Treating Aggression in the Psychiatric Emergency Service

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Reports indicate that the severely mentally ill, those patients with schizophrenia or bipolar disorder, are at increased risk of being violent to others. They are also at increased risk of being victims of violence or homicide. This article discusses the state of knowledge concerning the 3 most common classes of drugs used to decrease agitation in the psychiatric emergency service setting: benzodiazepines, conventional antipsychotics, and atypical antipsychotics. The decision whether to use benzodiazepines alone versus benzodiazepines combined with an antipsychotic, and whether that antipsychotic should be a conventional or atypical antipsychotic, hinges on considerations of mental health history, need for synergistic sedating effects, and the side effect profiles of the various medications.

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Patient agitation and violence have been the objects of scientific investigation in the United States since at least the early 19th century.[1] To date, empirical studies are limited by a lack of uniformity in defining what is meant by violence and aggression. Some studies have referred to violence as both verbal aggression and physical aggression; others as only physical aggression; and still others as physical aggression that results in significant injury.[2] Despite such differences in definition, we know that the understanding and management of agitation/aggression in the mentally ill are critical to patient and staff safety. Reports indicate that the severely mentally ill, those patients with schizophrenia or bipolar disorder, are at increased risk of being violent to others,[3] particularly so during acute exacerbations of their illness when they are likely to be seen in a psychiatric emergency service (PES) or an emergency room.[4,5]

This highly focused article will review the literature on managing patient agitation and aggression in the emergency setting. After a brief section on assessment, the primary focus will be on management of aggression in the PES through the use of psychopharmacology. Benzodiazepines, atypical antipsychotics, and conventional antipsychotics will each be reviewed separately. Each drug will be examined for current research findings and its use in combination with other drugs used to treat acute psychiatric illness. Readers are referred to the exceptional review by Allen[6] or the recently published Expert Consensus Guidelines[7] for further information about some of these topics.

ASSESSMENT

The ability to predict with certainty which patients will be violent is not clinically possible.[8,9] Actuarial statistical risk assessment of violence potential has been shown to be superior to clinical risk assessment.[2] In a clinical interview, the best that can be expected is that the clinician will use identified risk factors to make an evidence-based estimate of the likelihood of violence. These risk factors include frequency of prior risk, father's drug use, legal status, loss of consciousness history, abused as a child, father ever arrested, age, violence at admission, schizophrenia, drug abuse, unemployed, violent fantasies, and suicide attempts.[2(p140)]

In their efforts to ensure patient and staff safety, clinicians tend to overestimate patients' potential for violence. This strategy leads to the inclusion of many false positives. In this regard, one study found that clinicians would have to commit or detain 6 patients with risk factors for aggression to prevent 1 violent act.[8] There is clearly a need to refine our ability to more accurately predict imminent risk of violence. In an effort to develop an empirically based clinical evaluation of short-term risk, McNiel[10] categorized the available data into 4 sets of variables: (1) demographic/personal history variables, which include findings on history of violence, violent threats/fantasies, age, gender, history of child abuse, and so forth; (2) clinical variables such as diagnosis, relevant symptomatology, and treatment adherence; (3) situational vari-

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ables including social support, availability of weapons, relationship to potential victim; and (4) clinician variables such as the nature of the alliance with the patient and the potential cognitive biases of the evaluator. Clinicians have much to gain from reviewing and familiarizing themselves with this type of systematic and evidence-driven method of evaluation.

MANAGEMENT

While prediction of acute risk of aggression is challenging, effective methods of management for both acute and longer-term risk are available.[11,12] While this article primarily focuses on the psychopharmacologic management of violence and aggression, clinicians should make efforts first to establish whether the potential for violence can be managed at a verbal or behavioral level before proceeding to management with medications that carry a risk of undesirable side effects.

Behavioral Strategies

Engaging an agitated patient in a working alliance under emergency conditions can be a formidable task.[13] A major element in such an effort is the clinician's ability to convey empathy and authenticity. If a disturbed patient senses that he or she is being understood and is interacting with someone who is genuine, the patient may become less defensive and less potentially combative. The more decompensated the patient, however, the more challenging it is for the clinician to establish rapport. If it is clear that the patient is not readily forming an alliance, more structure will be needed to assist the patient in maintaining self-control.

