# Managing the Agitated Psychotic Patient: A Reappraisal of the Evidence

Michael H. Allen, M.D.

Under intense public pressure, regulatory agencies have recently defined circumstances in which medications will be considered a form of restraint, so-called "chemical restraint." This article proposes that the emergency management of the agitated patient be viewed as a brief departure from the usual physician-patient collaboration. Viewed in this way, the goal is simply to terminate the emergency in the manner most likely to be acceptable to patients and conducive to a more typical dialogue. To that end, the author reviews all controlled studies of medication treatment of agitation that have appeared in English since the advent of the neuroleptic medications. Issues of diagnosis, relative efficacy, dosage, route, onset, offset, safety, tolerability, and consumer preference are considered.

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Anyone who has ever witnessed a combative patient being placed into restraint and forcibly medicated must admit that it is a frightening exercise of power. Similar behavior in other settings might well be viewed as battery. Providers tend to think of physical restraint and involuntary medication as part of their therapeutic armamentarium as reflected in professional publications such as the American Psychiatric Association (APA) Task Force Report on Seclusion and Restraint.[1] However, the Medical Directors Council of the National Association of State Mental Health Program Directors (NASMHPD) has stated: "Seclusion and restraint should be considered a security measure, not a form of medical treatment" that should be used only as a "last resort measure."[2] In an extensive review of the literature, Fisher[3] concluded that restraint and seclusion "work" in the limited sense that they "can prevent injury and reduce agitation," but Fisher, the New York State Commission on Quality of Care,[4] NASMHPD, and others[5] have also described deleterious effects on patients, who perceive such measures to be coercive and traumatic. Contributing to the perception that at least some use of restraint and seclusion is unnecessary is the finding by Way and Banks[6] of wide variability in its utilization across sites that can be accounted for by institutional culture but not by patient factors.

While the value and frequency of restraint and seclusion have been questioned for some time, the traumatic aspects of these practices only recently captured the public's imagination. The focus of the New York State Commission on Quality of Care's report in 1994[4] was 111 fatalities over a 10-year period in New York facilities, but the most recent controversy was sparked by a dramatic series published in 1998 by the *Hartford Courant*. Entitled "Deadly Restraint," this series of articles provided vivid reporting of 142 deaths over a similar period nationwide and estimated that 50 to 150 such deaths occur each year.[7] This was soon followed by further reports from the National Alliance for the Mentally Ill (NAMI),[8] and the resulting groundswell became the impetus to federal and state legislative and regulatory efforts explicitly directed at reducing the use of restraint and seclusion.

In this context, the U.S. Health Care Finance Administration's (HCFA) new interim final rules[9] concerning restraint also define medications as a form of restraint under some circumstances. As such, "chemical restraint" is subject to the same regulation as physical restraint. According to 42 CFR 482.13(e), "A drug used as a restraint is a medication used to control behavior or to restrict the patient's freedom of movement and is not a standard treatment for the patient's medical or psychiatric condition."[9] A subsequent HCFA bulletin[10] (intended "for guidance only" pending interpretive guidelines) seems to suggest that the distinction between treatment and "chemical restraint" depends on the extent to which the patient has been assessed and medication prescribed as a part of a plan of care. Patient participation in the planning and conduct of treatment and the right to refuse unwanted treatment are central premises of the regulations. Medications

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prescribed prior to assessment, as often occurs early in an episode of emergency or acute inpatient care, would therefore seem to be classified as restraints.

Behavioral emergencies are not rare events. There are approximately 135,000 psychiatric emergency visits per year in New York state alone.[11] In 1983, one psychiatric emergency service survey reported that 15.6% of patients were restrained.[12] In a more recent survey of psychiatric emergency service medical directors, the mean ± SD rate of restraint for the 46 services was 8.4% ± 7.8%.[13]

Under these circumstances, it seems appropriate to review what is known about the pharmacologic management of agitation and examine the current standard of practice in light of rising demands for a more patient-centered approach to the management of behavioral disturbances.

## THE EVIDENCE BASE

Studies of agitation are ethically difficult to justify and practicably difficult to conduct. Hence, the number and design of studies are limited given the importance of the topic. For this reason, a number of open studies are included in Table 1.[14–36] For studies to be considered in this review, subjects had to be described as agitated, treatment had to be rendered immediately, and reassessment had to occur in minutes to a maximum of 2 hours for a total duration usually of 6 hours or less. An electronic search of the English-language literature from 1960 to 1990 was conducted using MEDLINE with the main search terms *agitation*, *psychiatric emergency*, and *chemical restraint.* Experts were also consulted for articles on the topic. These search methods were supplemented by manually searching relevant articles for additional references.

