Advanced Emergency Nursing Journal
Vol. 34, No. 4, pp. 306–318

APPLIED
PHARMACOLOGY

Column Editor: Kyle Weant, PharmD, BCPS

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Management of Acute Agitation in the Emergency Department

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ABSTRACT
Acutely agitated and combative patients are commonly seen and evaluated by health care providers in the emergency department. Treatment options have evolved significantly in recent years with the advent of intramuscular atypical antipsychotics and an expanded repertoire of patient-friendly oral formulations. Selection of the ideal pharmacologic treatment of an acutely agitated patient strengthens the patient–prescriber relationship and promotes adherence to future therapy. In this article, advantages and disadvantages of various treatment modalities for undifferentiated, psychotic, and nonpsychotic agitation are reviewed, including alternatives to the commonly prescribed haloperidol and lorazepam combination. Atypical antipsychotics may be superior in certain patients, with the added benefit of easier conversion to maintenance therapy. Special consideration is given to the treatment of acutely agitated geriatric patients suffering from delirium and/or dementia. Management of these patients should be guided by etiology and patient characteristics to obtain maximum therapeutic benefit. Although emergency department providers may only see a given patient once, the health care team must have an evidence-based approach to the care that is provided in the emergency department, as it can significantly influence the patient's overall course of treatment in the outpatient setting. **Key words:** agitation, antipsychotics, atypical antipsychotics, behavioral emergency, delirium, dementia, drug-induced agitation

THE EMERGENCY DEPARTMENT (ED) is often considered a place of refuge to address urgent health issues. ED health care providers should be able to go to work knowing that they are entering a safe work place, a standard for all sites of employment. Generally, these assumptions would be accurate but can be significantly altered when a patient becomes agitated. An agitated patient or family member can disrupt the normal aura of the ED and potentially place health care workers, staff, other patients, and themselves at risk. Agitation can be defined as excessive motor or verbal activity, which can manifest as assault, verbal abuse, threatening gestures and language, and physical destructiveness (Allen, Currier, Hughes, Reyes-Harde, & Docherty, 2001). Various studies and surveys have attempted to document the imprint of agitated patients on the health care system, and the results are alarming. A survey of 127 teaching hospitals in the United States in 1988 found that 32% of employees

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Disclosure: *The author reports no conflicts of interest.*

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DOI: 10.1097/TME.0b013e31826f12d6

received at least one verbal threat per day, and 18% had been assaulted one or more times with a weapon (Lavoie, Carter, Danzl, & Berg, 1988). A 2008 survey found that 65% of those surveyed witnessed a total of 3,461 physical attacks over a 5-year period, and 20% reported that weapons were brought into an ED on a daily or weekly basis (Kansagra et al., 2008). The ED has been overtly documented the most common workplace location for a physical assault and second most common for homicide (Currier, 2000; McAneney & Shaw, 1994; Pane, Winiarski, & Salness, 1991; Roll, 1996).

It is evident that the ED is a perilous arena that requires a systematic and effective approach to managing agitated patients. Unfortunately, ED personnel are not always trained in the proper management of violent patients, with only 20%–40% of hospitals having formal training in this area (Kansagra et al., 2008; Lavoie et al., 1988; McAneney & Shaw, 1994). Another concerning statistic is that only 6% of hospitals report having a written protocol to guide medication selection, dose, and route of administration selection in the management of these patients (Currier, 2000). The literature has postulated various factors associated with the potential to incite or exacerbate patients at risk for agitation, which include long wait times, 24-hr nature of the ED, and availability of medications (Blanchard & Curtis, 1999). In addition, patients could have medical histories that are linked with aggression and agitation, including substance abuse, schizophrenia, dementia, mania, and a host of other disorders.

