Chemical Restraint in the ED

December 1, 2012 by ACEP Now

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Sudden violence in the **emergency department** (ED) remains a common problem. **Psychiatric** disturbance, uncontrolled **pain**, intoxication, de-robing, and long wait times all contribute to the eruption of violence. Assaults involving health care workers in the United States occur at 4 times the rate seen in other industries1. Those predisposed to violent behavior include males, prisoners, intoxicated patients, or those with psychiatric illness[1]. When a patient begins to exhibit dangerous behavior, the **emergency physician** must be prepared to control the situation in a safe and effective manner.

Chemical restraint via antipsychotic and benzodiazepine medication, used in an effort to facilitate medical workup and **patient safety**, enjoys a long standing safety and efficacy record. Chemical restraint avoids adverse consequences associated with physical restraint, which include hyperthermia, dehydration, rhabdomyolysis, and lactic acidosis. Chemical restraint is indicated when a patient poses a danger to himself, others, or **hospital** property. Techniques involving verbal de-escalation and provision of patient comfort always should be attempted prior to employment of forceful measures. Before receiving medications, the patient should be placed into physical restraints by appropriate security staff in an effort to avoid **injury** to the patient, staff, or environment.[2]

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The most appropriate drug regimen for combative ED patients has been the subject of much study. Haloperidol and lorazepam “5 and 2” combination therapy for the violent medically undifferentiated patient enjoys overwhelming support; however, rapid acting IM formulations of atypical antipsychotics are gaining popularity. Orally dissolving (ODT) risperidone, intramuscular (IM) olanzapine, and IM ziprasidone, have found a new role in the treatment of agitated and violent patients. Atypical antipsychotics provide more tranquilization and less **sedation** than typical antipsychotics, while additional serotonergic activity lowers the incidence of extra pyramidal signs (EPS).1 Atypical antipsychotics offer a seamless transition from IM to oral dosing, a reduced side effect profile, and a faster onset of action than typical antipsychotics.[3,4]

The widespread use of haloperidol and lorazepam in the ED for all chemical restraint is multifactorial. Together, haloperidol and lorazepam block

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dopaminergic transmission and enhance GABA receptor binding to reduce agitation quickly – usually within 30 minutes. Known disadvantages regarding haloperidol/lorazepam combination therapy include: EPS, prolonged QT, ataxia, sedation, additive CNS depression, **geriatric** over-sedation, slower onset, and longer duration of action when compared to newer atypical antipsychotic regimens.

Until this decade, only typical antipsychotics were available for IM use, which is often needed in the uncooperative patient,[2] thus, a lack of familiarity with newer IM atypicals may have limited physician use. In addition, lack of rapid ED availability (Pyxis®, Omnicell®) and higher drug costs could play a role. AmerisourceBergen®, a large pharmaceutical distributor, lists a wide range of institutional acquisition prices. For example, IM haloperidol lists at $0.82 per vial, while IM olanzapine lists at $28.69 per vial.5 Increased acquisition costs may be directly related to drug availability in the ED. At the author's home institution, a large urban ED in Chicago, droperidol, quetiapine, ziprasidone, and aripiprazole are not available in any of the hospital pharmaceutical distribution machines.

Droperidol was routinely used in the ED for rapid tranquilization until 2001. Compared with haloperidol, droperidol has a faster onset of action, shorter duration of action, more consistent effects, and comparable side effects, even in severely intoxicated patients.[1,3,6] Droperidol remained the ideal drug for the combative ED patient who needed rapid re-assessment until 2001, when the FDA instituted a black box warning for prolonged QT syndrome and fatal arrhythmia.[7] Since the FDA warning, use in many EDs declined secondary to both medico-**legal** and safety concerns. Data underlying the FDA's decision was based on post marketing surveillance, not on peer reviewed medical literature.[8] For example, haloperidol at doses greater than 50 mg IV has been shown to cause QT prolongation to the same degree as droperidol, though it has no FDA black box warning and continues to be used in the ED with great frequency. Since the FDA warning, several large retrospective reviews have shown no increase in morbidity or mortality between droperidol and haloperidol.[9,10] A large Australian prospective ED trial described no difference in QT prolongation or other adverse effects in head to head trials between droperidol and midazolam.[11] Many ED's have removed the drug from formulary use, and until the FDA revisits safety data, it is unlikely that droperidol will regain common use.[1]

Learning Objectives

After reading this article, the physician should be able to:

- Review the history, current trends, and indications of chemical restraint in the Emergency Department.