Some patients can respond to verbal efforts to redirect them to the task at hand. For those who are fearful of loss of control, reassurance that they are in a protective setting and that it is acceptable to express feelings and thoughts with words but not with actions can prove helpful. If family or friends have accompanied the patient to the PES, there may be an opportunity to increase the patient's sense of safety by having a family member present. Of course, there are times when family involvement can be contraindicated because confidentiality could be compromised or the patient may be having an angry or negative interaction with the family.

If the patient is not responsive to verbal redirection or limit setting, the situation may be beyond the control of a single interviewer. One option is to involve another clinician in the evaluation, or, if necessary, call for a "show of force" and/or offer voluntary tranquilizing medication. Should these efforts fail to contain the patient's turmoil, however, clinicians typically turn to physical restraints and involuntary medication. Acute medications may be voluntary, coerced, or forced depending on the clinical circumstances.[14] Double-blind studies are needed in the area of acute behavioral control. In particular, more studies are needed that explore which behavioral techniques work best in minimizing physical restraints and involuntary medications.

The standard of clinical care in sedating a patient rapidly includes numerous medications and different routes of administering those medications. Below, the more frequently employed medications are reviewed.

Psychopharmacologic Strategies

Benzodiazepines. A key decision point in most recent approaches to PES treatment of agitation is whether one dose or a series of doses of benzodiazepines are used exclusively to sedate an agitated patient, or whether benzodiazepines are used in conjunction with antipsychotics in treating acute agitation. The rationale for using benzodiazepines alone in certain situations is that the risk of some side effects, such as extrapyramidal symptoms (EPS), can be minimized or eliminated.[15] Benzodiazepines have a relatively benign side effect profile, and concerns that benzodiazepines may cause paradoxical disinhibition do not appear to be supported by some research data from inpatient settings.[16]

1. Research findings of benzodiazepines. Allen[6] reviewed 24 studies comparing different medications for the acute management of agitation. Lorazepam alone compared well to haloperidol alone and was superior on measures of aggression and clinical global improvement.

At least 3 recent double-blind studies[17–19] have evaluated lorazepam alone versus lorazepam and haloperidol in combination. Per Allen's review,[6] 2 of the studies[17,18] reported that the combination of haloperidol and lorazepam was superior to lorazepam alone for acute agitation. The other study[19] found that lorazepam is superior to the combination of haloperidol plus lorazepam. However, in the Battaglia et al. study,[17] differences in the Agitated Behavior Scale were only significant at 1 hour (differences on a modified Brief Psychiatric Rating Scale [BPRS] were evident at hours 2 and 3), and the study did not control for dose.[6] In addition, the study arm receiving haloperidol alone had 3 times as many EPS as the groups receiving either lorazepam alone or lorazepam and haloperidol, although sample size was small and these differences were not statistically significant.[17]

Another study[19] compared the sole use of either benzodiazepines or conventional antipsychotics. Patients were randomly assigned to receive either 2 mg of lorazepam or 5 mg of haloperidol, either intramuscularly or orally, every 30 minutes as needed for up to 4 hours, with 73% (N = 30) of the patients requiring 2 doses of medication or fewer. At the end of 4 hours, no significant differences in BPRS or Clinical Global Impressions (CGI) ratings were observed, and statistically significant greater reductions in these scores were observed with lorazepam alone for the intermediate timepoints (hours 1, 2, and 3). The authors com-

ment that no episodes of EPS were observed in either treatment arm, but this may be a function of the short duration (4 hours) of treatment and patient observation. Extreme sedation was observed in 3 of the patients being given lorazepam and 2 of the patients being given antipsychotics. Oversedation with benzodiazepines may be related to a desire to quickly sedate patients without taking into account that peak levels of lorazepam typically are not observed until 60 to 90 minutes after administration.

2. Combination therapy with benzodiazepines. Benzodiazepines (especially lorazepam) form the lynchpin of most modern approaches to agitation. The Expert Consensus Guidelines for the Treatment of Behavioral Emergencies[7] recommend benzodiazepines, alone or in combination with antipsychotics (conventional or atypical), as the highest-ranked oral medication for agitation suspected to be due to a primary psychiatric disturbance.

