Atypical Antipsychotic Medications in the Psychiatric Emergency Service

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The physiologic and psychological impact of drugs administered in the emergency treatment of psychosis endures much longer than the patient's brief stay in the psychiatric emergency service (PES). Although newer antipsychotic agents with improved efficacy and side effect profiles are now available and generally recommended as first-line treatment for psychosis, the slow titration schedules and lack of intramuscular preparations for these drugs often lead to the preferential use, and perhaps overuse, of conventional antipsychotics in emergency situations. A recent survey found that most medical directors of psychiatric emergency programs would prefer to administer an oral atypical agent if such an agent were found to be effective, safe, reliable, and practical to use. Preliminary results have shown the atypical antipsychotic risperidone to have efficacy equal to that of the conventional agent haloperidol in a direct comparison in the PES; further study is required, however, to determine the appropriateness of the use of risperidone and the other atypical antipsychotics in the emergency treatment of psychosis. *(J Clin Psychiatry 2000;61[suppl 14]:21–26)*

The management of agitation and aggression accompanying acute psychotic illness poses particular challenges in the psychiatric emergency service (PES). A rapid response to treatment is essential to avoid the potential risk of violence or self-harm. Given the acuity involved, physicians and the treatment teams they support consider it imperative to intervene rapidly and definitively. However, once initial control of agitation has been achieved, the psychological and physiologic impact of interventions may extend long past a patient's time in the PES. Early sedation may be desirable to calm the patient, but once a patient is stabilized, sedation can have an undesirable impact on daily functioning and quality of life.

The central nervous system effects of traditional neuroleptics may endure much longer than has been appreciated, and patients remain at highest risk of dystonia for up to 3 days after typical neuroleptic initiation.[1] As such, the use of typical neuroleptic drugs should be weighed against more recently available alternatives. PES clinicians have an opportunity to initiate logical and effective clinical care with atypical antipsychotic drugs, since medications started in the PES may be continued through the inpatient and/or outpatient phases. Patients' decisions to follow through with outpatient treatment after discharge are almost certainly shaped by experiences they have within the hospital setting. Given decreased lengths of hospital stay, the experiences of patients in the emergency department are often freshly remembered at time of discharge. The choice of drug and route of administration in the PES is dictated by the clinical needs of the moment. What may be less appreciated is the importance of imprinting a positive experience based on mutual cooperation from the first moment hospital care is initiated in the PES.

Elsewhere in this Supplement, Allen[2] reviews the literature on the use of benzodiazepines and typical antipsychotic medications for treatment of agitation in the PES environment. As discussed, the use of benzodiazepines may be preferable for treatment of agitation not associated with psychosis or delirium. However, in clinical practice, "cocktails" of intramuscular neuroleptics and benzodiazepines, often in combination with anticholinergic medications, are routinely administered.[3] Patients who appear agitated or threatening but who are not psychotic also receive these combinations of medications, which are quite effective at inducing sedation or somnolence. Although from the clinicians' perspective this is a desired outcome, the longer-term side effect burden (e.g., akathisia, dystonia, parkinsonism, neuroleptic malignant syndrome) may become apparent only after the patient is discharged.

This article has 4 purposes: (1) to review existing guidelines for recommendations regarding acute treatment of agitated psychosis, (2) to review the scant literature on the use of atypical antipsychotic medications for acute treatment of aggression associated with psychotic illness, (3) to describe current clinical practice for treating agitation in

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the PES setting, and (4) to describe preliminary findings of a pilot study exploring the use of an oral atypical antipsychotic medication versus an intramuscular typical agent for treatment of psychotic agitation.

TREATMENT GUIDELINES

With the increasing evidence for the benefit of novel antipsychotics over conventional neuroleptics, treatment guidelines have changed rapidly over the past few years. Prior to 1997, conventional neuroleptics were still considered to be the first-line treatment for schizophrenia. In that year, the consensus recommendations of the American Psychiatric Association (APA)[4] were that conventional and novel antipsychotics were equivalent choices for treatment of positive symptoms. However, by 1999, the novel antipsychotics were recommended as first-line treatment for schizophrenia in most clinical situations.[5] One notable exception was in instances in which intramuscular preparations are necessary, since as yet no intramuscular atypical agent is commercially available. The novel antipsychotics continue to be recommended over the conventional agents by virtue of their well-established broader effect on both positive and negative symptoms of schizophrenia and their overall favorable safety profiles. However, the usefulness of atypical antipsychotics specifically in the first few hours of treatment of agitated psychotic patients is not addressed in existing practice guidelines. Use of these medications in emergency situations remains largely unexplored.