A total of 24 relevant studies met criteria for review. A typical study of this type includes subjects who have a mixture of diagnoses usually established post hoc with varying degrees of rigor. Most compare presumably equivalent fixed doses of 2 medications repeated at fixed intervals until a specified endpoint is achieved, a specified total is administered, or serious adverse events occur. Of these 24 studies, 18 were double blind, but only 2 were placebo controlled. The total number of subjects was 1143, but with 11 active compounds and placebo, the median number of subjects per treatment condition was only 15. Only 33 subjects received placebo, and the last study to use placebo was in 1977.

At this time, second generation antipsychotics are considered first-line treatments for the major psychoses, and a number of newer agents are in clinical trials. Of the newer agents, none are available in a parenteral form or have published data concerning their use in behavioral emergencies. None appears close to U.S. Food and Drug Administration (FDA) approval at this time, so this discussion will be largely restricted to available agents with significant published data.

### Defining and Measuring Agitation

One way of approaching the problem of agitation is to understand it as a temporary disruption of typical physician-patient collaboration. Understood in this way, target symptoms associated with agitation interfere with assessment and treatment during a period when immediate treatment is necessitated by dangerous behavior or the warning signs of such behavior. The result is that the physician must rapidly choose a strategy with little or no input from the patient, which is an undesirable situation for all concerned. The goal then is to do only what is necessary to assure the safety of the patient and others and facilitate resumption of more normal relations as soon as possible so as to understand the problems and chart the subsequent course together in the usual fashion.

While the cluster of signs and symptoms that mark agitation is easily described, appropriate endpoints are more difficult to specify. Sleep is sometimes treated as an endpoint, but sleep is not a guarantee of safety, and if the goal is patient participation in assessment and treatment planning, sleep delays rather than improves care. The literature distinguishes between mere somnolence and calming. Patients may be sleepy but still show signs of agitation or sleep soundly only to arouse in an agitated state. Ideally, they become more placid but alert and cooperative without falling asleep. For the purposes of this discussion, somnolence will generally be viewed as undesirable. Studies have only rarely measured both behaviors associated with agitation and simultaneously rated the patients' alertness in an effort to tease them apart.

A variety of other measures have been used in studies to measure agitation including the Brief Psychiatric Rating Scale (BPRS), Overt Aggression Scale, Agitated Behavior Scale, and modified versions of those instruments. Total BPRS is the most commonly reported measure, but is probably not the best measure. In 6 studies,[17,27,28,30,34] only idiosyncratic global measures were employed, and sedation and calming may have been conflated. Recently, investigators have begun reporting scores for the 10 items of the Positive and Negative Syndrome Scale (PANSS) described as the excitement/hostility component.

### Drug Selection

The selection of an agent for the management of an episode of agitation might be based on diagnostic or etiologic considerations, differences in effectiveness or side effects of candidate drugs, or, more pragmatically, the formulation of a drug as it affects route of administration, onset, and duration.

### Diagnosis

As noted, studies of agitation typically include a mix of functional diagnoses, and in recent years, substance abusers. Diagnosis has not been found to predict response

