valproate, lithium, benzodiazepines, or antiepileptic medications can also be considered although most studies are now historical (often with mixed diagnoses), and the evidence base overall is scant.[1,17,40] The 2009 Schizophrenia Patient Outcomes Research Team (PORT) Psychopharmacological Recommendations[41] singled clozapine out as the best treatment for hostility and aggression, providing cautious endorsements for the notion of a selective antiaggressive effect. However, clozapine can be associated with uncomfortable side effects and carries a risk of life-threatening agranulocytosis requiring intensive hematological monitoring. This requires a degree of motivation and cooperation that can be lacking in a patient with persistent aggressive behavior. Hence, long-acting injectable formulations of antipsychotics and/or complex polypharmacy are often considered under these circumstances.[17]

Pertinent Medicolegal Considerations

The issue of forced medication, hospitalization, and treatment of mentally ill individuals is highly controversial and varies across state jurisdictions and countries. In England, lack of mental capacity—often itself accompanied by aggressive behavior—is a common reason for involuntary detention, and it often also influences hospital care.[42] In Italy, the community-based model has a high tolerance for disturbed behaviors, and involuntary admissions account for only 13% of the total inpatient admissions (which are low anyway).[43] In the United States, violent behavior is one precipitant for involuntary hospitalization and potentially also forced medication treatment. In the landmark case of *Lessard v. Schmidt*,[44] the Federal District Court required specific legal safeguards to be in place but also concluded that mental illness did not constitute a state interest in detaining and forcibly treating individuals with mental illnesses. The *Lessard* decision led to adopting 3 definitions of dangerous behavior resulting from mental illness: self-injury including recent threats, suicide attempts, or serious bodily harm; substantial probability of physical harm; and omission of behaviors that could cause physical harm to self. Other landmark cases it was established that individuals even with serious mental illnesses had the right to refuse psychotropic medications in nonemergency situations.[45]

When a mentally disordered individual charged with a crime is unable to proceed to trial, it can be a result of psychosis interfering with that individual's ability to rationally understand their legal situation and their ability to consult with their attorney. Such deficits are often remedied by taking psychotropic medications; however, often individuals are unwilling to take medications for several reasons (eg, lacking insight or even side effects). To that end, the Courts have allowed hospitals to forcibly medicate individuals to restore competency in circumscribed situations although there is considerable inconsistency across rulings. In *Riggins v. Nevada*,[46] the decision to not suspend Riggins' antipsychotic medications during his trial for murder that ultimately resulted in him receiving a death penalty sentence was deemed unconstitutional because the medications supposedly interfered with his ability to communicate with his attorney. Subsequently, the Eighth Circuit of the United States ruled it was appropriate to medicate an individual to restore them to competency in order to be executed.[47] Most recently, in *Sell v. the United States*,[48] guidance is provided for the administration of medications to restore competency if 6 basic criteria were met. These criteria are that involuntarily medicating someone can occur if (1) the administration of the medications serve an important governmental interest, (2) the medication administration must directly further that interest, (3) it must be "substantially likely" the medication would restore competency, (4) the medications must be unlikely to interfere with the ability of the defendant to communicate with their attorney, (5) less intrusive measures are unlikely to restore competency, and (6) the medication must be medically appropriate.

Conclusions

The pharmacological management of patients with schizophrenia and persistent aggressive behavior requires the use of both short-term strategies to control acute episodes of agitation and also long-term methodologies to reduce the intensity and frequency of future episodes. Antipsychotic medication remains a foundational choice. For persistent violence, clozapine is the preferred choice. Mediocolegal, informed consent, and medication adherence considerations further complicate clinical decision-making processes.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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