The Psychopharmacology of Violence With Emphasis on Schizophrenia, Part 1: Acute Treatment

Leslie Citrome, M.D., M.P.H.

Violent behavior is a principal reason for hospital admission. One estimate is that 36% of psychiatric hospital admissions are preceded by violent or fear-inducing behavior.[1] However, a small proportion of patients are responsible for the majority of assaults, as evidenced by work done in the United States by Convit and colleagues[2] who demonstrated that 5% of the patients at a state-operated psychiatric facility were responsible for 53% of incidents. This finding was replicated in Australia, where 12% of patients were found to be responsible for 69% of incidents.[3] The degree of violence that a few patients have been involved in has led to stigmatization of the mentally ill in general, even though the bulk of the violence in today's world is perpetrated by persons without a bona fide mental illness. A recent epidemiologic study conducted in Sweden[4] estimated the population impact of patients with severe mental illness on violent crime and found that overall, the population attributable risk fraction of patients was 5%, suggesting that patients with severe mental illness commit 1 in 20 violent crimes.

Nevertheless, as clinicians we are in the position of effectively treating patients who are aggressive. In this column, we will begin with a discussion of definitions and the elements necessary for the evaluation of the aggressive patient. We will then review the short-term psychopharmacologic options available to manage acute agitation and aggression. A review of the psychopharmacologic options available to decrease the frequency and intensity of these episodes over the longer term will be published in next month's column. The content of these reviews is derived from the presentation entitled "The Psychopharmacology of Violence With Emphasis on Schizophrenia" available in the latest edition of the ASCP Model Psychopharmacology Curriculum.

Agitation is commonly used to refer to excessive motor or verbal activity, whereas *aggression* refers to actual noxious behavior that can be verbal, physical against objects, or physical against people.[5] Generally, the term *violence* denotes physical aggression by people against other people.[5] *Hostility* is loosely defined and can denote aggression, irritability, suspicion, uncooperativeness, or jealousy.[5] Hostility can be viewed as an attitude and is commonly measured as an item on a rating scale such as the Positive and Negative Syndrome Scale,[6] where the definition of hostility is "verbal and nonverbal expressions of anger and resentment, including sarcasm, passive-aggressive behavior, verbal abuse, and assaultiveness."[6(p33)] However, one can score relatively high on this item without actually being physically assaultive.

The etiology of violent behavior is multifactorial and requires assessment of the patient for possible comorbidities, such as somatic conditions or other psychiatric conditions, or adverse effects of medications, such as akathisia. For example, cooccurring substance abuse, dependence, and intoxication increase the risk of violent behavior.[7] The presence of hallucinations and delusions, neuropsychiatric deficits and poor impulse control, underlying character pathology, and a chaotic environment increases risk and further complicates both assessment and treatment.[5] Potential somatic conditions must be ruled out, especially in a patient who ordinarily has not been aggressive. Risk assessment includes obtaining the patient's history of violence, determining whether the patient has access to weapons, reviewing criminal justice records when available, and asking details about the content of delusions.[5]

The best therapeutic option is to intervene early before agitation and verbal aggression escalate into physical aggression. Environmental interventions include clearing the room, having staff available as a "show of force" or "show of concern," and allowing the patient to engage with one person in talking about his or her needs.[8] In a hospital setting, restraint or seclusion is an option. The principal intervention, however, is the prompt and effective use of nonspecific sedating or calming agents. Early use of medications will decrease the likelihood of harm to self or others, allow diagnostic tests or procedures to be done, attenuate psychosis, decrease the need for seclusion/restraint, and decrease the risk of staff and patient injury. Sleep is not desirable when evaluating the patient. Excessive sedation that results in the need for constant observation and assistance in toileting also places an excessive burden on nursing staff time.

Intramuscular administration of a medication results in a more rapid elevation of the plasma level of that medication, as well as a higher transient concentration compared to oral administration. This results in a faster reduction of the agitated behavior and, for that reason, is preferred when the danger is immediate and the potential consequences of that behavior are severe. Until recently, medication options were limited to lorazepam and first-generation antipsychotics.[9] Today, we have 2 second-generation antipsychotics available in a short-acting intramuscular formulation—ziprasidone and olanzapine. A third option, intramuscular aripiprazole, is expected to become commercially available in the relatively near future.

Although lorazepam has several advantages, including being reliably absorbed intramuscularly, having a short half-life (10–20 hours), and producing no active metabolites, it can cause respiratory depression in vulnerable patients (for example, those with lung disease) and at times disinhibition or paradoxical reactions. Lorazepam will treat underlying alcohol or sedative withdrawal and, for that reason, may actually be preferred for the emergency room patient whose history is unknown and for whom agitation secondary to alcohol or sedative withdrawal is suspected. Lorazepam is not recommended for prolonged use because of tolerance, withdrawal, and no or little effect on the core symptoms of psychosis.