**Table 1. Management of Agitation[a]**

| Study | Design | Drugs[b] | N | Measures | Outcome |
|---|---|---|---|---|---|
| Man and Chen, 1973[14] | Double blind | Haloperidol, 5 q 30 min<br>Chlorpromazine, 50 q 30 min | 15<br>15 | BPRS, Target Symptom Rating Scale, Global improvement | Equally effective: haloperidol, 124 min, chlorpromazine, 149 min; chlorpromazine, 50 mg, resulted in 2 cases of near-fatal hypotension |
| Reschke, 1974[15] | Random, double blind | Haloperidol, 1 q 30 min<br>Haloperidol, 2 q 30 min, mean = 3.7 doses, 7.4 mg<br>Haloperidol, 5 q 30 min<br>Chlorpromazine, 25 q 30 min<br>Placebo, q 30 min | 8<br>11<br>10<br>10<br>11 | Global (5-pt) scale, BPRS | Improvement in BPRS: placebo, 10%; chlorpromazine, 21%; haloperidol, 1 mg, 23%; haloperidol, 2 mg, 36%; haloperidol, 5 mg, 42%<br>Haloperidol, 2 or 5 mg > haloperidol, 1 mg, chlorpromazine, placebo ($p < .05$) |
| Anderson et al, 1976[16] | Random, rater blind | Haloperidol, 5 q 30 min, mean = 13 mg<br>Haloperidol, 5 plus 10 q 30 min, mean = 33 mg | 10<br>14 | BPRS | NS |
| van Leeuwen et al, 1977[17] | Prospective, random, double blind | Droperidol, 10 iv<br>Placebo, iv | 19<br>22 | Additional medication required at 3 min post blind medication | 6 droperidol vs 19 placebo ($p < .001$) required additional medication |
| Gerstenzang and Krulisky, 1977[18] | Prospective, double blind | Haloperidol, 5<br>Chlorpromazine, 50 | 30<br>28 | Global (4-pt) scale, BPRS at 60 min | 15 haloperidol patients' good control vs 3 chlorpromazine patients, ($p < .05$); 5 BPRS items: haloperidol > chlorpromazine ($p < .05$) |
| Fruensgaard et al, 1977[19] | Random, double blind | Haloperidol, 5 q 6 h<br>Loxapine, 50 q 6 h | 15<br>15 | Sleep, agitation (4-pt), aggression (4-pt) scales, CGI, BPRS | Sleep: loxapine > haloperidol, ($p < .01$); on agitation, aggression scores, loxapine had maximum benefit at 2 h, haloperidol at 6 h |
| Paprocki and Versiani, 1977[20] | Consecutive admission, double blind | Haloperidol, 2.5–5 q 6 h, mean = 11.5 mg<br>Loxapine 25–50 q 6 h, mean = 115.4 mg | 18<br>17 | BPRS, NOSIE, CGI | NS |
| Stotsky, 1977[21] | Random, double blind | Haloperidol, 4 or 8, mean = 15<br>Thiothixene, 4 or 8, mean = 10.1 | 15<br>15 | BPRS, Target Symptom Profile | NS |
| Neborsky et al, 1981[22] | Random, double blind | Haloperidol, 2 q 1 h, mean = 9.6<br>Haloperidol, 10 q 1 h, mean = 41 | 10<br>10 | BPRS, global (4-pt) scale | Single-dose haloperidol 10 mg > 2 mg ($p < .05$), on endpoint BPRS, low-dose had 37.7% reduction, high-dose had 45.2%, NS |
| Binder et al, 1981[23] | Random, double blind | Molindone, 25<br>Haloperidol, 5 | 11<br>13 | BPRS | NS |
| Resnick and Burton, 1984[24] | Random, double blind | Haloperidol, 5 im q 30 min<br>Droperidol, 5 im q 30 min | 16<br>11 | Additional medication for BPRS > 17 | 81% haloperidol vs 36% droperidol received additional medication ($p < .05$) |
| Dubin and Weiss, 1986[25] | Random, modified double blind | Loxapine, 25 q 30 min, mean = 75<br>Thiothixene, 10 q 30 min, mean = 31 | 30<br>28 | BPRS, CGI | Mean time to endpoint: loxapine 60 min, thiothixene 95 min ($p = .001$)<br>60 min, 60% loxapine vs 14% thiothixene ($p = .001$),<br>90 min, 79% loxapine vs 50% thiothixene |
| Tuason, 1986[26] | Parallel, double blind | Haloperidol, 5 and 2.5 or 5 q 60 min, mean = 25<br>Loxapine, 25 and 12.5 or 25 q 60 min, mean = 83 | 27<br>25 | BPRS items, CGI | NS |
| Garza-Trevino et al, 1989[27] | Open, random | Haloperidol, 5<br>Lorazepam, 4<br>Combination | 21<br>23<br>24 | VAS | Combination > haloperidol or lorazepam alone ($p < .05$) |
| Garza-Trevino et al, 1989[27] | Open, random | Haloperidol, 5, plus phenobarbital, 130<br>Thiothixene, 5, plus lorazepam, 4 | 27<br>26 | VAS | NS |

