A Review of Agitation in Mental Illness: Treatment Guidelines and Current Therapies

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Background: Agitation is an important therapeutic target in the acute and/or emergent setting, as well as for longer-term care of patients with psychiatric illness. ***Method:*** Select reviews and guidelines published (from 2000 to 2006) on the treatment of agitation in various psychiatric disorders were evaluated. ***Results:*** After maximizing the safety of all individuals in the presence of an acutely agitated patient, initial therapy generally involves verbal de-escalation. Pharmacologic management of acute agitation relies on typical antipsychotics, particularly haloperidol; benzodiazepines; and atypical antipsychotics. The selection of a specific agent (or combination of agents) should be guided by etiologic considerations, efficacy of the drug(s), side effects, potential drug interactions, and drug formulation. Seclusion or restraints are treatments of last resort due to safety issues. ***Conclusion:*** Compared with conventional antipsychotics (e.g., haloperidol), preliminary evidence indicates that atypical antipsychotics effectively reduce agitation, are better tolerated, and have fewer side effects. After an acute episode, atypical agents also help ease the transition from intramuscular to oral medication to promote ongoing treatment.

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Although expert consensus is currently lacking as to a precise definition of "agitation" in psychiatric illness, the U.S. Food and Drug Administration (FDA) Center for Drug Evaluation and Research has observed that several fairly consistent definitions for this behavioral phenomenon are currently available in the medical literature.[1] As cited by the FDA, these definitions of "agitation" include "exceeding restlessness associated with mental distress" (from *Dorland's Medical Dictionary*) and "excessive motor activity associated with a feeling of inner tension" (from the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition [DSM-IV]).[1] The complex behavioral disturbances that characterize agitation occur in a number of psychiatric disorders, including schizophrenia, bipolar disorder, dementia (including Alzheimer's disease [AD]), and substance abuse (drugs and/or alcohol). For example, agitation is recognized as one of the most common manifestations of bipolar mania, occurring with a frequency of almost 90%.[2] With respect to schizophrenia, it has been estimated that acutely agitated patients suffering from this disorder may currently account for as much as 21% of psychiatric emergency visits in the United States (900,000 visits annually).[3] In patients with dementia, agitation occurs in up to 50% of community-dwelling patients with AD and 70% to 90% of nursing home residents.[4] Among elderly nursing home residents, the presence of agitation in concert with dementia may markedly increase the financial burden of illness, not only by increasing the use of high-cost medical services, but also by increasing the risk of acute hospitalizations (by 15.6% over a 3-month study period).[5]

As a behavioral symptom, agitation remains an important therapeutic target, not only in the acute and/or emergent setting, but also with respect to the longer-term care of patients with psychiatric illness.[6] The intent of this review is to provide a summary of the various methods (environmental manipulations and/or modifications, pharmacotherapy, seclusion, and restraints) that are currently available to treat agitation. In addition, published guidelines will be discussed with respect to the treatment of this relatively common behavioral disturbance in persons with various forms of mental illness, particularly schizophrenia, bipolar mania, and dementia.

INITIAL APPROACH TO THE AGITATED PATIENT

When a patient presents with acute agitation or overt aggressive behavior, precautions must first be taken to modify or manipulate the environment to maximize the safety of all individuals present.[7] Appropriate environ-

mental modifications and/or manipulations[7] may include any or all of the following:

- Assuring that the patient is physically comfortable
- Decreasing external stimuli through the use of relative isolation (a quiet room or an individual examination room)
- Minimizing waiting time
- Communicating a safe, respectful, and caring attitude
- Removing all potentially dangerous objects
- Monitoring the way in which staff members approach the patient

Even the design of accessible toilet and shower units must be assessed and modified to limit the risk that parts will be broken off for the purpose of inflicting injury to self or others.[8] With respect to approaching the agitated patient, medical personnel and other staff should be educated to maintain calm, keep a safe distance, identify cues for violence, respect the patient's personal space, avoid direct confrontation, refrain from prolonged or intense direct eye contact, and avoid any body language that might be interpreted as threatening or confrontational.[7,8]

The first therapeutic approach to the agitated patient generally involves verbal de-escalation ("defusing" or "talking down"), with staff appearing calm and in control while simultaneously conveying empathy, professional concern for the patient's well-being, and assurances that the patient is safe from harm.[7] At this juncture, consultations from experts in pastoral care or social work also may be helpful for select patients.[3]