According to the guidelines, when no provisional diagnosis could be made on the basis of history or clinical presentation, the use of benzodiazepines alone garnered the highest degree of consensus. Benzodiazepines alone were also preferred for agitation suspected to be due to posttraumatic stress disorder (PTSD) or personality disorder. The degree of consensus varied, being less for agitation due to personality disorder than for situations with no provisional diagnosis or those due to suspected PTSD. Benzodiazepines alone were also one of the preferred choices for psychotic depression as well as benzodiazepines in combination with conventional or atypical antipsychotics (or the atypical antipsychotic risperidone alone). For agitation suspected to be due to schizophrenia or mania, benzodiazepines combined with conventional or atypical antipsychotics were the preferred approach. If parenteral medication was needed, either benzodiazepines alone (for PTSD, mania, or with no provisional diagnosis) or benzodiazepine combined with a conventional antipsychotic (for schizophrenia, psychotic depression, or also mania or no provisional diagnosis) was among the most popular treatment choices.

In addition, benzodiazepines alone were the most popular medication choice for oral or parenteral treatment of agitation presumed to be secondary to a general medical condition or most substance intoxication (alcohol, stimulant, or hallucinogen). The experts polled in the Expert Consensus Guidelines for the Treatment of Behavioral Emergencies also perceived that benzodiazepines were the treatment of choice among consumers.[7] Lorazepam by itself, in combination with other medication, intramuscularly, or orally is clearly a well-deserved mainstay in the acute psychopharmacologic management of agitated patients.

Atypical antipsychotics versus conventional antipsychotics. An important consideration regarding the use of antipsychotics for the acute treatment of agitation, alone or in combination with benzodiazepines, is the choice of an atypical or a conventional antipsychotic. The best evidence base exists for conventional antipsychotics because of their longevity in the market. However, as clinical experience with atypical antipsychotics grows, these medications are increasingly being used in the acute setting, and recent guidelines reflect this increased use.[7,20] One major advantage for conventional antipsychotics is their ability to be given in intramuscular form. Although the atypical antipsychotic ziprasidone has just been approved in an intramuscular form, it is still not available at the time this article was being written. Liquid forms of risperidone and a quick-dissolving form of olanzapine are also available and are clinically useful.

The use of conventional antipsychotics and, to a much lesser degree, atypical antipsychotics, is associated with risks of acute extrapyramidal side effects such as dystonia and akathisia. Dystonia typically occurs within hours of the first dose of neuroleptic and, in rare circumstances (such as with involvement of the laryngeal muscles), can be life threatening. Akathisia can also occur shortly after the first dose of neuroleptic. Akathisia promotes restlessness that increases psychomotor agitation and even may induce violence. It is important not to confuse psychomotor agitation due to akathisia with increased psychological agitation, because akathisia may be worsened by further doses of a neuroleptic.[15] Some empirical data suggest that clinicians correctly recognized akathisia less than 25% of the time.[21]

Acute EPS symptoms can often be expected to significantly decrease patient adherence to future antipsychotic use, both immediately and in the long-term. A much rarer possible side effect of administration of neuroleptic medication is neuroleptic malignant syndrome (characterized by extreme rigidity, hyperpyrexia, autonomic instability, and delirium), which represents a medical emergency.[15]

Recently, QTc prolongation has been a growing concern with the use of antipsychotics in general, and with certain antipsychotics specifically, given that the amount of QTc prolongation with "standard" doses of antipsychotic can vary by up to 5-fold considering medication and dose.[22,23] Thioridazine and droperidol have been observed to cause QTc prolongation in a dose-related manner and to increase the risk of cardiac arrhythmias in at least 1 study.[22] These authors recommend that thioridazine and droperidol be employed carefully.

Another concern with the use of antipsychotics is orthostasis, an adverse effect that also tends to be somewhat medication specific. For example, clinical lore exists that orthostasis is more frequently reported with low-potency antipsychotics such as chlorpromazine than with high-potency antipsychotics.[24] Low-potency antipsychotics have almost universally been replaced in the PES setting by high-potency antipsychotics such as haloperidol. Orthostasis can also be associated with the use of atypical antipsychotics.[25]

One of the reasons many clinicians consider combining an antipsychotic with a benzodiazepine is to more rapidly begin to treat the underlying psychosis that may be responsible for much or all of the agitation. A weakness in this logic is that neuroleptic medications require 1 to 3 weeks to reach their full antipsychotic efficacy.[11] The acute benefits of antipsychotic medication may be primarily due to its sedative properties. Many existing studies in the PES setting are limited by their extremely short duration.[6] Repeat assessments can not be made about many PES patients receiving just benzodiazepines or the benzodiazepine-conventional antipsychotic combination because these patients, once sedate, are often triaged to other clinical settings. At least 1 of the randomized trials acknowledged this shortcoming, indicating that almost all of their acutely treated patients were placed in inpatient units shortly after the 4-hour period of the study had expired.[26]

Atypical antipsychotics. Atypical antipsychotics are noted for their targeted mechanism of action, lower rates of motor side effects, and their efficacy in long-term treatment.