**Continued on next page**

**Table 1 (continued). Management of Agitation[a]**

| Study | Design | Drugs[b] | N | Measures | Outcome |
|---|---|---|---|---|---|
| Wyant et al, 1990[28] | Random | Haloperidol, 10<br>Midazolam, 5<br>Amobarbital, 250 | 5<br>5<br>5 | Motor agitation, hostility | Midazolam, amobarbital > haloperidol for motor agitation |
| Salzman et al, 1991[29] | Prospective, double blind | Haloperidol, 5<br>Lorazepam, 2 | 30<br>30 | OAS, BPRS | Aggression: lorazepam > haloperidol ($p < .01$) |
| Thomas et al, 1992[30] | Prospective, random, double blind | Haloperidol, 5<br>Droperidol, 5<br>Haloperidol, 5 iv<br>Droperidol, 5 iv | 21<br>25<br>12<br>9 | 5-pt combativeness scale | Droperidol im superior at 10, 15, and 30 but not 60 min<br>iv, NS |
| Chouinard et al, 1993[31] | Random, double blind | Clonazepam, 1–2<br>Haloperidol, 5–10 | 8<br>8 | IMPS, CGI | Endpoint, NS<br>Haloperidol faster than clonazepam |
| Battaglia et al, 1997[32] | Prospective, random, double blind | Haloperidol, 5<br>Lorazepam, 2<br>Haloperidol, 5, plus lorazepam, 2 | 35<br>31<br>32 | ABS, CGI, BPRS, Alertness | ABS, combination > lorazepam at 1 h only ($p = .014$), combination vs haloperidol, NS<br>Total doses, NS |
| Foster et al, 1997[33] | Random, double blind | Lorazepam 2 po concentrate or im q 30 min, mean = 3.64<br>Haloperidol, 5 po concentrate or im q 30 min, mean = 11.25 | 17<br>20 | BPRS, CGI<br>BPRS | CGI: lorazepam > haloperidol<br>NS |
| Richards et al, 1998[34] | Open, prospective, random | Lorazepam, 2 iv (< 50 kg), lorazepam, 4 iv (> 50 kg)<br>Droperidol, 2.5 iv (< 50 kg), droperidol, 5 iv (> 50 kg) | 100<br>102 | Global (6-pt) scale (1–2 = sleep) | Droperidol > lorazepam at 10, 15, 30, 60 min ($p < .001$)<br>8 droperidol-treated patients received additional medication vs 40 lorazepam-treated patients<br>Total emergency department time, droperidol 5.9 h < lorazepam 8.6 h ($p < .001$) |
| Bienek et al, 1998[35] | Random, double blind | Lorazepam, 2<br>Lorazepam, 2, plus haloperidol, 5 | 11<br>9 | OAS, VAS, CGI | Lorazepam + haloperidol > lorazepam, OAS ($p = .03$) and VAS ($p = .04$) |
| Dorevitch et al, 1999[36] | Random, double blind | Flunitrazepam, 1<br>Haloperidol, 5 | 15<br>13 | OAS, BPRS, CGI | OAS, flunitrazepam > haloperidol at 15, 30 min ($p < .01$) |

[a]Abbreviations: ABS = Agitated Behavior Scale, BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impressions scale, IMPS = Inpatient Multidimensional Psychiatric Scale, NOSIE = Nurses' Observation Scale for Inpatient Evaluation, OAS = Overt Aggression Scale, VAS = visual analog scale.
[b]mg i.m. unless i.v. indicated.



in studies of this type. Studies of agitation in homogeneous populations comparing different classes of agents are very limited. Available data would suggest that delirium should be approached according to the underlying etiology, if known. Delirium in the medically ill is generally treated with high-potency neuroleptics. Breitbart and colleagues,[37] for example, found neuroleptics superior to lorazepam in both efficacy and side effects in a prospectively defined group of patients with acquired immunodeficiency syndrome (AIDS) delirium.

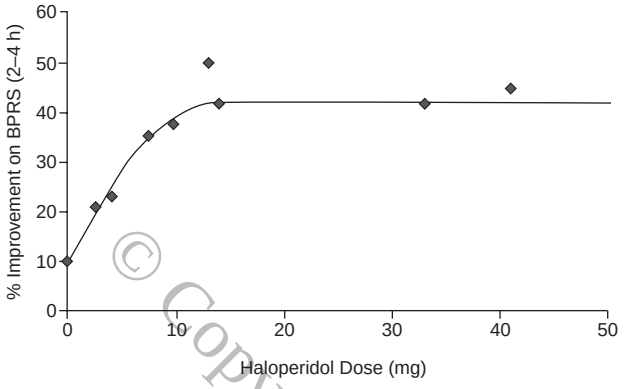
Alcohol withdrawal is another case in which diagnosis is highly relevant. The APA Practice Guideline for the Treatment of Substance Use Disorders[38] recommends benzodiazepines for alcohol withdrawal states, and the HCFA bulletin[10] previously mentioned offers the use of benzodiazepines in behavior disturbances associated with alcohol withdrawal as an example of appropriate use of medications for treatment rather than restraint.

Some substances of abuse, particularly hallucinogens, and many medications have anticholinergic properties that contribute to their toxicity. Antipsychotics should be avoided in suspected anticholinergic delirium owing to their own anticholinergic side effects or the need to use anticholinergic medications for extrapyramidal symptoms (EPS) if they develop. Cocaine toxicity also includes seizures, and antipsychotics are not protective against seizures as are benzodiazepines. One report[39] suggests that stimulant abuse increases the likelihood of EPS. Hence, although well-designed studies are lacking, benzodiazepines may be a more rational choice in acute substance use emergencies for reasons of both efficacy and tolerability.