If, despite initial interventions, a patient's agitation becomes so severe that the threat of assault to self or others becomes an immediate concern, the first goal of treatment is to do only what is necessary to assure the safety of the patient and others while simultaneously facilitating the resumption of more normal interpersonal relations.[9,10] Later, once the patient has calmed, there should be improved opportunities to understand the patient's problems and, hopefully, chart his or her subsequent treatment course.[9,10]

PHARMACOLOGIC MANAGEMENT OF THE AGITATED PATIENT

Pharmacologic management of the agitated patient may serve either as primary therapy or as an adjunct to other efforts at de-escalation as just described.[7] Recent discussions have brought several important issues to the fore in the delineation of appropriate pharmacologic management of the agitated patient.

Definition of Treatment Endpoint
Prospective endpoints for the treatment of agitation have not been well defined. Although sleep is sometimes

used as a valid treatment target for agitation reduction,[6] it often does not guarantee safety and it definitely conflicts with the goal of patient participation in treatment planning.[11] Moreover, sleep has not been found to be a condition that is essential for either improvement in patient agitation or a decrease in core psychotic symptoms. Instead, tranquilization (a calming process separate from total sleep induction) is now viewed by many clinicians as the therapeutic endpoint for the treatment of agitation.[12]

Variability in Assessment Instruments
In clinical studies, definitions of "agitation" have often lacked precision.[13] To date, a wide variety of scales have been used to measure agitation, including the Brief Psychiatric Rating Scale, the Overt Aggression Scale, the Overt Agitation Severity Scale, the Agitated Behavior Scale, and modified versions of these instruments.[11] Also, as of the year 2000, many investigators have begun assessing agitation by means of 10 items on the Positive and Negative Syndrome Scale (PANSS) described as the excitement/hostility component.[11] Unfortunately, the lack of agreement and/or standardization of assessment instruments for the study of agitation has sometimes made it difficult to compare efficacy results across studies. The various agitation scales differ significantly in their assessment approaches[10]; hence, consolidation or extrapolation of efficacy findings toward a unified clinical conclusion is challenging.

Issues Regarding Informed Consent
Informed consent or informed refusal of care poses unique challenges with respect to the treatment of agitated psychiatric patients.[3] The most important element of informed consent is the assessment of decisional capacity, for example, through the use of the Mini-Mental State Examination.[3] The mere existence of a particular preexisting diagnosis or therapy does not preclude the ability of the patient to participate in medical decision-making. With that said, however, the ability of a highly agitated patient to truly provide "informed consent" prior to participation in a clinical trial has recently been questioned. The underlying issue may be summarized as follows: If the patient were sufficiently competent to absorb and understand information about the trial and voluntarily decide to participate, would his or her level of agitation be truly "high," even in light of reportedly high agitation scale scores? Future discussion and resolution of this issue remain of great importance in the valid interpretation of efficacy results from treatment studies involving agitated patients, especially patients with the most severe symptoms.

SPECIFIC PHARMACOLOGIC TREATMENTS FOR AGITATION

The pharmacologic management of acute agitation has traditionally employed 3 separate classes of medications:

Table 1. Atypical Antipsychotic Formulations for the Treatment of Agitation

Agent	Oral Solution	Orally Disintegrating Tablets	Intramuscular Injection	Tablets	Capsules
Risperidone[17]	✓	✓	✓	✓	
Olanzapine[18]		✓	✓	✓	
Ziprasidone[19]			✓		✓
Aripiprazole[20]	✓			✓	
Quetiapine[21]				✓	

typical antipsychotics, particularly haloperidol; benzodiazepines; and, most recently, atypical antipsychotics. Each class of medication is discussed separately in the following section. At the conclusion of that discussion, an overview of guidelines applicable to the use of these medications in various subtypes of agitated patients is provided.