Aside from removing the catalyst for agitation, providers need to be aware of how to manage patients when they become combative. The Joint Commission has developed a detailed guideline and collection of standards for restraining patients (www.jointcommission.org). The primary goal of the management of agitation is to maintain a safe environment for everyone in the ED (Allen et al., 2001). Immediate and effective management prevents injury to staff and other patients while calming the patient in order to facilitate proper care. Ineffective management could delay care, increase admission time, or result in additional injury. Management should also focus on retaining trust between the care provider and the patient. This can be done by assuring that the patient is abreast of the situation and has some input in the treatment choice, if the patient is capable of making decisions. Often, just general conversation helps relieve stress and anxiety (Downey, Zun, & Gonzales, 2007). If verbal communication fails, the provider may turn to using either involuntary physical or pharmacological restraints. If pharmacological interventions are to be used, it is prudent that the practitioner understand the current guideline recommendations, the available evidence behind these guidelines, the desired properties of the agents to be selected, and proper dosing in order to prevent adverse drug events and medications errors. Thus, the purpose of this review was to provide insight on the current management practices, the literature supporting these practices, and the characteristics of desired therapy.

PHARMACOLOGIC MANAGEMENT

For patients in whom nonpharmacologic therapies fail or are not indicated, medication may be an effective treatment modality for acute agitation. The goals of pharmacologic therapy for agitation include, (1) calming the patient without oversedation, (2) decreasing dangerous and aggressive behaviors, and (3) allowing treatment of the patient's underlying disease by the health care team. The treatment guidelines published by the American College of Emergency Physicians, the National Institute for Health and Clinical Excellence, and Expert Consensus Guidelines series share several overarching principles that are worthy of discussion, including whether to use oral or parenteral routes of administration, how and when to initiate pharmacologic therapy, optimal agents for varying etiologies of agitation, and individualization of therapy for special populations including the elderly and drug-intoxicated patients (Allen, Currier,

Carpenter, Ross, & Docherty, 2005; Lukens et al., 2006; National Collaborating Centre for Nursing and Supportive Care, 2005).

Individualization of Pharmacologic Therapy

Specific patient characteristics including comorbidities and potential drug interactions should be considered when evaluating the various therapeutic options for acute agitation (see Table 1) (Battaglia, 2005; Battaglia et al., 1997; Currier & Trenton, 2002; Luke, Tomaszewski, Damle, & Schlamm, 2010; Rabins et al., 2007; Rappaport, Marcus, Manos, McQuade, & Oren, 2009). For example, patients with a history of hepatic or renal failure may require dose adjustments or selection of an alternate drug. Safety in pregnant patients varies among the pharmacologic agents available. Pharmacodynamic and pharmacokinetic changes in the elderly are also cause for concern, as they may result in exaggerated toxicities in this population. Treatment selection for agitation depends greatly on the underlying cause of the disturbance. However, patients regularly present to the ED with unknown etiologies, comorbidities, intoxications, and limited medical histories. A review of medications brought in with the patient and/or a history from caregivers may provide essential information in this area. In addition, urine drug screens are useful in ruling out drug-induced agitation, but their routine use is controversial (Lukens et al., 2006). Emergent cases often require sedation without knowledge of the origin of agitation. In these cases, the goal is to sufficiently calm the patient in order to permit a thorough medical evaluation to identify the cause.

Oral Versus Parenteral Administration

Oral medications, including solutions and dissolving tablets, are preferred whenever possible to intramuscular or intravenous routes, as patients consider the latter two options to be coercive and abusive (Villari et al., 2008). Patients who feel that they have been coerced or abused by their physician are less likely to adhere to treatment. In a recent survey, 93% of patients rank oral as their preference during a behavioral emergency (Villari et al., 2008). Fortunately, commonly used treatments for agitation are available in oral routes, including haloperidol, lorazepam, olanzapine, ziprasidone, and risperidone. Because of the variability of oral medications available, it is also possible to implement multiple oral combination therapies, including haloperidol and lorazepam. Some combinations of oral medications have been proven to be at least as effective as intramuscular combinations with improved side effect profiles (Currier & Simpson, 2001; Villari et al., 2008). Although intramuscular routes sometimes have a more rapid onset of action and provide faster resolution of dangerous behaviors, they are associated with a higher incidence of acute dystonia and other movement disorder-related adverse events than oral medications that may outweigh their benefits in some patients (Preskorn, 2005). In general, the oral route is preferred whenever possible.