## Effectiveness

There is very little evidence of differences in effectiveness that are not accounted for by dosage or kinetics. Haloperidol has been used in most studies, but a number of neuroleptic drugs including thiothixene,[21] molindone,[23] and loxapine[20,26] have been compared with haloperidol and found to be equally effective. Chlorpromazine is often mentioned for behavior disturbances because of its seda-

Figure 1. Haloperidol Dose-Response Curve[a]




[a]Adapted from Baldessarini et al.[43] Abbreviation: BPRS = Brief Psychiatric Rating Scale.

tive side effects. However, haloperidol is superior to chlorpromazine at typical doses.[15,18]

Another alternative is droperidol, a butyrophenone approved by the FDA but available only by injection and used primarily in anesthesia. In rats, it is a more potent cataleptic than haloperidol and yet has a 10-fold higher median lethal dose.[40] Anecdotally, droperidol has strong support as a calming agent in behavioral emergencies. One of the few placebo-controlled studies[17] in the literature has also demonstrated the effectiveness of droperidol for agitation. However, there are only 3 comparative studies, all flawed.[24,30,34] The largest prospective, randomized study[34] of agitation is one that compares droperidol to lorazepam. Unfortunately, the study was open label and used only a single idiosyncratic rating of improvement, need for additional medication, and total time in the emergency department as outcomes. A similar study[24] used the total BPRS score as the criterion for additional medication, but again reported only the numbers of additional injections. Haloperidol-treated subjects required more injections to reach a BPRS of 17 or less. Thomas et al.[30] found i.m. droperidol to have a faster onset than haloperidol, but the 2 agents were equivalent at 1 hour. These studies suggest that droperidol is certainly quicker and perhaps more potent but not more efficacious (see below). Studies using droperidol have not been designed to measure the relative contribution of sedation.

More recently, benzodiazepines have achieved popularity because of their safety and tolerability. All available evidence suggests that, in this context, benzodiazepines are at least as effective as haloperidol alone. Lorazepam has received the most study,[29,32–35,41] but there are controlled data for midazolam,[28] clonazepam,[31] and recently flunitrazepam.[36] In studies that compared haloperidol, 5 mg, with lorazepam, 2 mg, lorazepam appeared equal on some measures[29,32,33] but superior on measures of aggression[29] and clinical global improvement.[33] Flunitrazepam, 1 mg, has also been reported superior to haloperidol, 5 mg, using the Overt Aggression Scale.[36] Midazolam, 5 mg, has been reported superior to haloperidol, 10 mg, on a measure of motor agitation.[28] If aggression is the main target symptom that warrants "chemical restraint" in a behavioral emergency, these studies taken together suggest that the benzodiazepines at dosages in current use may have the advantage over haloperidol. Battaglia et al.[32] found lorazepam alone more sedative than haloperidol alone.

Whatever the efficacy of single agents, the practice of combining haloperidol, 5 mg, and lorazepam, 2 mg, in the same syringe has become the most common approach to the rapid tranquilization of the agitated psychotic patient in psychiatric emergency settings.[42] Interestingly, this approach is not used in other medical settings, where it is more common to use a single agent i.v., often in doses typical of the early high-potency era.

A number of combinations have been demonstrated to be safe and effective. Two studies have compared the most popular combination of haloperidol, 5 mg, and lorazepam, 2 mg, with haloperidol, 5 mg alone, or lorazepam, 2 mg alone.[32,35] These studies found advantages in favor of the combination on some measures at some points in time, that is, more medicine was more effective, at least initially. Differences between the treatments disappeared within 2 to 4 hours, perhaps as a result of the additional doses administered in the interval. The issue of dosage, then, confounds interpretation of these studies.

## Dosage

Only 3 studies[15,16,22] have compared multiple doses of any medication for agitation. All 3 used haloperidol, and only 1 included a placebo. No dose-finding studies of benzodiazepines were identified for agitation. Baldessarini and colleagues[43] combined the 3 available studies of haloperidol[15] to produce a dose-response curve (Figure 1). Placebo produced a 10% improvement on the BPRS. Doses between 7.4 and 41 mg produced 36% to 45% improvement, and 2.5 mg and 4 mg produced intermediate response. What it suggests is that a single dose of haloperidol, 7.5 to 10 mg, might be expected to produce all the immediate benefit possible for most patients and that exceeding this dose will be associated only with additional side effects.