Typical Antipsychotics

Typical antipsychotics exert their antianxiety effect by inhibiting dopaminergic transmission in the brain.[6] Taken collectively, the literature published worldwide suggests that haloperidol is one of the most frequently used typical antipsychotics administered for the treatment of acute agitation,[6] and many authors[3] consider this drug to be the treatment of choice for this behavioral problem. Haloperidol can be administered orally, intramuscularly (IM), or intravenously (IV). When administered intramuscularly or intravenously, the drug has an onset of action within 30 to 60 minutes, an elimination half-life of up to 12 to 36 hours, and a duration of effect of up to 24 hours.[14]

Important adverse events associated with the use of typical antipsychotics (e.g., haloperidol) may include extrapyramidal symptoms (EPS), cardiac arrhythmias, and neuroleptic malignant syndrome (NMS).

Extrapyramidal symptoms. Haloperidol may produce EPS, including dystonia, akathisia, and parkinsonian-like effects (rigidity of the limbs, resting tremors, slowed movements, etc.).[3] These events are of major concern, not only because of their impact on the patient's physical symptoms, but also because of their potential to increase patient distress and medication refusal.[6] Dystonic reactions are particularly common following intramuscular administration of haloperidol, especially in muscular young men. To decrease the risk of EPS, anticholinergic medications, such as benztropine, diphenhydramine, or trihexyphenidyl, may be used to address these symptoms prophylactically.[6] Akathisia is also a concern because this side effect can be difficult to assess in patients who are already restless.

Cardiac arrhythmias. All typical antipsychotics have quinidine-like cardiac effects, potentially increasing the risk for cardiac arrhythmias through prolongation of the corrected QT interval (QTc).[6] Although there have been reports of sudden death occurring during tranquilization with

typical antipsychotics, including haloperidol, the role played by the antipsychotic in these deaths remains an unsettled issue since most fatalities had multiple probable causative factors.[6,15,16] Some published reports have linked haloperidol with cardiac arrhythmias; however, among the typical antipsychotics, haloperidol is considered to have a relatively low risk for increasing QTc.[6]

Neuroleptic malignant syndrome. Although NMS is generally a rare complication of typical antipsychotic use (0.2% of patients treated), the risk of this problem may increase in highly agitated patients, especially when relatively large amounts of an typical antipsychotic are given over a short period of time.[6] This is particularly true for patients who are poorly hydrated, restrained, and kept in poorly ventilated holding areas.[6,11]

In recognition of the potential adverse events that may occur with typical antipsychotic use, it is imperative that any patient treated for acute agitation should have periodic monitoring of vital signs, together with evaluations for EPS, particularly muscular rigidity.

Atypical Antipsychotics

The most recent milestone in the treatment of advanced psychotic illness involves the development of atypical antipsychotics, a family of second-generation agents that are associated with reduced EPS. Table 1 lists available atypical antipsychotics and their various formulations for the treatment of agitation.[17–21]

As alternatives to haloperidol, preliminary evidence indicates that these agents are effective in reducing agitation, better tolerated, and have fewer side effects.[7,22,23] After resolution of an acute episode, atypical antipsychotics also help ease the patient's transition from intramuscular to oral medication and promote ongoing treatment.[7,22,23] In terms of gauging patient satisfaction, it has been reported that a small percentage of agitated patients treated with intramuscular atypical antipsychotics have voluntarily requested another dose of the medication during the acute phase.[24]

Currently, accurate assessment of the anti-agitation utility of atypical antipsychotics has been limited by the fact that recent clinical trials involving these agents have typically focused on the treatment of medically stable, nonintoxicated, protocol-compliant patients who were able to consent to treatment.[6] Given that limitation, a recent 2006 Clinical Policy Statement issued from the American College of Emergency Physicians[25] has cited the following efficacy results in published reports.

Ziprasidone. Ziprasidone, the first atypical antipsychotic available in a fast-acting intramuscular preparation, reaches peak plasma concentrations in 30 to 45 minutes and has an elimination half-life of 2 to 4 hours.[26] Ziprasidone (20 mg IM) reduced symptoms of acute agitation in patients with known psychotic disorders[27] and showed

efficacy comparable to that of traditional therapies (usually haloperidol with lorazepam) in undifferentiated patients with agitation.[24]

Olanzapine. Olanzapine is a dopamine/serotonin antagonist belonging to the thienobenzodiazepine class. It reaches maximum concentration in 15 to 45 minutes and has an elimination half-life of 30 hours and a duration of action of up to 24 hours.[28] Intramuscular olanzapine was found to be equivalent to haloperidol in reducing symptoms of acute agitation in 2 studies involving patients with schizophrenia.[29,30] In patients with bipolar mania, olanzapine (10 mg) produced a greater reduction in agitation scores than lorazepam (2 mg) at 2 hours, although results of the different therapies were equivalent at 24 hours.[31]

