Emergency Treatment of Acute Psychosis

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The author reviews the evolution of emergency psychiatric practice over the past 20 years—from the concept of high-dose antipsychotic medication to the more rational treatment approach for acute psychosis made possible by modern pharmacodynamic insight and the availability of new pharmacotherapeutic agents. A decision tree for current practice in the rapid tranquilization of agitated, apparently psychotic patients is described. *(J Clin Psychiatry 1998;59[suppl 1]:57–60)*

A major impetus for the founding of psychiatric emergency services 20 or 30 years ago was the concept of "rapid tranquilization."[1] The concept was that patients would come in to an emergency service, acutely psychotic, would be given high doses of antipsychotic medication, and would be able to leave the emergency room well enough compensated to avoid hospitalization. Over the years, the limitations to this concept have become increasingly apparent, but modern understanding of pharmacodynamics and the availability of new pharmacotherapeutic agents now allow a more rational treatment approach for acute psychosis. Unfortunately, many clinicians are still using outdated approaches, such as high-dose conventional antipsychotics, rather than more rational treatment approaches. This paper will review the development of emergency psychiatric practice over the last 20 years and will describe a decision tree for rational current practice.

TWENTY YEARS AGO

Twenty years ago was the golden age for high-dose antipsychotics. Some studies used doses equivalent to 1000 mg of haloperidol.[2] Doses of 100 mg were relatively common in clinical practice.[3] This was also a time when many psychopharmacologists recommended against routine use of anticholinergic agents.[4] Not surprisingly, this era led to an enormous number of dystonic reactions, and even today, it is frequent to meet patients who believe that they are "allergic" to haloperidol because of the extreme extrapyramidal reactions they may have had in the past. A frequent practice at that time was to give repeated doses of antipsychotic every 30 minutes or even every 15 minutes until the patient was tranquilized or asleep.[3]

TEN YEARS AGO

Table 1 lists several synonyms which have been used to describe the acute treatment of psychotic episodes. Only one of these synonyms has withstood the test of time. Both rapid *neuroleptization* and *psychotolysis* imply that these psychoses are being rapidly made to vanish by treatment with antipsychotic medications. In fact, clinical experiences have not proven this to be the case. Patients who are acutely tearing up an emergency room because they are hearing voices will, after treatment with antipsychotic medications, usually become less agitated, less hostile, and less suspicious, but will generally still describe hearing voices, although they will usually say the voices are less loud, less frightening, or easier to ignore.[5] *Rapid digitalization* describes the attractive, but completely discredited, notion that antipsychotic medications can be dosed like digitalis such that a high loading dose can be followed by a lower maintenance dose, giving rise to a faster onset of action. Unfortunately, studies have been very consistent in demonstrating that higher doses initially, in fact, do not lead to a more rapid response.[6] *Chemical restraint* is probably the least appropriate term to use for medicolegal as well as for clinical reasons. Court decisions about the appropriate use of seclusion and restraint have been quite variable in their exact stipulations, but have been remarkably consistent in mandating that chemicals be used for treatment, rather than restraint, of patients.[7] The only term which has stood the test is the most modest, that is, *rapid tranquilization*, which implies giving patients medication to make them less agitated and hostile.

Given this relatively modest definition of rapid tranquilization, we are left with the questions of what drugs to use, how much, by what route, and for how long. Any of the high-potency antipsychotics (e.g., fluphenazine, haloperidol, loxapine, thiothixene, trifluoperazine) will give

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Table 1. Synonyms for Rapid Medication of Psychotic Patients

Rapid tranquilization
Rapid neuroleptization
Rapid digitalization
Psychotolysis
Chemical restraint

Table 2. Scorecard Comparing Haloperidol and Lorazepam for Treatment of Acute Psychosis*

Effect	Lorazepam	Haloperidol
Safe, even in the medically ill	Yes	Yes
Minimal postural hypotension	Yes	Yes
No major drug interactions	Yes[a]	Yes
Controls agitation	Yes	Yes
Specific for psychosis	No	Yes
Extrapyramidal reactions	No	Yes
Respiratory depression	Possible[b]	No
Paradoxical hostility	Maybe	No