If the most effective dose of haloperidol is 10 mg, then perhaps the more appropriate dose of lorazepam is 4 mg. Only one study[27] has reported a dose of lorazepam other than 2 mg and that was in combination with thiothixene. Bienek et al.[35] have observed that a larger dose of lorazepam might produce effects similar to the combination treatment and went on to state that "haloperidol may be unnecessary." Studies that compare the combination of both drugs with lorazepam, 4 mg, and/or haloperidol, 10 mg, are necessary to establish the superior efficacy of

the combination, and, in the absence of such studies, the superiority of the combination should be considered unproved. It should be recalled that the major advantage of the combination when it was initially described was a reduction in side effects consequent to reduced haloperidol utilization rather than superior efficacy for agitation per se.[41]

**Onset and Route of Administration**

In addition to efficacy, time until onset is also important. In managing the agitated violent patient, faster onset may mean fewer injuries and less time in restraint. Shorter transit time in the emergency setting should also be associated with reduced emergency service utilization and more rapid access to the next appropriate level of care. Intravenous administration is associated with onset in 1 to 5 minutes for most compounds, but i.v. care is available in a small minority of psychiatric settings.[13] Intramuscular administration is generally slower than i.v., but droperidol is an exception. Droperidol i.m. is absorbed so rapidly that there is little difference between i.m. and i.v. administration.[44] Thomas et al.[30] reported statistically significant differences between i.m. droperidol and i.m. haloperidol after only 10 minutes. Onset of haloperidol i.m. is usually given as 30 to 60 minutes, and Thomas et al.[30] found the effect of haloperidol was still rising at 1 hour while the offset of droperidol was beginning. Total time in the emergency department was significantly less for droperidol-treated subjects at 5.9 hours versus 8.6 hours for lorazepam. This rapid and profound effect accounts for the popularity of droperidol in some parts of the country. However, it cannot be thought of as a part of the usual treatment of any psychiatric condition, which, despite its advantages of relative safety and rapid onset and offset, seems to cast it as a "chemical restraint."

Intramuscular absorption of lorazepam and midazolam is also rapid and complete, with onset at 15 to 30 minutes. Midazolam is water soluble and can also be administered intranasally. Intramuscular diazepam and chlordiazepoxide are absorbed slowly and erratically and are not recommended for this use.[45] Clonazepam i.m., by contrast, appears to be slower in its onset than haloperidol i.m., at least in manic patients, the only population in which it has been studied.[31] In general, oral benzodiazepines are also rapidly effective. In fact, the abuse potential of diazepam is related to its rapid absorption and sharp onset. The onset of action of oral haloperidol is significantly slower than that of oral benzodiazepines and should be considered last if speed is an issue.

Rapid offset is usually less desirable. Assessment, transfer, and adjustment to another setting must occur, and offset of the initial treatment during that process may subject patients and staff in the next care setting to another episode of agitation perhaps requiring additional physical restraint. While droperidol allows for quick movement, the downstream effects have not been studied. It is the author's impression that droperidol benefits the initial treatment setting, but may leave the patient uncovered during transfer and admission to subsequent services. Haloperidol and lorazepam have a more suitable duration of action. Clonazepam has an even longer half-life and is often recommended for manic patients, who predictably require repeated administration of benzodiazepines.

**Cooperation**

With the exception of droperidol, the therapeutic differences between the i.m. and p.o. routes are relatively minor. The major advantage of the i.m. route is in involuntary treatment. Currier (elsewhere in this issue)[46] has found that most agitated patients will assent to oral medication and, in a survey of 51 psychiatric emergency services, the medical directors estimated that only 1 in 10 emergency patients require an injection.[13] HCFA regulations concerning "chemical restraint" call for it to be a last resort, which would suggest that oral medication should be offered whenever it is possible to speak with the patient.

A final concern, then, is the patient who appears to accept oral medication but does not swallow it, so-called "cheeking." Foster et al.,[33] in a study comparing haloperidol with lorazepam, used both i.m. and oral concentrate and found no significant difference between the 2 routes of administration. In light of the relatively minor advantages of injections against the serious concerns of patients regarding that route of administration, Dubin and Feld[47] have argued in favor of oral concentrates. At this time, only risperidone of the second generation antipsychotics is available in this form, and in one study, the combination of oral risperidone concentrate and lorazepam was found to be equivalent in efficacy to i.m. haloperidol and lorazepam.[46]

**Frequency**

One difficulty in discussing dosage for behavioral emergencies is that the endpoint is an ill-defined target. Undertreatment is associated with continued risk, while most emergency psychiatrists agree that inducing sleep in patients is also undesirable.[13] In controlled studies utilizing blinded raters and criteria for repeated administration, the majority of subjects receive multiple injections, usually at 60-minute intervals, up to 6 injections in the study described by Battaglia and colleagues,[32] for example. Despite multiple injections of haloperidol, lorazepam, and the combination, all 3 groups averaged about the same rate of improvement, 40%, within several hours. This finding is strikingly consistent with Baldessarini and colleagues'[43] conclusions about the haloperidol dosage described above. Again, droperidol is an exception. Richards et al.[34] found that only 8% of droperidol-treated patients required a second injection versus 40% for lorazepam-treated subjects.