When the oral route is not feasible, the intramuscular route is preferred to the intravenous route. Intravenous administration may provide faster resolution of agitation than intramuscular but is associated with safety hazards for both the patient and the caregiver and is more likely to cause adverse events, such as orthostasis, dystonia, and cardiovascular and/or respiratory compromise. If the intravenous route is used, sufficient monitoring and immediate access to rescue equipment must be ensured. Supplies that should be readily available include oxygen, agents to treat the potential adverse reaction from the intravenous administration (e.g., benztropine, diphenhydramine, etc.), and advanced cardiac life support medications and equipment (Allen et al., 2005; National Collaborating Centre for Nursing and Supportive Care, 2005).

Undifferentiated Agitation

For patients in whom the etiology of agitation is unknown, the first step of treatment is to exclude organic causes, such as hypertensive

Table 1. Medications used in the management of acute agitation—review of pharmacodynamic and pharmacokinetic properties.

	Lorazepam	Haloperidol	Ziprasidone	Olanzapine
Route	IM and PO	IM and PO	IM and PO	IM and PO
Typical dose	IM: 0.5–1 mg PO: 1–2 mg	IM: 5 mg PO: 5–10 mg	IM: 10–20 mg PO: 20 mg	IM, initial dose: 10 mg IM, repeat doses: 2.5–10 mg PO: 10 mg; maximum dose for rapid treatment of agitation: 40 mg
Renal impairment	IM/PO: 1 mg	Use caution	PO: No change IM: Use caution	IM/PO: No change
Hepatic impairment	Use caution	Use caution	No change	Use caution; monitor closely Consider PO/IM dose: 5 mg
Elderly	IM/PO: 1 mg Maximum: 3 mg/day	Use caution	Use caution PO: 5 mg	IM: Consider 2.5–5 mg
Intoxicated with CNS depressants	Avoid	Acceptable	Avoid	Avoid
Sympathomimetic intoxication	Safe	–	Avoid	Avoid
Repeat dosing	30–60 min	30–60 min	10 mg every 2 hr 20 mg every 4 hr	IM: every 2–4 hr PO: every 2 hr until clinical endpoint or limiting SEs
Maximum dose/day	–	–	40 mg	30 mg
Onset	IM: 15–30 min	IM: 20–30 min	IM: ≥15 min	IM: 15 min
Peak	IM: 60–90 min PO: 2 hr	IM: 30–45 min PO: 2–6 hr	IM: <60 min PO: 6–8 hr	IM: 15–45 min PO: 6 hr
Half-life	12–15 hr	18 hr	2–7 hr	21–54 hr
Duration	6–8 hr	Up to 24 hr	–	–
Contraindications	Hypersensitivity Acute narrow-angle glaucoma Sleep apnea Severe respiratory insufficiency (except during mechanical ventilation)	Hypersensitivity Parkinson's disease Severe CNS depression Coma	Hypersensitivity Prolonged QTc interval Recent MI Uncompensated heart failure Concurrent use of other QTc-prolonging agents	Hypersensitivity

(*continues*)

Table 1. (*Continued*)

	Lorazepam	Haloperidol	Ziprasidone	Olanzapine
Pregnancy risk factor	D	C	C	C
Side effects	Respiratory depression, ataxia, excessive sedation, paradoxical disinhibition	EPS, cardiac arrhythmias, NMS	QTc prolongation	Postural hypotension
Notes	Use caution in concomitant CNS depressant intoxication	Risk of EPS may be greater in young males and with higher doses	Prolongs QTc interval more than haloperidol, olanzapine, or risperidone	Concurrent use with IM/IV benzodiazepines is not recommended
	Separate from olanzapine by at least 1 hr	Preferred to benzodiazepines in patients intoxicated with CNS depressants	IM not recommended in patients with schizophrenia already taking PO	
	Risperidone	**Aripiprazole**	**Lorazepam and Haloperidol**	
Route	PO	IM and PO	IM and PO	
Typical dose	2 mg maximum dose for rapid treatment of agitation: 12 mg	IM: 9.75 mg (range, 5.25–15 mg) PO: –	5–10 mg haloperidol + 1–2 mg lorazepam	
Renal impairment	Decrease	No change		
Hepatic impairment	Decrease	No change		
Elderly	Decrease	No change	1–2 mg haloperidol + 0.5–1 mg lorazepam	
Repeat dosing	2 hr	IM: 2 hr	30–60 min	
Maximum dose/day	–	PO: 30 mg		
Onset	–	IM: 45–60 min	–	
Peak	1 hr	IM: 1–3 hr PO: 3–5 hr	–	
Half-life	20 hr	75 hr	–	
Contraindications	Hypersensitivity	Hypersensitivity	–	
Pregnancy risk factor	C	C	D/C	
Notes	Consider decreased dose and extending the interval for elderly or debilitated patients, those with severe hepatic or renal impairment, and those predisposed to hypotension or for whom hypotension would pose a risk	Absorption of PO delayed by high fat meal Liquid is more rapidly bioavailable than tablet	Faster sedation than either agent alone Fewer EPS than haloperidol alone	