Risperidone. Risperidone is a benzisoxazole derivative with a high affinity for dopamine/serotonin receptors. Risperidone (2 mg orally) given in combination with lorazepam (2 mg) appeared to be comparable to the combination of haloperidol (5 mg) plus lorazepam (2 mg) for the short-term treatment of agitated psychosis in patients who would accept oral medications.[25] However, interpretation of the results from this trial is complicated by possibly higher levels of agitation in the haloperidol-lorazepam group as compared with the risperidone-lorazepam group.[25]

Aripiprazole. Aripiprazole, the most recent atypical antipsychotic to become available, is a dopamine D_2 partial agonist with serotonin 5-HT_{1A} partial agonist and 5-HT_{2A} antagonist activity. Theoretically, by increasing dopamine activity in hypodopaminergic regions while decreasing dopamine activity in hyperdopaminergic areas of the brain, aripiprazole will confer potent antipsychotic activity without the side effects of conventional antipsychotic medications. Aripiprazole is currently approved for the treatment of schizophrenia and the treatment of acute mania and mixed episodes associated with bipolar disorder. As reviewed elsewhere in this supplement (see Caine, pp. 22–31), a recently presented analysis of drug-manufacturer data (a total of 9 FDA registration and post-marketing trials) has shown that aripiprazole, along with several other atypical antipsychotics evaluated, is effective in consistently controlling agitation in schizophrenic patients with high baseline levels of agitation (as measured by PANSS excitement component) in patients with bipolar mania (as measured by decreases in total Young Mania Rating Scale scores), and in patients with highly agitated AD and associated psychosis.

In terms of side effects, an open-label, randomized, prospective study by Harrigan and colleagues[32] concluded that, like with haloperidol, maximum-recommended daily dosages of olanzapine, ziprasidone, quetiapine, and risperidone prolonged the QTc at the steady-state peak plasma concentration. Prolongation of the QTc was least for olanzapine, and none of the antipsychotics resulted in a QTc that exceeded 500 ms. For olanzapine, a 20-mg decrease in systolic blood pressure has been noted in approximately 12% of patients,[25] necessitating the careful monitoring of orthostatic vital signs, especially if repeated dosages of olanzapine are to be administered. In light of European reports[6,25] of 8 fatalities following combination therapies that utilized olanzapine, intramuscular olanzapine should not be coadministered with other medications, especially benzodiazepines or other central nervous system depressants.

Benzodiazepines

Benzodiazepines are thought to exert their anti-agitation effects through the facilitation of γ-aminobutyric acid (GABA) neurotransmission.[6] Some available evidence suggests that in the context of agitation, benzodiazepines are either as effective as the typical antipsychotic haloperidol[11] or are superior to that drug, especially in the treatment of psychotic or manic agitation.[33–36] Among the benzodiazepines, lorazepam is generally the most popular choice for use in agitation. It is the only benzodiazepine with complete and rapid intramuscular absorption, an elimination half-life of 12 to 15 hours, and a duration of action of 8 to 10 hours.[37] Lorazepam has few drug-drug interactions and requires no involvement of the cytochrome P450 system. When compared with haloperidol (5 mg), lorazepam (2 mg) has been shown to be superior to the typical antipsychotic on measures of both aggression[36] and clinical global improvement.[34]

While lorazepam remains the most popular benzodiazepine for use in agitation, other benzodiazepines (e.g., clonazepam, diazepam, chlordiazepoxide, midazolam, and flunitrazepam [not available in the United States]) have been studied as single-agent therapy for acute agitation and have demonstrated tranquilizing effects comparable to those of haloperidol.[6] Although midazolam has been found to be superior to haloperidol on measures of motor agitation, most patients fell asleep after intramuscular administration (2.5 to 15 mg) of this drug, and the duration of effect was short (1–2 hours).[38] With respect to diazepam and chlordiazepoxide, the use of these medications is complicated by their erratic intramuscular absorption rates and by the fact that they generate active metabolites that have long half-lives.[6] Clonazepam, a high-potency benzodiazepine with a long elimination half-life (20 to 80 hours), has complete but inconsistent intramuscular absorption,[37] and its mechanism of action is poorly understood.[6] Overall, it appears to have limited efficacy for the treatment of agitation.[6]