1. Research findings with atypicals. Atypical antipsychotics may decrease hostility and overt physical aggression, at least during longer-term administration. This effect has been especially noted for clozapine, but literature suggests other atypicals may share this effect.[27] With the exception of clozapine, risperidone may have the best evidence among the atypicals for efficacy in treating aggression over longer-term treatment.[27]

Currier and Simpson[28] found that oral risperidone with oral lorazepam worked as well as intramuscular haloperidol and intramuscular lorazepam. Both treatment groups showed similar improvement on the Positive and Negative Syndrome Scale for schizophrenia (PANSS) agitation subscales and the CGI scale, with similar times to sedation. However, despite the fact that the mean PANSS scores were almost identical between the 2 groups, the possibility that the group receiving intramuscular haloperidol and lorazepam had more severe psychotic agitation cannot be totally excluded. Eighty percent of the patients in the haloperidol group either refused oral medication or were unable to verbally specify their preference. A single patient receiving intramuscular haloperidol with intramuscular lorazepam developed dystonia within the 24-hour study period, while 1 patient treated with the oral risperidone-lorazepam combination required haloperidol for continuing agitation. Likewise, although the mean times to sedation were almost identical for the 2 groups, more than twice as many patients receiving the risperidone-lorazepam combination were not asleep after 2 hours (5 subjects [17%] vs. 2 subjects [7%]). Being sedate yet awake may be a clinical advantage as it allows for further psychiatric assessments and possibly more timely triage.

A subanalysis of the U.S. multicenter trial comparing risperidone with haloperidol for psychiatric inpatients found that risperidone had a superior effect for the treatment of aggression.[27] Another study found risperidone to be equivalent to conventional antipsychotics at treating aggression in patients with chronic schizophrenia.[29,30] Chengappa et al.[30] also found that the atypical risperidone appeared to have significantly decreased the seclusion rate at a state psychiatric hospital.

The popularity of the atypicals may be due to their superior efficacy, better tolerability, or both. Csernansky et al.[31] reported that the atypical risperidone was superior to haloperidol in the prevention of relapse in patients with schizophrenia.

2. Atypical antipsychotics and combination therapy. Expert consensus guidelines now recommend oral atypical antipsychotics in combination with benzodiazepines as highly as an oral conventional antipsychotic with a benzodiazepine.[7] Other guidelines prefer atypical antipsychotics over conventional antipsychotics for the acute setting, for schizophrenic patients, and for bipolar patients.[20,32]

A related approach is outlined by Currier and Simpson[28] for the treatment of psychotic agitation. In an open trial, they used a protocol of 2 mg of lorazepam plus 2 mg of liquid risperidone, with a repeat dosage allowed in 1 hour. This strategy was comparable to lorazepam (2 mg) plus haloperidol (5 mg) intramuscular given with the same schedule.

3. Atypical antipsychotics: intramuscular and oral solutions. The intramuscular form of ziprasidone has just been approved by the U.S. Food and Drug Administration and made available in October 2002. Early indications of this new formulation indicate that it is both safe and effective in acutely sedating agitated patients.[25] Studies suggest it compares well with intramuscular haloperidol in terms of acute sedation.[25] This agent may be better tolerated by patients as it appears to have fewer movement disorders than haloperidol.[25] The sedating effect of this medication appears to be dose related, with 10 or 20 mg providing the greatest efficacy.[24]

A double-blind placebo-controlled study of intramuscular olanzapine compared with intramuscular haloperidol in the acute treatment of agitation found them to be similar except that patients treated with olanzapine had no acute dystonic reactions compared with a 7% rate for those treated with haloperidol.[23] In addition, no significant QTc changes were observed in any patients.[23]

While intramuscular and oral preparations are commonly used, intravenous sedation is not frequently employed in PES or inpatient psychiatric wards. Concerns about QTc lengthening have been reported for intravenous haloperidol, usually at high doses among critically ill patients. One report described 6 patients in the critical care setting who developed torsades de pointes after very high doses of intravenous haloperidol, typically ≥ 35 mg i.v. over 2 to 27 hours. A single case was described of a patient with a normal QTc who developed torsades de pointes after being treated with 9 mg of i.v. haloperidol over 7

hours.[33,34] In some countries other than the United States, intravenous sedation is the norm.[35]

Conventional antipsychotics. The rationale for the use of conventional antipsychotics remains their strong evidence base and the long, safe history of their intramuscular formulations in acute use.