Note. IM = intramuscular; PO = oral; MI = myocardial infarction; CNS = central nervous system; EPS = extrapyramidal symptoms; NMS = neuroleptic malignant syndrome; IV = intravenous; SE = side effects; QTc = prolongation of the QT interval on electrocardiogram.

encephalopathy, hypoglycemia, and hypoxia. This process is sometimes termed "medical clearance." When no easily treatable organic cause is identified, and the patient is a danger to himself or others, chemical sedation may be required without firm knowledge of the

etiology. The ideal drug in this situation is one that has a rapid onset of action, is effective, well tolerated, and is associated with minimal drug and disease state interactions.

Lorazepam is an ideal treatment for undifferentiated acute agitation. This medication can be given intramuscularly, intravenously, or orally in increments of 1–2 mg (Battaglia, 2005). It has very few drug interactions because it is glucuronidated rather than metabolized by cytochrome P450 enzymes. The lack of drug interactions is especially valuable in cases of drug-induced agitation not complicated by central nervous system depression due to opiates, narcotics, or alcohol. Lorazepam is the drug of choice for alcohol withdrawal, and unlike both typical and atypical antipsychotics, it will not exacerbate agitation due to sympathomimetic, antidepressant, or anticholinergic intoxication (Battaglia, 2005). All formulations of the typical and atypical antipsychotics may cause serotonin syndrome, neuroleptic malignant syndrome, and electrocardiographic changes, including QTc prolongation, extrapyramidal symptoms (EPS), and dystonia in such patients (Lukens et al., 2006). Lorazepam is equal or superior to haloperidol in terms of efficacy and is also better tolerated (Battaglia, 2005). Midazolam may have a faster onset than lorazepam, but its need for frequent redosing and higher risk of oversedation makes lorazepam the benzodiazepine of choice in most institutions for control of acute agitation in the ED (Battaglia, 2005; Knott, Taylor, & Castle, 2006; Rund, Ewing, Mitzel, & Votolato, 2006).

The administration of lorazepam is not without its risks, however. Side effects of benzodiazepines include excessive sedation, respiratory depression, ataxia, and paradoxical disinhibition. The risk of paradoxical disinhibition is higher in patients with structural brain damage, mental retardation, and dementia (Battaglia, 2005; Currier & Trenton, 2002). The danger of respiratory depression is of particular concern in patients with concomitant alcohol, barbiturate, opiate, or other central nervous system depressant use and in those with respiratory disorders that limit air movement such as chronic obstructive pulmonary disease (Battaglia, 2005). Markers of respiration should be monitored frequently in the aforementioned patients at risk of respiratory depression as well as geriatric patients treated with benzodiazepines, and advanced airway support must be available in case of respiratory failure.