In contrast, in clinical settings, it is relatively rare that patients receive multiple injections for a single episode of

agitation. A number of factors possibly contribute to this difference. The initial response in the emergency setting may be partial but clinically adequate to achieve cooperation with further assessment and treatment. However, this partial response will often decay over the ensuing hours, and more serious agitation may erupt again later. It is also possible that appropriate staff are not available or that physical restraints are used instead of medications. Reassessment should occur every 15 minutes for patients in restraints and approximately 30 minutes after i.m. administration and 30 to 60 minutes after oral administration of medications. Onset should occur within these times. Nonresponders should receive additional medication promptly. Oral concentrate should be offered regularly for any residual symptoms, and vigilance should be maintained for the reemergence of agitation. Early intervention with oral medication as often as every few hours can prevent escalation to the point of another emergency requiring injection.

### Safety and Tolerability

Since differences in efficacy and onset are slight, side effects become a major consideration. Differences in side effects are substantial and important to patients. In one study[48] of hospitalized patients, side effects were given as the major reason for refusing medications. Kissling[49] considers side effects an important factor in the roughly 3-fold increase in relapse of schizophrenic patients in routine care compared with the lower rate in controlled studies. Barbiturates, although still used commonly elsewhere, are no longer recommended in the United States because of their more general depressant effects, particularly on respiration. In the earliest study in this review, Man and Chen[14] reported that 2 of 15 subjects given 50 mg of chlorpromazine i.m. suffered near-fatal hypotension.

High-potency neuroleptic drugs are generally viewed as much safer than low-potency neuroleptics and barbiturates. Neuroleptic malignant syndrome (NMS) occurs with a frequency of perhaps 1%, and torsades de pointes is quite rare. NMS is of particular concern in highly agitated patients with poor hydration restrained in poorly ventilated holding areas. Less lethal but more common, EPS are a significant cause of patient distress and medication refusal. Van Putten[50] found that 67% of patients who were reluctant to take antipsychotics had akathisia compared with 2% of those who were more agreeable. Weiden et al.[51] found that routine clinical care identified only a quarter of the EPS detected by systematic examination of the same patients. In a recent review of the efficacy and safety of droperidol, Chambers and Druss[40] concluded that side effects similar to those of other typical neuroleptics occur at a comparable or perhaps lower rate because of its short half-life. Akathisia is the most worrisome because it is common and may worsen agitation.[52] One of the major advantages of newer antipsychotics is a lower rate of these troubling side effects.[53]

Benzodiazepines have excellent safety records compared with neuroleptics. Concerns expressed with benzodiazepines have not been well documented and remain more anecdotal or theoretical. One is "disinhibition." This refers to the potential release of impulsive behavior that might otherwise have been blocked. Cowdry and Gardner[54] found that chronic alprazolam worsened the behavior of a group of patients with borderline personality disorder. However, Rothschild[55] has stated in a comprehensive review of this issue that "there is no evidence that [any benzodiazepine] will make somebody do something out of their ordinary behavior." It may be that the accumulation of benzodiazepines in vulnerable patients is associated with behavioral toxicity, but worsening has not been noted in acute trials in emergency settings.[56]

Another concern with the benzodiazepines is respiratory depression when combined with alcohol or other sedatives. This has been a particular concern with midazolam.[57] Midazolam is unique in that it is water soluble and can be administered intranasally, and it has been widely used in a variety of settings. A retrospective review[58] of 389 cases of midazolam use in one emergency department for a variety of indications including behavioral emergencies found 2 cases of respiratory depression, both in patients also receiving fentanyl. The respiratory depression was reversed by naloxone, and there were no long-term adverse consequences. There were also 2 brief hypotensive episodes possibly attributable to other medications present. Clearly, careful monitoring is indicated, but benzodiazepines appear to be remarkably safe in appropriate settings.

A final concern about benzodiazepines is dependence liability, but again, this would not appear to be an important consideration for the brief periods under discussion. Certainly, if a patient in recovery from addiction expresses concern and requests an alternative, that request should be respected.

An interesting question that has not been addressed to the author's knowledge is the relative safety of medications and physical restraint. Medications would appear to be much safer and capable of reducing the use of the more hazardous restraint and seclusion. Way and Banks[6] found, though, that measures of medication use and restraint and seclusion use were not correlated at the institutional level. Further study of the interaction of medication and physical restraint is clearly warranted.