CLINICAL DATABASE OF ATYPICAL ANTIPSYCHOTICS IN AGGRESSION

The benefits of atypical antipsychotic medications for treatment of chronic aggression are increasingly well established. Antiaggressive properties are related to unique serotonergic and dopaminergic profiles and may also involve histaminergic effects acutely.[6–8] Use of atypical medications in the emergency setting has been limited by the slow titration schedules required to avoid intolerable side effects. Another significant barrier to use has been the lack of an atypical antipsychotic available in an intramuscular preparation.

Clozapine

The antiaggressive characteristics of clozapine are well established in chronically psychotic individuals and may result in part from serotonergic properties.[7–9] Glazer and Dickson[10] describe significant reductions in restraint and seclusion use in schizophrenic patients treated with clozapine in a state hospital. Acute agitation may be reduced by the highly antihistaminergic properties of clozapine. However, because of serious potential side effects, including seizures and agranulocytosis, clozapine initiation is contraindicated at sedative doses in the PES.

Risperidone

Risperidone has been shown to ameliorate both positive and negative symptoms of schizophrenia and to exhibit low rates of extrapyramidal side effects in recommended dosages.[11,12] Czobor and colleagues,[13] in a subanalysis of the U.S. multicenter comparative trial between risperidone and haloperidol, noted a superior effect of risperidone for treatment of aggression. Chengappa and colleagues[14] described a significant decline in seclusion and restraint in a state hospital population treated with risperidone. At dosages of 4 to 6 mg/day, risperidone does not differ from placebo in producing extrapyramidal side effects in patients with psychosis. Buckley and colleagues[8] also found that risperidone was as effective as haloperidol in treating aggression in patients with chronic schizophrenia. Risperidone is available in a liquid preparation that has more rapid bioavailability than the tablet form.[15] The liquid concentrate has recently been studied prospectively as an alternative for treatment of psychotic agitation, as described in more detail below.

Olanzapine

Olanzapine has demonstrated efficacy in the treatment of positive, negative, and affective symptoms of schizophrenia.[16] In an analysis of the multicenter clinical trials, Beasley and colleagues[17] demonstrated equal efficacy of olanzapine and haloperidol in the treatment of agitation and aggression. The antihistaminergic (H_1) potency of olanzapine is over 160 times that of diphenhydramine,[18] which may explain the associated side effects of both sedation and weight gain.[16] New-onset diabetes mellitus and diabetic ketoacidosis have also been reported in olanzapine-treated patients; weight gain was reported in only 4 of 7 patients who developed diabetes mellitus.[19] In the emergency setting, antihistaminergic properties may be calmative initially. "Loading" strategies have been devised to harness this side effect. However, to date no published reports document the utility or safety of this practice. Olanzapine is currently available only in tablet form.

Quetiapine

Two 6-week, double-blind, randomized studies[20,21] compared the use of quetiapine (5 dosages ranging from 75–750 mg/day) and haloperidol (fixed dose of 12.5 mg/day). Using subscales of the Brief Psychiatric Rating Scale, quetiapine was found to be superior to haloperidol in reducing agitation at a dose of 600 mg/day. Improvement in aggression and hostility were independent of effects on psychosis.[20,21] In spite of these findings, a recommended slow titration protocol precludes the use of quetiapine in the emergency setting. Currently, this medication is available only in tablet form.

Ziprasidone

Ziprasidone mesylate is the first atypical antipsychotic to enter late-stage clinical development as a rapid-acting

intramuscular formulation. Clinical data are available only in abstract form and include two 24-hour randomized, double-blind trials (N = 196)[22]; one 7-day open-label trial comparing 5 to 20 mg/day of ziprasidone with 5 to 40 mg/day of haloperidol (N = 132); and a fixed-dose, 7-day trial comparing ziprasidone and haloperidol switched from i.m. to p.o. routes at day 3. Outcome measures included the Behavioral Agitation Rating Scale (BARS) developed by Pfizer Inc. The authors suggest that ziprasidone, 10 and 20 mg i.m., were both rapidly effective (within 2 hours) in reducing agitation and aggression without causing profound sedation or movement disorders. Mean change in the corrected QT interval was slightly less for ziprasidone than haloperidol (+2.14 ms and +2.22 ms, respectively). If these findings are replicated after the drug is clinically available, ziprasidone may represent a significant advancement in the emergency treatment of psychotic agitation.