In terms of side effects, benzodiazepines produce EPS less frequently as compared with typical antipsychotics[11] and do not have significant cardiac effects.[6] However, benzodiazepines do have the capacity to cause respiratory depression, ataxia, excessive sedation, or paradoxical disinhibition.[6] In light of this safety profile, clinicians often avoid using benzodiazepines in patients with chronic

obstructive pulmonary disease or conditions that limit pulmonary reserve.[39] Likewise, dose adjustments may be necessary in elderly patients who, as a special subpopulation, are generally more susceptible to excessive sedation and ataxia.[40]

GUIDELINES FOR PHARMACOTHERAPY IN AGITATION

The selection of a specific agent (or combination of agents) for the management of agitation should be guided by diagnostic or etiologic considerations. Acutely agitated patients often have major psychiatric illness that promotes the agitated behavior, with severe agitation commonly observed in psychotic illnesses, such as schizophrenia, schizoaffective disorder, and the manic phase of bipolar disorder. Other diagnoses associated with the occurrence of severe agitation are drug- (cocaine, amphetamines, and hallucinogens) and alcohol-intoxicated states. Because these diagnoses present special considerations, evidence-based guidelines suggest that drug- or alcohol-induced delirium should be approached according to the underlying etiology, if that etiology is known.[11,41] One of the reasons for this approach is the fact that anticholinergic properties often are associated with substances of abuse (e.g., hallucinogens); hence, psychotropic medications such as antipsychotics (which have their own anticholinergic effects) may potentiate the toxicity of the drugs of abuse. As a rule, antipsychotics should be avoided when anticholinergic delirium is suspected.[11] Instead, benzodiazepines may be a better choice, especially when the potential for seizures exists, as with cocaine toxicity.[11] Although benzodiazepines are recommended for alcohol withdrawal states, these medications should be used with caution because the sedative and respiratory depressant effects are additive with those of alcohol and other central nervous system depressants.[11]

In addition to etiology, other important factors in the choice of pharmacologic therapy for agitation include the efficacy of a specific drug (or combination of drugs), known side effect profile, and potential drug interactions.[11,41] For practical purposes in the clinical setting, drug formulation is also of vital importance because it not only affects the route of administration (a factor that particularly impacts the treatment of the agitated, uncooperative patient), but also the onset and duration of the therapeutic effect.

Table 2 summarizes select reviews and guidelines regarding the pharmacologic treatment of agitation in various psychiatric disorders published between 2000 and 2006.[2,3,6–8,11,25,42–46] As may be appreciated from a review of the citations presented in this table, the treatment of agitation has drawn the attention of experts from diverse specialties, including psychiatry, emergency medicine, geriatrics, internal medicine, and general practice. In terms

of therapeutic recommendations, a 2000 review by Allen[11] indicated that during the period between 1960 and 1990, the most common approach to rapid tranquilization in the emergency setting was a combination of haloperidol and lorazepam. Likewise, in a more recent review,[6] haloperidol and lorazepam were similarly found to be the most widely used agents. This is especially true in the case of agitated, uncooperative patients whose medication history (with respect to prior exposure to antipsychotics) is unknown[43] or for acutely agitated, undifferentiated patients.[25] For patients with known psychiatric illness (i.e., schizophrenia) for which antipsychotic treatment is indicated, an extra dose of the same typical or atypical agent that the patient is already on has been recently recommended by a subcommittee of the American College of Emergency Physicians.[25] Conversely, in the psychiatric emergency services setting, an earlier consensus survey indicated that benzodiazepines may be the initial choice of therapy for the agitated, uncooperative patient with a history of prior exposure to antipsychotics.[43] With respect to atypical antipsychotics, a 2005 review by Marco and Vaughan[3] concluded that due to the recent introduction of parenteral forms of these drugs, atypical antipsychotics are gaining in popularity as first-line drugs in the treatment of agitation.