Haloperidol, a typical antipsychotic, is another agent that is used extensively in the treatment of undifferentiated agitation. When given intramuscularly or intravenously, 10–20 mg/24 hr is recommended to reduce the frequency of adverse events (Baldessarini, Cohen, & Teicher, 1988; Neborsky, Janowsky, Munson, & Depry, 1981; Ulrich, Neuhof, Braun, & Meyer, 1998). Careful medication selection is necessary when administering this agent intramuscularly because there exists a corresponding intramuscular depot preparation that can result in medication errors. In addition to their extended duration of action, the intramuscular depot products should not be given intravenously in this situation, as these formulations are associated with an increased risk of arrhythmias. Oral doses of 7.5–10 mg produce immediate effects and tend to result in fewer side effects than higher doses (Baldessarini et al., 1988). Although effective, it has many undesirable side effects including akathisia and dystonia. Akathisia, which may be confused with true agitation, is the number one cited reason for medication refusal by patients (Battaglia, 2005; Currier & Trenton, 2002). Dystonic reactions are more common in muscular young men and may be treated with diphenhydramine, trihexyphenidyl, or benztropine (Battaglia, 2005). Premedication with an anticholinergic agent should be considered, and most certainly made available, if haloperidol is to be used without a concomitant benzodiazepine (National Collaborating Centre for Nursing and Supportive Care, 2005). Typical antipsychotics do have the ability to decrease the seizure threshold and thus may not be the ideal choice for a patient with suspected sympathomimetic, antidepressant,

or anticholinergic intoxication (Battaglia, 2005; Lukens et al., 2006).

Another typical antipsychotic, droperidol, was the drug of choice for agitation in many institutions less than a decade ago. Although higher doses have been studied, the recommended dose for acute agitation is 5 mg intramuscularly. Droperidol has been shown to have a faster onset of action and greater efficacy than haloperidol, but this enhanced efficacy is also associated with an increased risk of oversedation (Battaglia, 2005; Currier & Trenton, 2002; Lukens et al., 2006). Concerns regarding droperidol's propensity to prolong the corrected QTc led the US Food and Drug Administration to apply a black box warning to the drug, which has greatly reduced its use in EDs because of safety and legal concerns. Haloperidol appears to have less risk of QTc prolongation in comparison with droperidol (Battaglia, 2005). However, because the warning was applied, many studies including data from thousands of patients have shown no link between droperidol and clinically significant cardiac arrhythmias (Battaglia, 2005; Rund et al., 2006; Shale, Shale, & Mastin, 2003). Clinically, the difference in QTc prolongation between haloperidol and droperidol appears to be negligible (Battaglia, 2005; Rund et al., 2006; Shale et al., 2003). Nevertheless, the Food and Drug Administration's ruling has effectively made haloperidol the typical antipsychotic of choice in US EDs. The monitoring of QTc intervals in patients receiving haloperidol as well as other antipsychotics, such as ziprasidone, may be warranted, as there is an increased risk with these therapies.

The combination of lorazepam and haloperidol is the cornerstone of care for undifferentiated agitation in many institutions (Battaglia, 2005). Benefits to the simultaneous use of these drugs compared with the use of either agent alone include decreased time spent in seclusion or restraint, faster onset of action, fewer injections, and decreased incidence of EPS. The two agents can also be combined in one syringe to minimize the number of injections (Battaglia, 2005; Battaglia et al., 1997). Coadministration of lorazepam with haloperidol negates the need for prophylactic anticholinergics. Side effects are minimal, with sedation about equal to the administration of lorazepam alone (Battaglia, 2005; Battaglia et al., 1997). Several case studies using intravenous doses of up to 480 mg haloperidol with up to 480 mg lorazepam in medical intensive care unit patients within a 24-hr period of time have demonstrated that the combination of these two agents is both safe and effective (Adams, Fernandez, & Andersson, 1986). Furthermore, the combination can be given orally to moderately agitated patients compliant with treatment.

The "9-1-1 cocktail" consisting of haloperidol 9 mg, lorazepam 1 mg, and benztropine 1 mg used to be popular in certain areas of the United States but its use is not supported by evidence (Battaglia, 2005). Benztropine was added to the classic combination of haloperidol and lorazepam in the hope of further decreasing the risk of patients developing EPS. However, there is no evidence to support an additional benefit of benztropine and this addition may even worsen delirium in demented and/or intoxicated patients (Battaglia, 2005).

Psychotic Agitation

Patients may present with acute agitation to the ED that is secondary to a psychotic illness, often referred to as psychotic agitation. These patients may be violent and a danger to themselves and providers in the ED. In these situations, rapid control of the patients' agitation is crucial. However, control of their agitation is just the first step in their care (Currier, 2000).