CURRENT USUAL PRACTICE FOR TREATING AGITATION IN THE PES

In 1999, the American Association for Emergency Psychiatry sponsored a survey of PES directors throughout the United States.[23] The goal was to describe current PES structures and function with particular emphasis on medication practices for a variety of clinical situations, including agitated psychosis. One major goal of this work was to serve as a launch point for training efforts and clinical algorithm development.

The survey was sent to 56 medical directors of leading American psychiatric emergency programs. The survey instrument was a 70-item questionnaire that took approximately 1 to 2 hours to complete and that addressed a variety of topics, including the setting in which the care occurred and the type of care, including medical and nonmedical interventions. The response rate was 91%. The majority were university-based training sites for medical students and residents. A variety of clinical services were provided, including initiation of medications for admitted patients (offered in 82% of sites) and medications for discharged patients (70% of sites). Respondents indicated that a mean ± SD of 400.7 ± 258.7 patients were evaluated each month, although in major urban centers up to 3 times that number are seen. Less than half of the patients evaluated in the PES are admitted to hospitals (mean ± SD = 181.9 ± 224.4). Psychosis (28.5%), substance use disorders (25.1%), unipolar depression (22.9%), and Axis II disorders (21.7%) represent the most frequent diagnostic categories for all patients treated in this setting.

Approach to Violent Patients

The PES is perceived to be a relatively dangerous environment, and recent data suggesting that over half of admitted psychiatric patients have a history of interpersonal violence support these conclusions.[24] Although most recipients of PES services are not violent, the attitude driven by this perception may determine clinical practice, including choice of drugs and route of administration. Respondents did describe high rates of violence toward staff by patients. The mean ± SD number of assaults per year at each site was 8.0 ± 17.5, of which 56.5% resulted in lost time from work. There was a 6-to-1 odds ratio of nurses being assaulted relative to doctors, most likely related to nurses' role in restraint application. Mechanical restraints were used in a mean ± SD of 8.5% ± 7.8% of patients, and the mean ± SD duration of restraint was 6.1 ± 6.4 hours. Ordering of restraint and seclusion was limited to licensed clinical staff at all sites. In all sites surveyed, initiation of restraints was driven solely by clinical condition of the restrained patients, and acceptable reasons for restraint initiation included acute danger of harm to self and/or others. In no setting was restraint and seclusion considered appropriate to manage the busy PES environment. Overall, the results suggest that restraints are being used relatively judiciously.

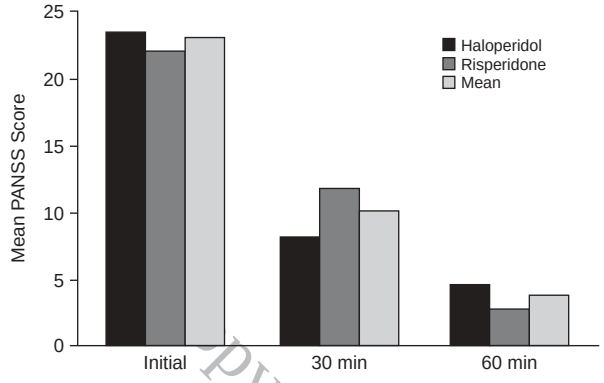
Medications were the other major form of treatment for agitated patients.[23] The mean ± SD number of all patients who required emergency medication for agitated behavior was 16.2% ± 19.2%. Nonetheless, in spite of the relative frequency of involuntary medication administration, only 6% of sites reported having written protocols guiding medication type, amount, and route of administration. A majority—70.3%—advocated the use of an intramuscular "cocktail" consisting typically of haloperidol, a benzodiazepine, and an anticholinergic agent. Intramuscular formulations were favored by 64% of respondents for control of agitation. Of patients started on an oral agent for control of all symptoms of psychosis, 41.9% were started on an atypical agent. Overall, 72% of PES directors recommended or highly recommended the use of atypical antipsychotic medications in the PES. Atypical medications were most strongly advocated in certain clinical situations, including lung disease, mental retardation, head trauma, the presence of a sedative administered, frail old age, tardive dyskinesia, and the presence of extrapyramidal symptoms (Table 1).