Clinicians have many years of experience using first-generation antipsychotics. They universally cause sedation when given at a high enough dose, and many different intramuscular preparations are available. Low-potency agents such as chlorpromazine can be contrasted with high-potency agents such as haloperidol in terms of propensity for sedation, postural hypotension, anticholinergic effects, and decrease in the seizure threshold. A considerable disadvantage of these agents is their risk for causing extrapyramidal side effects, including akathisia, which can be confused with the underlying agitation, and acute dystonia, which will lead to substantial problems in convincing the patient to continue with medication.

Combinations of agents are often used, perhaps the most popular being the combination of haloperidol and lorazepam.[10] This combination may act faster than either agent alone, and fewer injections may be required. There is a decreased incidence of extrapyramidal effects with this combination compared to giving haloperidol alone. It is simple to administer—both can be given in the same syringe; however, continuation of haloperidol for long-term antipsychotic treatment may not be optimal because of ongoing risk of extrapyramidal effects and tardive dyskinesia and the fact that efficacy is largely limited to positive symptoms.

Second-generation antipsychotics are available today in a variety of formulations relevant to acute use. These include liquid

risperidone and aripiprazole; oral disintegrating tablets of olanzapine, risperidone, and aripiprazole; and short-acting intramuscular formulations of ziprasidone and olanzapine. Advantages include a lower risk of extrapyramidal effects and tardive dyskinesia and efficacy that may be of a broader spectrum than first-generation agents in terms of negative symptoms, mood symptoms, and cognitive dysfunction.

The acute use of intramuscular olanzapine was evaluated in 4 randomized double-blind placebo and active comparator studies among patients with schizophrenia,[11,12] bipolar mania,[13] and dementia[14]; however, olanzapine is not approved by the U.S. Food and Drug Administration (FDA) for dementia. Superior onset of efficacy was demonstrated compared with intramuscular haloperidol[11] and intramuscular lorazepam,[13] and no adverse event was significantly more frequent for intramuscular olanzapine compared with intramuscular haloperidol or intramuscular lorazepam. The recommended dose of olanzapine is 10 mg (with lower doses of 2.5 to 5.0 mg for vulnerable patients such as the elderly or medically infirm).

The acute use of intramuscular ziprasidone was evaluated in 2 randomized clinical trials comparing 10 mg versus 2 mg[15] and 20 mg versus 2 mg.[16] There appears to be a dose response, with 20 mg being consistently more efficacious than 10 mg in reducing agitation.[15,16] Superiority to intramuscular haloperidol in terms of reduction of psychopathology and decreased risk of extrapyramidal side effects is evidenced in open-label randomized clinical trials.[17–19] Although the product label warns of prolongation of the QTc interval, it is of the same magnitude as seen with oral ziprasidone and similar to that seen with haloperidol; thus, routine electrocardiogram monitoring is not required.[20]

The acquisition cost of a 2-mg dose of intramuscular lorazepam is $1.02 and that of 5 mg of intramuscular haloperidol is $1.72 (cost to Rockland Psychiatric Center, Orangeburg, N.Y., January 12, 2006). This is substantially lower than for 20 mg of intramuscular ziprasidone ($9.58) or 10 mg of intramuscular olanzapine ($17.16). However, the additional cost incurred when there is a complication, such as an acute dystonic reaction, far exceeds the cost of the medicine itself. Avoidance of akathisia can be priceless.

New products are on the horizon, including an intramuscular formulation of aripiprazole.[21] Head-to-head comparisons of the intramuscular formulations of the second-generation antipsychotics have not yet been published.

In summary, the new intramuscular formulations of the second-generation antipsychotics provide a useful tool for the emergency treatment of agitation. Once the acute episode is appropriately managed, the major therapeutic challenge will be for the reduction in frequency and intensity of future episodes. This will be discussed in the next issue of ASCP Corner.

Addendum: As we go to press, aripiprazole intramuscular has received FDA approval for marketing for the indication of agitation associated with schizophrenia or bipolar disorder, manic or mixed.

Dr. Citrome is with the Department of Psychiatry, New York University School of Medicine, New York, and the Nathan S. Kline Institute for Psychiatric Research, Orangeburg, N.Y.

He is a consultant for GlaxoSmithKline, Eli Lilly, Pfizer, Bristol-Myers Squibb, and Jazz; has received grant/research support from Barr, AstraZeneca, Eli Lilly, Pfizer, Janssen, and Forest; has received honoraria from Abbott, AstraZeneca, Eli Lilly, Pfizer, and GlaxoSmithKline; serves on the speakers or advisory boards for Abbott, AstraZeneca, Eli Lilly, and Pfizer; and is a stock shareholder in Merck, Pfizer, Eli Lilly, and Bristol-Myers Squibb.

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