Regarding alternate forms of therapy for special populations, patients with bipolar disorder may be treated with lithium, divalproex sodium, or carbamazepine for an acute manic episode.[2,42] Antipsychotics and benzodiazepines are considered adjunctive treatments in this population.[2] For the geriatric patient with psychotic mania, a 2004 survey of geriatric specialists[44] favored the combination of a mood stabilizer plus an antipsychotic. However, a later review by Young[42] favored the use of a mood stabilizer and the elimination of other, unnecessary psychotropic agents.

For agitated geriatric patients with dementia, monotherapy with an atypical antipsychotic was favored in a 2004 survey of geriatric specialists.[44] Moreover, as of 2005, Hansberry and colleagues[47] observed that atypical antipsychotics, especially risperidone and olanzapine, had come to be the de facto preferred treatment for agitation in patients with dementia, with or without psychosis. With respect to aripiprazole, Mintzer and colleagues[48] recently demonstrated that aripiprazole produced overall clinical improvement and significant decreases in agitation symptoms in long-term (10-week) studies of highly agitated patients with AD and associated psychosis.

Despite the apparent efficacy and utility of atypical antipsychotics in treating agitation associated with dementia, the off-label use of these atypical agents, which are approved only for the treatment of schizophrenia and mania, recently has generated concern from the FDA due to reports of higher death rates, as compared to placebo, among elderly patients with dementia.[49] Consequently, the drug labeling of atypical antipsychotics must now include

Table 2. Select Reviews and Guidelines Regarding the Pharmacologic Treatment of Agitation in Various Psychiatric Disorders From 2000 to 2006

Treatment Focus	Publication Type/Methodology	Selected Pharmacologic Treatment Recommendations	Publication (Year)

Adult psychiatric patient in the emergency department	Clinical policy statement, American College of Emergency Physicians subcommittee review and critical analysis of the medical literature (1980 to 2005)	Acutely agitated patients
		1. Level A
		   None specified
		2. Level B
		   Benzodiazepine or conventional antipsychotic as initial monotherapy for treatment of acutely agitated, undifferentiated patients
		   If rapid sedation is required, consider droperidol instead of haloperidol
		   Antipsychotic (typical or atypical) monotherapy for management of agitation and initial drug therapy of patients with known psychiatric illness for which antipsychotics are indicated
		   Combination of oral benzodiazepine (lorazepam) and oral antipsychotic (risperidone) for agitated but cooperative patients
		3. Level C
		   Combination of a parenteral benzodiazepine and haloperidol may produce more rapid sedation than monotherapy in the acutely agitated patient in the emergency department
			Lukens et al (2006)[25]

Emergency management of agitation in schizophrenia	Review	Acute agitation Historically, typical antipsychotics have been first-line treatments, partly due to their availability as IM preparations Atypical antipsychotics are gaining in popularity as first-line agents due to the recent introduction of parenteral forms of olanzapine and ziprasidone; both of these drugs are at least as effective as haloperidol in producing rapid tranquilization Benzodiazepines may be effective as single agents or in combination with haloperidol, droperidol, olanzapine, or other antipsychotics	Marco and Vaughan (2005)[3]
Pharmacologic management of acute agitation	Review/MEDLINE database search (1960 to 2004) of acute agitation	Traditional treatments IM injections of typical antipsychotics, given alone or in combination, have been the treatment of choice over the past few decades Haloperidol and lorazepam are the most widely used agents, but side effects (eg, EPS, sedation) have been problematic Atypical antipsychotics IM risperidone is well tolerated and has been widely used since 2002; however, caution is required due to drug's propensity to increase QTc IM olanzapine has shown improved efficacy and fewer adverse events than haloperidol, but must be used according to strict prescribing guidelines Limited evidence supports efficacy of IM ziprasidone	Battaglia (2005)[6]
Acutely violent patient	Review	Rapid tranquilization Rapid tranquilization has become a standard of care that is safe and effective Traditional approach uses a typical antipsychotic (standard is haloperidol), with or without a benzodiazepine such as lorazepam Atypical antipsychotics (risperidone, olanzapine, ziprasidone) in liquid, IM, or rapidly dissolving tablet form are becoming important alternatives to the traditional approach	Petit (2005)[7]
Geriatric bipolar disorder	Review/MEDLINE database search for articles written in English regarding pharmacologic treatment of bipolar disorder in the elderly (1966 to May 2005)	Treatment of manic states First step is use of mood stabilizers, together with elimination of other unnecessary psychotropics Few data exist for efficacy of atypical antipsychotics in elderly bipolar disorder patients. However, preliminary studies suggest that olanzapine, quetiapine, and clozapine show some efficacy Valproate may be effective, especially in patients with "organic" causes, dementias, mental retardation, or bipolar mania	Young (2005)[42]

Table 2. Select Reviews and Guidelines Regarding the Pharmacologic Treatment of Agitation in Various Psychiatric Disorders From 2000 to 2006 (cont.)