Even in the emergency setting, trust between patient and health care provider influences long-term outcomes of treatment (Hovens, Dries, Melman, Wapenaar, & Loonen, 2005). The ED team must choose the initial medication carefully, especially for patients with psychotic agitation who are likely to embark on continuous therapy once stabilized. Staff should consider not only the best choice for rapid symptom control but also the long-term implications of the

therapy they choose, such as the efficacy, side effects, quality of life, and average time to discontinuation. Discontinuation of antipsychotic therapy is common in patients with psychosis, and optimizing drug selection from the start may decrease rates of therapy alteration once stabilized, thereby improving treatment outcomes (Battaglia, 2005; Buckley & Correll, 2008; Kane & Sharif, 2008).

Benzodiazepines are an option in patients with known psychotic agitation, but it is important to remember that they will not treat any underlying psychotic component such as bipolar mania or schizophrenia. They are the preferred treatment for patients with psychotic agitation with concomitant sympathomimetic or antidepressant intoxication (Battaglia, 2005). Haloperidol does have antipsychotic effects, but alternative treatments with greater efficacy and tolerability are available to treat known psychotic agitation.

Atypical antipsychotics are perhaps the most effective treatment for psychotic agitation (Currier & Trenton, 2002). As a class, they offer several significant advantages over benzodiazepines and typical antipsychotics. For example, conversion from intramuscular to oral for maintenance therapy is simplified, with decreased risk of breakthrough symptoms and possibly improved future compliance (Currier & Trenton, 2002). Atypical antipsychotics, except olanzapine, may be combined with lorazepam if additional calming is required. Agents in this class also have favorable side effect profiles and are preferred by patients, as the risk of akathisia and EPS is greatly decreased compared with traditional antipsychotics such as haloperidol. The atypical agents have equal or greater efficacy in patients with schizophrenia, schizoaffective syndrome, and bipolar mania than typical antipsychotics (Currier & Simpson, 2001; Villari et al., 2008). Disadvantages of atypical antipsychotics include the low, but possible, risk of EPS that increases in a dose-dependent manner (Villari et al., 2008). The occurrence of EPS may be exacerbated by these agents in anticholinergic- or stimulant-induced agitation or intoxication and should not be used unless the etiology of agitation is confirmed to be psychotic (Whelan, Dargan, Jones, & O'Connor, 2004). An increased risk of death has been associated with the atypical antipsychotics when they have been used to treat dementia-related behavioral disturbances.

Ziprasidone is an atypical antipsychotic that is available in both intramuscular and oral dosage forms (Rund et al., 2006). However, the oral form has not been studied as a treatment for acute agitation in the ED. This agent works in a dose-dependent manner with few side effects, even at the higher end of the dosing scale. A 20 mg intramuscular dose has not been shown to cause EPS, akathisia, respiratory depression, tachycardia, or excessive sedation. The most frequently reported adverse effect is somnolence that has been reported to last as long as 4 hours and appears to be dose-related. Other adverse effects include nausea and injection site pain (Daniel, Potkin, Reeves, Swift, & Harrigan, 2001; Pane et al., 1991; Rund et al., 2006). A 10 mg dose may be more appropriate for elderly patients who are more susceptible to adverse reactions and are likely to have interacting disease states (Rund et al., 2006). Caution should be used in patients with renal impairment due to the β-cyclodextrin excipient in the parental formulation (Preskorn, 2005). Studies have looked at the accumulation of this excipient as it is present in other medications; however, no specific adverse effects have been observed in humans. Animal studies in dogs and rats have shown that the most notable effects include renal tubular vacuolation and the presence of foamy macrophages in the liver. Although kidney and liver toxicities were noted, they occurred at doses 50-fold greater than the typical human dose (Luke et al., 2010). Compared with others in its class, ziprasidone has a greater tendency to increase the QTc interval. Its use should be avoided in those with prolonged QTc syndromes or who are on concurrent QTc prolonging medications (Battaglia, 2005). An alternate atypical antipsychotic such as risperidone or

olanzapine may be preferable to ziprasidone in these patients. One study showed that ziprasidone may be safe in patients with drug intoxication and medical complications, but more research is needed to validate this finding (Battaglia, 2005).