Table 1. Percentage of Respondents Endorsing Use of Drug Class by Clinical Condition[a]

Condition	Atypical Antipsychotic	Typical Antipsychotic	Benzodiazepine
Chronic obstructive pulmonary disease	98.0	88.2	20.0
Mental retardation/ developmental delay	96.1	84.3	72.5
Head trauma	98.0	80.4	43.1
Sedative on board	80.4	78.4	9.8
Frail old age	88.2	64.3	30.4
Tardive dyskinesia	98.0	21.6	98.0
Extrapyramidal side effects	92.2	27.5	100.0

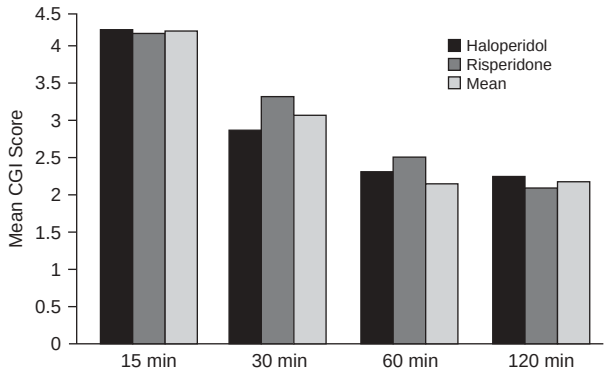
[a]Data from Currier et al.[23]

Figure 1. Mean Positive and Negative Syndrome Scale (PANSS) Scores Over Time[a]



[a]Data from Currier and Simpson.[25]

Figure 2. Change in Clinical Global Impressions Scale (CGI) Scores Over Time[a]



[a]Data from Currier and Simpson.[25]

Consensus was found surrounding some important issues affecting clinical practice in the PES. Respondents clearly indicated that patient cooperation, not profound sedation, is the desired endpoint of medication use. Respondents advocated the use of oral agents whenever possible, and liquid forms were preferred to tablets owing to rapid onset and ease of checking patient compliance. Although there continues to be a heavy reliance on intramuscular medications in the PES, respondents indicate that an oral atypical agent would be desirable if such a medication proved safe, effective, reliable, and practical to use.

ORAL ATYPICAL VERSUS INTRAMUSCULAR TYPICAL ANTIPSYCHOTIC MEDICATION FOR TREATMENT OF PSYCHOTIC AGITATION

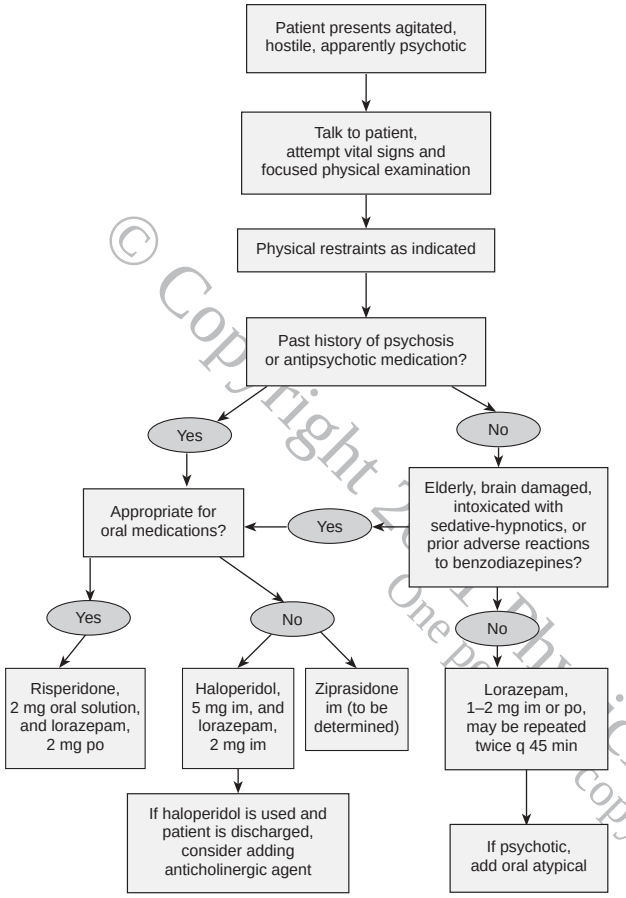
The advantages of intramuscular formulations in an emergency setting—the clinician can be sure the patient received the drug, for example—are undermined by the fact that many patients do not like intramuscular administration. Recently, Currier and Simpson[25] studied the feasibility of using an oral atypical antipsychotic for treatment of agitation in the PES. The object was to determine the relative efficacy, safety, and tolerability of oral risperidone (liquid concentrate) versus intramuscular haloperidol, both in combination with lorazepam, for the emergency treatment of psychotic agitation.