Olanzapine (Zyprexa®) IM has shown superior effect for patients with acute agitation related to psychosis, bipolar mania, and Alzheimer's dementia when compared to haloperidol.[3] IM olanzapine enjoyed faster onset, greater efficacy, and reduced adverse event rate when compared in head to head prospective trials with either haloperidol, lorazepam, or combination therapy.[3 12,13,14,15] Specifically, IM olanzapine exhibits less dystonia and akathisia in addition to a distinct calming effect as opposed to frank sedation.[1,3] Unfortunately, olanzapine IM has

- Understand the safety and efficacy of atypical antipsychotics in the management of the violent patient.
- Assess the newest data surrounding chemical restraint in the Emergency Department.
- Learn the pharmacokinetics and dosing of the most common medications used to aid the combative patient.
- Know how to safely chemically restrain the agitated elderly patient.

been shown to be synergistic with other CNS depressants; for this reason it should not be used with severely intoxicated patients, those taking benzodiazepines or those under other drug induced states. Eight case studies reported fatalities with olanzapine combination treatment (benzodiazepines or other antipsychotics), and no randomized controlled trials have examined olanzapine safety in those with significant co-morbidities that would lead to CNS depression.[4] In addition, olanzapine portends mild hypotension and significant anticholinergic effects.[14] For example, the drug would be contraindicated in a patient taking diphenhydramine or jimson weed, as it could exacerbate an anticholinergic delirium.[13] Though most of the data surrounding olanzapine use remains in the psychiatric literature, two studies have shown beneficial results in the undifferentiated ED population.[1,12]

Ziprasidone (Geodon®) IM also has significant advantages over haloperidol. Ziprasidone exhibits faster onset of action, lack of over-sedation, superior efficacy, reduced EPS, an easier transition to oral ziprasidone, reduced adverse effects and improved medication tolerance.[1,3] As with olanzapine, most of the positive data stems from psychiatric literature. However, one study conducted in a psychiatric emergency department compared IM ziprasidone to lorazepam / haloperidol combination therapy, and showed a similar side effect profile.[16] In addition, one prospective, randomized, double blinded study comparing use of droperidol vs. ziprasidone in undifferentiated ED patients did show a 40% reduced restraint time.[17] Conversely, ziprasidone has been shown to increase the QTc more than any other atypical antipsychotic, with increases similar to those seen in haloperidol. The data varies, with most studies showing QTc increases 16-28 from baseline, and none with QTc's increasing more than 500.[18] Though ziprasidone has been studied in a wide variety of patients, it currently holds FDA approval only for use in those with schizophrenia or bipolar mania.

Aripiprazole® is a dopamine / serotonin / alpha 1 / H1 agonist with recent conversion to IM formulation. This drug has been well studied only in those with severe agitation for bipolar mania or schizophrenia. When compared with haloperidol, the 10 mg IM formulation showed less EPS and reduced over-sedation.[19,20,21] No studies have been performed in the undifferentiated ED population.

Recently, risperidone ODT (Risperdone®) has been described as a viable form of chemical restraint. In patients who can be convinced to take oral medication, it is as effective as IM haloperidol or haloperidol / lorazepam combination therapy in reducing agitation in the undifferentiated ED population, without

significant differences in adverse effects.[1,22,23] The obvious benefit to ODT therapy involves protecting staff from needle stick injuries.

Benzodiazepines are useful for chemical restraint as they provide both sedation and anxiolysis. Lorazepam is rapidly effective with a short half-life and no reactive metabolites. Major adverse effects include a pregnancy class D verification and respiratory depression. Patients with co-depressants such as alcohol, barbiturates, opiates, or COPD deserve increased vigilance. Lorazepam is the only benzodiazepine (with midazolam a close second) that has shown consistent, complete, rapid IM absorption; ideal for the combative patient.[1,3] With monotherapy, studies have shown no benefit to psychotic symptoms at 24 hours.[3] Combination therapy with antipsychotic medications works to blunt akathisia (restlessness), reduce antipsychotic dosing, reduce EPS through reduced dosing, speed up reduction of agitation, and reduce time spent in seclusion or restraints without any increase in adverse event rates.[3,24] Finally, as typical antipsychotics are well known to lower the seizure threshold, some practitioners would assert for routine benzodiazepine use in order to blunt this effect. However, there are no studies to date directly describing this. Regardless, the improved safety and efficacy profile of combination therapy firmly establishes its use in chemical restraint.