1. Research findings for conventional antipsychotics. Haloperidol has by far the best evidence base among conventional antipsychotics for the treatment of aggression. A recent review lists 20 double-blind studies involving the use of haloperidol to treat agitation.[6] However, presumably for safety reasons, all but 1 of these studies involved active drug comparisons rather than placebo controls. Several new studies[6] have compared haloperidol with atypical antipsychotics. A review of several studies examining haloperidol dosing for acute psychosis found little to no additional benefit after 10 to 15 mg of haloperidol i.m. had been administered.[36] The same study cited previous results that indicated roughly 50% of patients might experience some EPS at an approximately 10-mg dose of haloperidol. However, whether such an extremely low therapeutic index matches actual clinical experience is questionable.[36] Nevertheless, clinicians should consider that EPS may be easily triggered at doses equal to or close to doses that can easily be achieved in the treatment of acute agitation.

2. Conventional antipsychotics and combination therapy. In the past, some emergency services have favored the use of droperidol over haloperidol. Limited head-to-head evidence (2 trials) suggests that droperidol alone may have a faster sedative effect or require less additional medication[6] (perhaps in part due to droperidol's greater intrinsic sedating properties). However, at least 2 recent studies have found an association between droperidol and clinically significant QTc lengthening.[22]

Substance abuse. Statistics indicate that 60% of schizophrenic patients have a lifetime prevalence of substance abuse. Substance abuse comorbidity significantly increases the likelihood of violence.[37] Experts now recommend atypical over conventional antipsychotics for this patient population.[7,20,32] Expert opinion supports the use of a benzodiazepine even if the patient has a history of substance abuse[7,38] and often favors this approach.[7] However, Allen[6] correctly raises concerns about respiratory depression from the interaction of benzodiazepines with alcohol intoxication or opiate sedative use. This concern appears greatest with midazolam. In 2 cases[6] of respiratory depression with midazolam in patients taking fentanyl, the respiratory depression was reversed with naloxone.

CONCLUSIONS

There are those who feel that the field of psychiatry has become more coercive, quoting statistics that involuntary admission to locked psychiatric facilities has increased by 70% from 1986 to 1996.[39] However, this increase in involuntary admissions is more likely attributable to a marked decrease in psychiatric hospital admissions for patients and a decreasing length of stay for those patients who are admitted. Now treatment of these patients has largely shifted to the outpatient setting. As a result, expertise in the treatment of agitated patients in the PES setting is becoming more and more vital for any psychiatrist who sees acutely decompensated patients.

This article discussed the state of knowledge concerning the 3 most common classes of drugs used to decrease agitation in the emergency room setting: benzodiazepines, atypical antipsychotics, and conventional antipsychotics. The decision between the use of benzodiazepines alone versus benzodiazepines combined with an antipsychotic, and whether that antipsychotic should be a conventional or an atypical antipsychotic, hinges upon considerations of efficacy and the side effect profile of the particular medications. Lorazepam by itself or in combination remains an invaluable agent. Atypical antipsychotics are now firmly and safely established in the acute care of the agitated, psychotic patient.

Finally, more research is needed to determine which behavioral approaches alone or in combination with medications are most effective in helping out-of-control patients regain composure. Consensus guidelines are valuable contributions to the scientific literature, but more double-blind studies are needed to determine which medications are most effective, including their side effect profiles, in the acute setting.

Drug names: chlorpromazine (Thorazine, Sonazine, and others), clozapine (Clozaril and others), droperidol (Inapsine and others), fentanyl (Actiq and others), haloperidol (Haldol and others), lorazepam (Ativan and others), naloxone (Narcan and others), olanzapine (Zyprexa), risperidone (Risperdal), ziprasidone (Geodon).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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