Treatment Focus	Publication Type/Methodology	Selected Pharmacologic Treatment Recommendations	Publication (Year)
Pharmacotherapy in academic psychiatric emergency services (PES)	Expert Consensus Guidelines/survey mailed to 56 medical directors of PES facilities (91% response)	Agitated, uncooperative patient with no known medical history Majority of respondents reported following a written or informal protocol 70% of protocols involved a parenteral "drug cocktail" of a high-potency typical antipsychotic and a benzodiazepine 15.9% used a benzodiazepine alone 6.8% used a high-potency typical antipsychotic alone 4.5% used risperidone alone Agitated, uncooperative patient with medical history and no prior exposure to antipsychotics 60% recommend a benzodiazepine alone Agitated, uncooperative patient with history of prior exposure to antipsychotics 81.6% favored benzodiazepine alone, with subsequent initiation of an antipsychotic in the context of informed consent dialogue	Allen and Currier (2004)[43]
Use of antipsychotic agents in older patients	Expert Consensus Guidelines/survey of 48 leading experts in geriatrics (geriatric psychiatrists and geriatric internists/family physicians)	Agitated dementia or delusions First-line: antipsychotic monotherapy (risperidone, quetiapine, olanzapine) High second-line: combination of a mood stabilizer plus an antipsychotic No first-line recommendation for agitated dementia without delusions Late-life schizophrenia First-line: antipsychotics. Atypical antipsychotics favored, with 93% of experts rating risperidone as first-line; 67%, quetiapine; and 60%, aripiprazole Psychotic mania: treatment of choice is a combination of a mood stabilizer plus an antipsychotic	Alexopoulos et al (2004)[44]
Management of behavioral and psychiatric symptoms in dementia and the treatment of psychosis in people with history of stroke/transient ischemic accident	Royal College of General Practitioners summary of guidance for patient management	Indications for specific drugs Acute situation: lorazepam, haloperidol Aggression: haloperidol, zuclopenthixol, carbamazepine, sodium valproate Agitation: zuclopenthixol, trazodone, sodium valproate Potential for sedation and/or serious side effects noted for specific drugs Cholinesterase inhibitors in AD if clinical response is seen "The majority view…was that the newer antipsychotics are likely to have a favorable side-effect profile compared to traditional antipsychotics. They may however still cause cerebrovascular events, sedation, extrapyramidal side effects, and agitation."	Royal College of General Practitioners (2004)[45]
Behavioral emergencies	Treatment guidelines/written survey with 808 decision points completed by 50 experts	Combination of a benzodiazepine and an antipsychotic was preferred for patients with suspected schizophrenia, mania, or psychotic depression. There was equal support for high-potency conventional or atypical antipsychotics (particularly liquids) in oral combinations with benzodiazepines	Allen et al (2003)[46]
Violent psychotic patient	Review	Agitation/excitement High potency typical antipsychotics, olanzapine, clozapine, or risperidone (in that order of choice) Aggression Historically, typical antipsychotics have been mainstay of treatment of aggression with active psychosis Mounting evidence for efficacy and tolerability of atypical antipsychotics (risperidone liquid, olanzapine IM, ziprasidone IM)	Buckley et al (2003)[8]
Bipolar disorder	Review	Acute manic episode Lithium, divalproex sodium, and carbamazepine are the cornerstone of treatment Antipsychotics and benzodiazepines are adjunctive treatments during acute manic or mixed episodes	Keck et al (2001)[2]
Agitated psychotic patient	Review of 24 studies (1960 to 1990)	Psychiatric emergency setting Initial evidence for mood-stabilizing effects of atypical antipsychotics Most common approach to rapid tranquilization is combination of haloperidol and lorazepam	Allen (2000)[11]