*Adapted from reference 8.
[a]Some additive effect with other sedatives.
[b]Respiratory depression possible with high or repeated doses.

adequate sedation without excessive side effects. Benzodiazepines can achieve the same results. Twenty years ago, when the hope was that psychosis would be "lysed" in the emergency room, benzodiazepines were not ordinarily considered. By 10 years ago, however, with the general understanding that our goal in treatment was tranquilization rather than elimination of the psychosis in the short run, benzodiazepines were considered an appropriate alternative choice.[5,6] Table 2 shows a scorecard comparing lorazepam with haloperidol. Both of these drugs are safe even in medically ill patients and have no major drug interactions, which is desirable since many patients who need to be rapidly tranquilized are not able to give a reliable history. Both cause minimal postural hypertension and control agitation. Benzodiazepines, of course, do not cause extrapyramidal reactions and also are not associated with neuroleptic malignant syndrome, a complication which was well known by 10 years ago and which may be associated with high or rapidly escalating doses of antipsychotic medications.[9] The two major potential drawbacks of benzodiazepines are the possibility of respiratory depression when given in very high doses or in addition to other sedative hypnotics, and the possibility of paradoxical hostility.[10] In practice, the paradoxical hostility appears to be relatively unusual and confined primarily to patients who are either (1) elderly, (2) brain damaged or mentally retarded, or (3) already intoxicated with other sedative hypnotic drugs.[11]

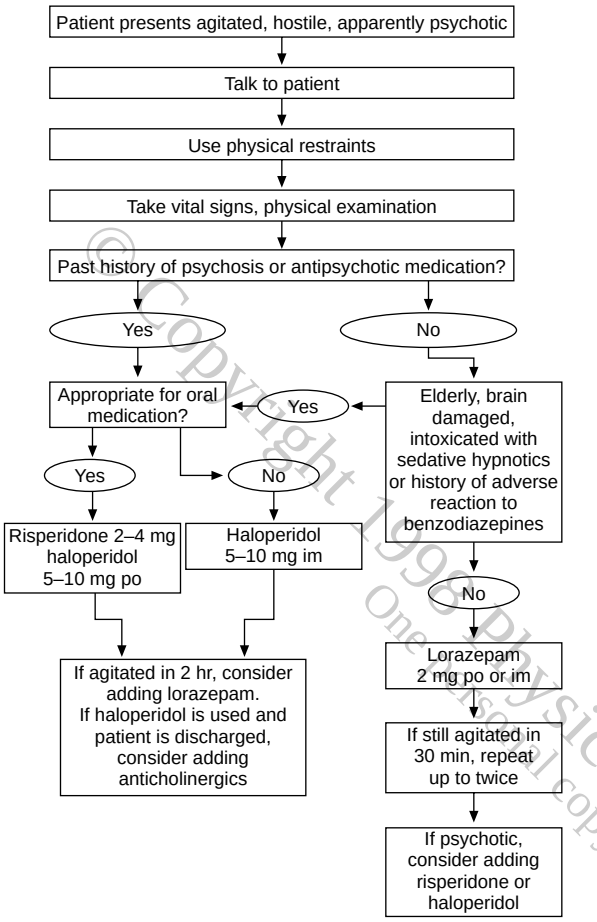
Drugs that clearly do not make any sense for rapid tranquilization include low-potency antipsychotics, which often have a postural hypertensive effect; chloral hydrate or sodium amytal, which tend to put patients to sleep at about the same dose necessary to sedate them; and intramuscular benzodiazepines other than lorazepam or midazolam, since the other benzodiazepines are slowly and erratically absorbed from intramuscular administration. Fluphenazine decanoate or haloperidol decanoate are clearly inappropriate choices for rapid tranquilization since they do not reach therapeutic plasma levels for several days. If a patient does respond to acute treatment with a short-acting antipsychotic, however, it may be a good idea to get the patient's consent to administration of a longer acting agent at the time the patient leaves the emergency service.