## DISCUSSION

It is important to remember that the studies cited here did not occur in a vacuum. Historically, the treatment of the agitated patient has evolved through several stages of social as well as technological change. In the early phenothiazine period, side effects of the low-potency neurolep-

tics limited the dosage that could be administered safely. Later, with the advent of the high-potency neuroleptics, much higher doses were possible. This period was characterized by poor understanding of the neuroleptic dose-response relationship and produced concepts such as "psychotolysis"[59] and "rapid neuroleptization."[60] It is now known that only 60% to 70% dopamine-2 ($D_2$) receptor binding is required for the specific antipsychotic effect of neuroleptics in schizophrenia and that $D_2$ blockade is simply the first step in a complex cascade of events.[61] Lower doses of neuroleptics are now recommended for mania as well.[62] The strategy of more moderate doses of neuroleptics such as haloperidol, 5 mg, repeated at frequent intervals was shown to be equally effective with fewer side effects. This practice came to be known as "rapid tranquilization" and tended to result in lower total daily doses of neuroleptics on the order of 15 to 20 mg of haloperidol per day.

Benzodiazepines were then introduced into this practice environment, characterized by what we would now see as lower but still high total daily doses of high-potency neuroleptics. Benzodiazepines were coadministered with neuroleptics, further reducing the total daily dose. This treatment was shown to be as effective as a neuroleptic alone with a reduction in side effect burden.[63]

This certainly represents progress from the provider's point of view when compared with high-dose rapid neuroleptization. However, in the era of second-generation antipsychotics and consumer empowerment, the use of typical neuroleptics is no longer consistent with best practices for any of the major conditions contributing to agitation,[64] nor does it comport with the current emphasis on patient rights. According to a survey of patient preferences in a psychiatric emergency service,[65] patients favored medication over restraint or seclusion by a 2:1 margin. Their first choice was benzodiazepines, and few patients ranked benzodiazepines last. By contrast, neuroleptics were the last resort for almost one third of respondents.[65] Interestingly, no clinical trial has attempted to gather information about subjective experience or patient preference. If most patients prefer benzodiazepines in this situation, then there should be significant evidence in favor of other strategies to overcome this preference.

On the basis of available evidence, it would appear that lorazepam alone is superior to haloperidol alone for agitation. It is specifically superior to haloperidol for the target symptom of aggression. The 2 studies[32,35] that purport to show the superiority of the combination of haloperidol and lorazepam to either one alone did not use comparable doses and at most can be said to demonstrate that the combination is better in the first few hours. It may well be that an equivalent initial dose of lorazepam would have eliminated these differences as well.

The focus on evidence pertaining to relative efficacy should not obscure the more important question of effectiveness. After all, this discussion is related to generally brief phases of illnesses that often require a lifetime of care. After terminating the behavioral emergency, the patients' attitudes toward treatment and caregivers will likely have a much greater effect on functional outcome than the modest pharmacologic differences that have been demonstrated.

The circumscribed goal in a behavioral emergency is termination of the emergency and resumption of a more typical physician-patient relationship with its emphasis on informed consent and long-term outcome. In the minority of cases where an injection is required, the least offensive medication should be used. If and when a condition is diagnosed for which an antipsychotic is indicated, atypical antipsychotics have significant advantages over typical neuroleptics in reducing both the positive symptoms and the hostility that tend to drive hospitalization.[66] Patients should be offered choices, taking into consideration such long-term consequences as tardive dyskinesia and weight gain. Where additional sedation is required, a benzodiazepine can be made available in addition to the antipsychotic medication.

Since dose-finding studies for the available medications for the indication of agitation are inadequate, future studies should begin with dose finding rather than relying on assumptions about equivalence based on other target symptoms. Perhaps most importantly, consumer preferences need to be explored and taken into consideration. Studies designed to measure the effect of different medication strategies on utilization of restraint and seclusion are indicated. As new and "better" injectable medications come to market, forcible medication should not be used as a substitute for talking with patients in crisis.

*Drug names:* alprazolam (Xanax and others), amobarbital (Amytal), chlordiazepoxide (Librium and others), chlorpromazine (Thorazine and others), clonazepam (Klonopin and others), diazepam (Valium and others), haloperidol (Haldol and others), lorazepam (Ativan and others), loxapine (Loxitane and others), midazolam (Versed), molindone (Moban), naloxone (Narcan and others), risperidone (Risperdal), thiothixene (Navane).

*Disclosure of off-label usage:* The author of this article has determined that, to the best of his knowledge, droperidol, lorazepam, and midazolam are not approved by the U.S. Food and Drug Administration for the treatment of agitation and psychosis.

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