This was a prospective, nonrandomized, rater-blinded, double-arm study comparing 2 classes of antipsychotic medications in oral and intramuscular formulation, both in combination with the benzodiazepine lorazepam, for the treatment of agitated patients who presented to a large urban emergency department. Assessments and diagnoses were made on arrival or shortly thereafter. After being informed about possible side effects, patients were given a choice of the following treatments: risperidone (2 mg liquid concentrate) plus oral lorazepam (2 mg) or haloperidol (5 mg i.m.) plus lorazepam (2 mg i.m.); the latter was the standard of care at this institution. The liquid formulation of risperidone was chosen because of its rapid bioavailability and ease of checking patient compliance versus the tablet form. Raters were blinded to the study condition. Two rating scales were used: (1) 5 directly observable items from the Positive and Negative Syndrome Scales (PANSS) and (2) the Clinical Global Impressions scale (CGI). Ratings were performed immediately prior to drug administration and at 30, 60, and 120 minutes after drug dose. Other outcomes measured included time to sedation, time to awakening, need for repeat doses, drug crossovers, adverse events, and side effects. Sixty subjects were enrolled, comprising 39 men and 21 women. The mean age was 37.5 years, with a range of 19 to 58 years. The admitting diagnoses were primarily psychosis NOS.

No significant difference was found in the ratings of agitation or psychosis at the time of entry into the study. As determined by improvement in PANSS scores, both groups of patients improved significantly over time, with no between-group differences emerging (Figure 1). Response did not vary by patient sex. Similar findings were noted with CGI data (Figure 2). One patient who was enrolled in the risperidone group subsequently received intramuscular haloperidol after 1 hour owing to lack of control of agitation. One dystonic reaction was recorded within 24 hours in the haloperidol group. No adverse outcome was reported in the risperidone group.

Oral risperidone and lorazepam appeared to be as effective as haloperidol when given in combination with a benzodiazepine. Improvement was, however, dependent on patient acceptance of oral medication, and the overall rate of acceptance could not be calculated in this pilot study. Nonetheless, these data suggest that oral atypical antipsychotic medications may be safer than and as effective as current practice for at least a significant subgroup of patients normally treated intramuscularly.

Figure 3. Flow Chart for "Rapid Tranquilization" of Agitated and Apparently Psychotic Patients[a]



[a]Adapted from Hillard,[27] with permission.

CONCLUSIONS

The decision of type, route, and dose of medication chosen in the PES has implications that extend long beyond the relatively brief period of time the patient spends in the emergency setting. The availability of new drugs to treat psychotic agitation will allow us to rethink our approach. A growing body of literature supports the use of atypical antipsychotic medications for control of agitation.[26] However, the usefulness of these medications in the PES has been largely unexplored.

Tremendous variability exists in approach to agitation, both across geographic regions and across providers within regions. A discrepancy exists between what emergency psychiatrists suggest is best practice and what they actually do in the real-world setting. This discrepancy may be prompted by a reliance on the intramuscular route of administration.

In many settings, intramuscular medications are first-line treatment for agitation with or without psychosis. Figure 3, adapted from Hillard,[27] suggests an algorithm for treating agitation in the PES environment. As always, verbal interventions should precede more intensive interventions. For safety of both staff and patients, in the author's view physical restraints should be applied prior to involuntary medication administration. Use of benzodiazepines in clinically effective doses is advisable for agitated patients whose behavior is not very likely due to psychosis. In psychotic individuals, combination of an oral atypical antipsychotic with a benzodiazepine may be preferred. If intramuscular medications are necessary, typical neuroleptics such as haloperidol or droperidol remain available. Hopefully, with the advent of short-acting intramuscular atypical agents, the older drugs will be completely supplanted.

There will most likely always be a subset of agitated patients for whom parenteral treatment is the only feasible alternative. However, in many PES environments, the emphasis on immediate behavioral control promotes an overreliance on intramuscular medications. Whatever the medication and route of administration, an attempt to engage a patient in a dialogue about medication choice can set a tone of respect and cooperation that becomes increasingly important as treatment progresses.

Drug names: clozapine (Clozaril and others), diphenhydramine (Benadryl and others), haloperidol (Haldol and others), lorazepam (Ativan and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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

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