FIVE YEARS AGO

By 5 years ago, there was general acceptance that doses of antipsychotic medication higher than 10 to 15 mg of haloperidol or its equivalent were not substantially better than lower doses and, in fact, might lead to poorer outcomes.[6] It was also generally understood that repeated doses of antipsychotics at 30-minute intervals, which had been the practice earlier, did not make pharmacodynamic sense in that it took about 1.5 to 2 hours after administration for peak tranquilization by orally administered antipsychotics.[12] It was also generally understood that intramuscular administration could give an onset of action within 1.5 hours and that intravenous antipsychotics could give an onset generally within an hour.[13] Intravenous antipsychotics never came to be widely used because generally patients who might be candidates for them were not patients anyone would start on intravenous treatment. Intravenous antipsychotics, at the present time, are used almost exclusively in intensive care units where patients already have indwelling intravenous lines and where the staff has very low tolerance for psychotic behavior. Intravenous antipsychotics are generally safe and have been reportedly used in very medically compromised patients in incredibly high doses (e.g., 10 mg q 15 minutes for 2 weeks),[14] but there is evidence for their causing arrhythmias (such as torsade de pointes)[15] in some cases.

Alternative drugs in use 5 years ago included midazolam, which is frequently used in emergency medicine as a pre-endoscopy agent. Unfortunately, it causes substantial anterograde amnesia in many cases,[16] which is positive when patients forget about their endoscopy procedure, but is negative when they are unable to remember their possibly therapeutic reaction with emergency department staff. Concern about respiratory depression from intravenous midazolam has recently led to a warning in the package insert that dosage must be individualized and must never be given rapidly. Droperidol, a drug similar to haloperidol, is marketed as a preanesthetic agent and is still used in many parts of the country in milligram doses equivalent to haloperidol. It probably has a shorter duration of action and a lower incidence of extrapyramidal symptoms than does haloperidol, but may have greater hypotensive effects. Droperidol is available only in intravenous formulation so patients who are helped by it in the emergency room cannot be sent out taking the same medication by mouth.[17]

Figure 1. Flow Sheet for "Rapid Tranquilization" of Agitated and Apparently Psychotic Patients



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Three relatively new drugs are now available for antipsychotic treatment. The first available was clozapine, which turned out to be inadvisable for rapid tranquilization. Although very sedating, it also causes severe orthostatic hypertension and other anticholinergic side effects.[18] Risperidone, on the other hand, has a lower rate of extrapyramidal symptoms than does haloperidol, but lacks the severe orthostatic hypertension and anticholinergic side effects of clozapine.[19] Olanzapine has similar drawbacks to clozapine.[20] In emergency situations for patients ordinarily taking clozapine or olanzapine, it is reasonable to restart them on these medications at doses similar to what they were taking previously. These agents, however, are probably not the best medications to give patients for the first time in an emergency room situation.

Figure 1 shows a rapid tranquilization decision tree. The first approach is, of course, to try to calm the patient by verbal means, but if this is unsuccessful, then the next approach is to use physical restraints. These are safe, effective, and well tolerated when applied by knowledgeable personnel. At this point, it is possible to take vital signs and do some physical examination, which, in some cases, will lead to the recognition of a medical disorder that needs emergency treatment, such as acute hyperthyroidism.

The first branch point on our decision tree is whether the patient has a past history of psychosis or antipsychotic medication. Initial treatment with a benzodiazepine is probably preferable to initial treatment with an antipsychotic. If the patient is at least somewhat cooperative and seems to prefer oral administration, that approach is reasonable although frequent readministration of antipsychotic medications does not make pharmacologic sense. Readministration of a benzodiazepine up to twice for a total of about 6 mg of lorazepam may be reasonable.