Abbreviations: EPS = extrapyramidal symptoms, IM = intramuscular, QTc = corrected QT interval.

a boxed warning describing this risk and noting that these drugs are not approved for the treatment of behavioral symptoms in elderly patients.[49]

SECLUSION AND RESTRAINTS

If the agitated patient continues to exhibit emergent and imminently dangerous behavior despite the precautions and therapies described in this report, some practitioners suggest the use of seclusion or restraints,[7] although each of these modalities is often considered a "treatment-of-last-resort."[8] Currently, seclusion rooms are used in a minority of emergency departments across the United States, and the use of seclusion has been declining, possibly due to regulatory concerns and complications associated with the practice.[50] Regarding complications reported in conjunction with the use of seclusion, a recent survey of U.S. emergency department medical directors[50] concluded that patient escape from seclusion (30.1% of all complications) was the most common adverse event, followed by staff injury (29.2%), patient injury (19.8%), and increased harmful behavior (11.3%).

Although it has been estimated that physical restraints are currently employed in the treatment of approximately 8.5% of patients in emergency departments,[43] their use remains a potentially dangerous management option and should be employed sparingly.[8] While restrained, highly agitated patients may develop significant medical complications or sustain serious physical harm.[8] In terms of clinical guidelines, the use of physical restraints should be limited to cases in which the safety of the patient, other patients, or the hospital staff is threatened.[3] When applied, physical restraints should be employed in the least restrictive manner possible and for the least amount of time (as mandated by the clinical situation).[3] Also, as required by the Joint Commission of Accreditation of Healthcare Organizations, institutions must have policies in place that deal with the use of restraints, stipulating physician orders, nursing documentation, types of restraints, and patient monitoring and assessment.[3]

SUMMARY

Agitation is a complex behavioral disturbance that may occur in a number of psychiatric disorders. When a patient presents with acute agitation or overt aggressive behavior, precautions must be taken first to modify the patient's environment so as to maximize the safety of all individuals present. Next, initial attempts at therapy generally involve verbal de-escalation ("defusing" or "talking down"), with staff appearing calm and in control while simultaneously conveying empathy, concern, and assurances that the patient is safe from harm. At this juncture, consultations from experts in pastoral care or social work also may be helpful. If the agitated patient continues to exhibit emergent and imminently dangerous behavior, some practitioners suggest the use of seclusion or restraints, although these modalities are generally considered as treatments of last resort due to serious safety issues. With respect to pharmacologic management, pharmacotherapy may serve either as primary therapy or as an adjunct to other efforts at de-escalation. Pharmacologic management of acute agitation has traditionally employed 3 separate classes of medications: typical antipsychotics, particularly haloperidol; benzodiazepines; and, most recently, atypical antipsychotics. The selection of a specific agent (or combination of agents) for the management of agitation should be guided by diagnostic or etiologic considerations. Other important factors include efficacy, side effect profile, potential drug interactions, and available formulations (the determinant of the route of administration). In the year 2000, the most common approach to rapid tranquilization in the emergency setting was a combination of haloperidol and lorazepam, and these agents continue to be widely used, especially in acutely agitated, undifferentiated patients and agitated, uncooperative patients with no known medication history. For patients with a known psychiatric illness for which antipsychotic treatment is indicated, antipsychotic monotherapy (typical or atypical) has been recommended, although some practitioners favor benzodiazepines as an initial choice. With respect to atypical antipsychotics, the recent introduction of parenteral forms of these drugs has led to their increasing popularity as first-line treatments for agitation.[3] Because all medications used to treat agitation carry a risk of side effects, it is imperative that any patient receiving pharmacotherapy for acute agitation be closely monitored for the onset of adverse reactions.

Drug names: aripiprazole (Abilify), benztropine (Cogentin and others), carbamazepine (Carbatrol, Equetro, and others), chlordiazepoxide (Librium and others), clonazepam (Klonopin and others), clozapine (FazaClo, Clozaril, and others), diazepam (Valium and others), diphenhydramine (Benadryl and others), divalproex sodium (Depakote), droperidol (Inapsine and others), haloperidol (Haldol and others), lithium (Lithobid, Eskalith, and others), lorazepam (Ativan and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), trazodone (Desyrel and others), ziprasidone (Geodon).

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