Olanzapine is an atypical antipsychotic available in intramuscular and oral formulations, including a rapidly dissolving oral tablet (Battaglia, 2005). It has equal or greater efficacy and fewer side effects than either haloperidol or lorazepam for acute agitation in patients with schizophrenic, schizoaffective, bipolar, or dementia (Battaglia, 2005; Villari et al., 2008). A downside to the acute use of olanzapine is the potential to cause orthostatic hypotension due to alpha blockade (Knott et al., 2006). Health care providers should be cognizant of this side effect when using this agent in ambulatory patients, especially in elderly or dehydrated patients. Although the combination of olanzapine with a benzodiazepine is included in some recommendations, it has been associated with hypoventilatory syndromes and severe respiratory depression (Battaglia, 2005; Caine, 2006; Rund et al., 2006). The risks of this combination appear to outweigh the benefits; however, if intramuscular forms are used simultaneously, they should be given at least 1 hr apart to minimize side effects (National Collaborating Centre for Nursing and Supportive Care, 2005).

Risperidone is available in oral and long-acting intramuscular forms, neither of which is suitable for patients noncompliant with emergency treatment (Battaglia, 2005). Risperidone may be more likely to cause EPS than olanzapine but is less likely to cause EPS than typical antipsychotics (Villari et al., 2008). It is often preferred to olanzapine when oral treatment is possible because it has a faster onset of action (Knott et al., 2006). However, a study conducted by Villari et al. (2008) demonstrated the two to be of equal efficacy in acutely agitated patients.

Several studies have been conducted to compare the combination of atypical antipsychotics and lorazepam versus haloperidol with lorazepam (Currier & Simpson, 2001; Hovens et al., 2005; Veser, Veser, McMullan, Zealberg, & Currier, 2006; Villari et al., 2008). The results of these studies showed no significant difference; however, they trended toward equal to or increased symptom reduction and improved side effect profiles with the atypical antipsychotics (Currier & Simpson, 2001; Hovens et al., 2005; Veser et al., 2006; Villari et al., 2008).

Agitation Due to Antipsychotic Rebound

In some cases, acute agitation may be due to rebound from switching or discontinuing an antipsychotic therapy (Buckley & Correll, 2008). The actual occurrence of this etiology is likely underreported. The rates of antipsychotic discontinuation and switching among psychiatric patients are startlingly high. Studies have shown that discontinuation rates of antipsychotics are as high as 74% and patients are switched from one antipsychotic to another at least two times per year (Lieberman et al., 2005; Mahmoud, Engelhart, Janagap, Oster, & Ollendorf, 2004). When antipsychotic drugs antagonize receptors in the brain, production or sensitivity of those receptors may increase, a process known as upregulation. All antipsychotics work on dopamine-2 receptors, but atypical antipsychotics also block serotonin-2 receptors. This difference explains why the two classes are similar in efficacy but have different effects on motor skills. When a patient is switched from, or ceases to take, a medication that resulted in an upregulated receptor due to antagonism, five possible symptoms may ensue: agitation, parkinsonism, akathisia, insomnia, and anxiety (Buckley & Correll, 2008). These symptoms are due to overstimulated receptors in the brain. Various treatment strategies for rebound have been described, including benzodiazepines, antihistamines, valproic acid, benztropine,

and utilization of a longer crossover period (Buckley & Correll, 2008). Withdrawal symptoms typically occur between days 7–10 of the switch or discontinuation. Clinicians unfamiliar with antipsychotic rebounding may interpret acute agitation as medication failure, thus leading to changes in therapy; with few exceptions, abrupt switching of antipsychotics is neither advisable nor necessary (Buckley & Correll, 2008).

Special Considerations for Treating the Elderly

Those who provide care to delirious or demented elderly must be cognizant of several points. First of all, consideration should be given to any special precautions noted for the selected drug on the Beers list (Rappaport et al., 2009). This is a list of medications that may be inappropriate for use in the elderly due to their risk/benefit ratio. As with the treatment of other conditions in this population, a monotherapeutic approach with small starting doses is ideal (Nassisi, Korc, Hahn, Bruns, & Jagoda, 2006). This approach helps avoid drug and disease state interactions, in addition to reducing the chance of patient or caregiver error in drug administration.