If the patient calms down enough to be assessed to be clearly psychotic, it is reasonable to add haloperidol or risperidone to the benzodiazepine. Antipsychotic plus benzodiazepine even in high doses has been shown to be a safe and effective combination. If the patient has a history of paradoxical reaction to benzodiazepines, is intoxicated with sedative hypnotics, is elderly (over 70), or is brain damaged, an antipsychotic approach may be more appropriate. If a patient has a past history of psychosis or antipsychotic medication, the antipsychotic approach is also indicated. If the patient needs an intramuscular approach, haloperidol 5–10 mg is indicated (10 mg for young healthy people, and 5 mg for older individuals [usually those > 70 years old]). If a patient is appropriate for an oral approach, risperidone 2–4 mg is reasonable, unless the patient prefers something else. This is higher than the initial dose recommended on the package insert, but is generally very well tolerated. The much lower incidence of extrapyramidal side effects often makes oral risperidone more tolerable for patients than oral haloperidol. In either case, antipsychotics are generally not readministered within the first 2 hours. If a patient needs further tranquilization, adding 2 mg of lorazepam p.o. or i.m. is acceptable and safe. If patients are not hospitalized, prophylactic anticholinergics should strongly be considered if haloperidol or another high-potency antipsychotic has been used for rapid tranquilization.

SPECIAL CONSIDERATIONS IN THE TREATMENT OF ACUTE MANIA

Acutely manic patients, whether bipolar I or schizoaffective, are among those most difficult patients to stabilize. Often they will require both antipsychotics and benzodiazepines together for any sedation. Recent data have confirmed that high doses of haloperidol (over about 10 mg) do not lead to increasing effectiveness.[21] One case report suggested that risperidone might actually lead to worsening of manic symptoms.[22] While this does not appear to be the case frequently, risperidone monotherapy may not be

Table 3. Relative Receptor Affinities of Newer and Forthcoming Antipsychotics*

	D_1	D_2	5-HT_{1a}	5-HT_{2a}	α_1	α_2	Histamine H_1	Muscaranic M_1
Approved								
Haloperidol[a]	+++	++++	…	+	++	…	…	…
Clozapine[b]	++	++	+	+++	+++	+++	++++	+++++
Risperidone[c]	++	++++	++	+++++	+++	+++	++	…
Olanzapine[d]	+++	+++	…	++++	+++	…	++++	+++++
Quetiapine[d]	+	++	…	+	++++	+	++++	+++
Investigational								
Remoxipride[c]	…	+	…	…	…	…	…	…
Sertindole[d]	+++	+++++	++	++++	+++	…	+	+
Ziprasidone[d]	+	++++	[e]	++++	++	…	+	…

*From reference 25. Ratings reflect the author's judgment of relative potencies (+ to +++++) based on comparison of published IC_{50} at K_i values for these agents.[26–29] Abbreviations: α = α-adrenergic, D = dopamine, 5-HT = serotonin.
[a]Prototype typical neuroleptic.
[b]Low EPS.
[c]Dose-dependent EPS.
[d]Thorough efficacy and side effect data are not currently available.
[e]Norepinephrine reuptake inhibition, 5-HT_{1a} agonist.

very effective in treating acute mania.[23] An alternative approach for acutely manic patients is oral loading of divalproex sodium in a dose of 20 mg/kg, along with lorazepam or other benzodiazepine for sedation.[24]

THE FUTURE

Table 3 lists the receptor binding profiles associated with the three currently available "atypical" antipsychotics and with three that are going to be available soon. There are too many question marks currently to know whether the newer agents will have advantages for rapid tranquilization. Another agent, however, that should be available soon is injectable risperidone, which is likely to find a place in the rapid treatment of acute psychosis.

Drug names: chloral hydrate (Noctec and others), clozapine (Clozaril), divalproex sodium (Depakote), droperidol (Inapsine), fluphenazine (Prolixin and others), haloperidol (Haldol and others), lorazepam (Ativan and others), loxapine (Loxitane), midazolam (Versed), olanzapine (Zyprexa), risperidone (Risperdal), sodium amytal, thiothixene (Navane), trifluoperazine (stelazine).

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