Historical use of combination therapy with antipsychotics and benztropine (Cogentin®) or diphenhydramine (Benadryl) attempted to improve sedation and blunt extra pyramidal effects. In reality, Benztropine offers little to no immediate benefit for use in combination therapy, as the rate of EPS is very low in standard combination therapy (haloperidol and lorazepam). Should EPS occur, benztropine is rapidly effective.[3] In addition, benztropine can worsen any delirium or other altered state caused by an anticholinergic effect, and is currently not recommended as a part of first line combination therapy.[25] Diphenhydramine can be used to treat EPS, but its use in combination therapy as a sedative adjunct has been studied several times with poor results. Additions of diphenhydramine to chloral hydrate for pediatric sedation, versed for pediatric sedation, and meperedine for colonoscopy, have all shown no additional benefit.[26,27,28,29]

Elderly patients requiring chemical restraint (usually due to dementia, delirium, or psychosis) deserve further consideration. When possible, oral medications should be used, but this is not always feasible. Olanzapine IM 2.5 mg, haloperidol IM 0.25 – 0.5 mg, risperidone ODT 1 mg, or quetiapine 50 mg PO are examples of first line, low dose medications useful in controlling elderly agitation.[30,31] Importantly, atypical antipsychotics such as olanzapine are preferred to typical antipsychotics, especially in patients exhibiting symptoms of Parkinsonism, as typical antipsychotics can exacerbate these symptoms.31, 32 Benzodiazepine use in the ED for elderly chemical restraint would be less than ideal given the increased risk for ataxia and dangerous over-sedation. Should benzodiazepines be absolutely required (non-effect or contraindicated antipsychotics), reduced dosing scales should be used – a good rule of thumb being "start low and go slow," with a typical initial dose of lorazepam at 0.5 mg.[32,33] Pitfalls in the geriatric population abound. Delirium must be clearly differentiated from agitation related to dementia as the delirious elderly patient has a 2-3 fold increase in death at 30 days.[31] In the delirious patient, anticholinergic medications such as olanzapine should be avoided as they can cause an acute exacerbation of symptoms (anticholinergic crises). Finally, over-sedation of the elderly can more easily lead to dehydration, falls, respiratory depression, aspiration pneumonia and death.[2]

In conclusion – haloperidol and lorazepam combination therapy for chemical restraint remains first line for use in medically undifferentiated emergency department patients. Ziprasidone 20 mg IM can be considered first line therapy for patients with no history of prolonged QT syndrome who exhibit agitation secondary to known psychiatric disorders such as bipolar mania or schizophrenia. Newer data has begun to validate its use as a first line therapy in the undifferentiated ED patient population. As with ziprasidone, olanzapine 10 mg IM should be considered first line therapy for those patients not subject to other CNS depressants, and who have a primary psychiatric diagnosis. Though newer studies showing safety and efficacy in the undifferentiated ED population have not yet progressed to prospective, randomized, double-blinded, placebo controlled trials, the benefits described above warrant further rigorous study. Care must be taken to safeguard the elderly patient or those with severe co-morbidities from over-sedation.

Benzodiazepines are second line drugs in these instances; if absolutely necessary, they should be started at half the normal dose. Droperidol has been shown to be superior to haloperidol with a similar side effect profile; however, its use in the ED remains elusive out of continued safety concerns and FDA recommendations for pre-treatment EKG's, and post administration cardiac monitoring (impossible in the agitated patient). Haloperidol and lorazepam combination therapy remains the most studied drug regimen for the agitated undifferentiated emergency department patient; widespread routine use of atypical antipsychotics in this patient population pends further study and improved provider familiarity.

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Disclosures

Dr. Sellers, Dr. Aldeen, and Dr. Solomon have disclosed that they have no significant relationships with or financial interests in any commercial companies that pertain to this article.

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