Elderly patients tend to be more susceptible to adverse drug reactions. Using small doses and adjusting for organ dysfunction and other changes will help avoid these. Many drugs used to treat agitation have magnified side effects of particular relevance for geriatric patients. For example, anticholinergic side effects may worsen cardiovascular or prostate/bladder problems (Rabins et al., 2007). Benzodiazepines are more likely to cause oversedation, worsening cognition, delirium, increased risk of falls, and respiratory depression, especially in patients with comorbid chronic obstructive pulmonary disease or other respiratory diseases (Nassisi et al., 2006; Rabins et al., 2007). Some drugs are more prone to worsening cognition than others. Ziprasidone seems to cause the least cognitive impairment, whereas clozapine, risperidone, and traditional antipsychotics caused the most (Buckley & Correll, 2008).

Some delirious patients will require treatment for agitation before the cause is identified because they are a danger to themselves or others or are impeding medical evaluation. In 1999, the American Psychiatric Association published a guideline recommending haloperidol as the drug of choice for delirious patients. Haloperidol was shown to be more effective than lorazepam in controlling symptoms of delirium in hospitalized patients with autoimmune deficiency syndrome, but there have been few studies that included elderly patients (Nassisi et al., 2006). Haloperidol remains an ideal choice for treatment of the agitated delirious patient, unless a lowered seizure threshold poses a risk (such as in sympathomimetic intoxication). Benzodiazepines are the drug of choice for delirium due to alcohol withdrawal and sympathomimetic toxidromes (Nassisi et al., 2006).

After excluding or treating organic causes of delirium, such as substance intoxication, withdrawal, medications, hypoxia, hypoglycemia, hypotension, acute myocardial infarction, and sepsis, the clinician may consider dementia as the cause of agitation (Nassisi et al., 2006). Atypical antipsychotics have been shown to have some benefits over typical antipsychotics here. For example, they cause less cognitive impairment and fewer dyskinetic symptoms than typical antipsychotics (Nassisi et al., 2006). They have been proven effective in long-term treatment of agitation in the elderly, and in those patients with Alzheimer's, vascular dementia, and chronic dementia. As of 2005, risperidone had the most data supporting its use for the treatment of dementia in the elderly. Unfortunately, there is no intramuscular formulation for acute use in agitated patients at this time (Caine, 2006; Nassisi et al., 2006).

Atypical antipsychotics are not without drawbacks in the elderly population. In 2004, the Food and Drug Administration applied a black box warning to atypical antipsychotics due to the increased risk of mortality among elderly patients with dementia (Caine, 2006; Nassisi et al., 2006). However, in 2004, an Expert Consensus Guidelines survey of

geriatric practitioners found that 90% of them recommended atypical antipsychotics as the drug of choice for dementia with agitation and delusions and 60% for dementia without delusions as maintenance treatment (Caine, 2006). The National Institute for Health and Clinical Excellence guidelines warn against the use of olanzapine or risperidone in dementia-associated agitation altogether (National Collaborating Centre for Nursing and Supportive Care, 2005). As the black box warning appears to be for safety concerns with long-term use, there is debate over whether the risk of increased mortality is relevant in the context of emergent use in the ED.

CONCLUSION

Lorazepam and haloperidol have been the standard of care in institutions across the world for many years, and they remain effective choices, especially in patients with certain drug intoxications or agitation of unknown origin. However, the advent of intramuscular atypical antipsychotics has changed the playing field. In patients with a known psychiatric history, atypical antipsychotics have been shown to have equal or superior efficacy, safety, and tolerability, with the added benefit of simplified conversion to maintenance therapy. Should subsequent research support its use in these patients, ziprasidone may well become a first-line choice for agitated, intoxicated psychotic patients. Although the future of atypical antipsychotics is bright and well supported in the literature, it is important to remember that their use is not ideal in patients with certain possible drug intoxications, and much of the literature has been supported by drug companies. Oral administration is preferred whenever possible, although patient and staff safety should be of primary concern and the intramuscular route should be used if necessary. Although EDs may only see a patient sporadically, the treatment choices made there have significant influence on the patient's course of treatment in the outpatient setting. Conscientious medication selection guided by evidence-based recommendations should be the standard of care in every ED.

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