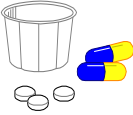


The Agitated Assaultive Patient: Psychopharmacologic Approaches



Aggression and Agitation Pharmacology: an Overview

- No one drug is specific for the management of violent behavior.
- All drugs used in the treatment of aggressive syndromes have originally been developed for other clinical applications.
- Agent choice should depend upon the working diagnosis.
- Management of violence can be divided into:
 - Specific techniques to treat the underlying disorder versus medications that may have some general effectiveness in reducing violence.
 - Medications that are useful for immediate control versus medications that are useful long term.
- A key problem in assessing effectiveness is that very violent acts tend to be rare... and no medication completely eliminates them. Careful record-keeping is essential.

Pharmacology: The Treatment Approach *Spectrum*

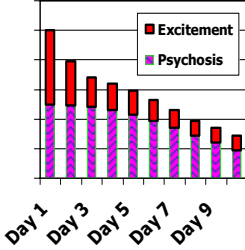
From identifying & treating the underlying psychopathology (with expectation that violent behavior will resolve secondarily)

Treating the violence-aggression with psychopharmacologic agents (depending upon the comorbid conditions present, e.g., psychoses, epileptic syndromes, adolescents/children with behavior disturbances...)

Ultimately the personality disorders are the most difficult to treat with medications

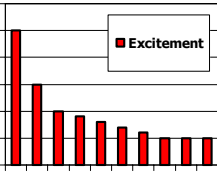
LM Conn, JR Lion. Psychiatr Clin North Am 1984 Dec; 7(4):879-886.
TM III, A Wadud. J Nerv Ment Dis 1975 Feb; 160(2-1): 83-99.

Phases of Acute Treatment

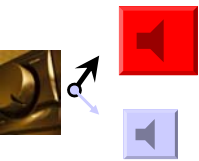


- Phase 1: First two to three days is primarily reduction of "agitation" or arousal.
- Phase 2: Days 3-21 is the reduction of core psychotic symptoms

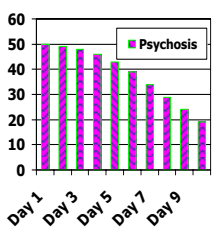
Phase 1: Reduce Agitation or Arousal



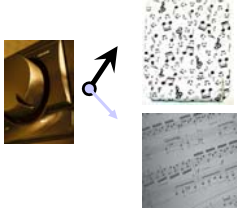
Norepinephrine



Phase 2: Treat Core Psychotic Symptoms



Dopamine / *Serotonin*



Expert Consensus: How to Chose a Medication

Most important factors to consider Other factors to consider

Availability of I.M. formulation

Speed of onset

History of medication response
 Produces clinically useful sedation
 Limited liability for causing intolerable or dangerous side effects
 Patient preference
 Availability of liquid formulation

Promoting long-term compliance
 History of noncompliance and availability of a depot formulation

Bold italics = factors of choice

Effectiveness Criteria for IM Agent

- Rapid onset
- Adequate symptom control with single injection
- No serious adverse effects
 - No dystonia
 - Low cardiac toxicity
- Reliable effect as PRN intervention
- Calming effect without excessive sedation
- Easy transition to oral therapy

Expert Consensus: Medication Combinations

- **Most important factors to consider:**
 - greater efficacy for symptoms of arousal
 - faster onset of action
 - reduction of side effects
- **Other factors to consider:**
 - ability to use lower doses of each of the component medications
 - inducing sleep
 - greater efficacy for underlying condition



Agitation Studies

- Michael Allen reviewed 20 studies, 1029 subjects, 9 drugs.
- 17 double blind, 2 placebo controlled (n=33).
- Most small n's.
- Mixed diagnoses ascertained subsequently.
- Few dose finding studies.
- Common design a single dose of similar active agents repeated at fixed intervals.

Michael Allen. 2000



Agitation Studies

- **Little evidence of immediate differential effectiveness not accounted for by dosage.**
 - Acute IM:
 - High potency AP superior to low potency, but may be due to dosage.
 - Trends favor IM LOR over HAL for aggression.
 - Oral.
 - Risperidone and clozapine superior to HDL for

Michael Allen. 2000 / hostility.



Agitation Studies

- Data from AAEP survey found that only 10% of all psychotic patients received injectable medications
- Doug Hughes at Cambridge Hospital, developed consensus around patient choice and reduced this to 1.2%

Michael Allen. 2000

Comparator Dose Selection

- IM haloperidol 7.5 mg
 - 5 - 10 mg doses most commonly used
 - Dose response analysis suggests that doses that exceed 7.5 - 10 mg do not appreciably increase immediate efficacy, but may cause additional side effects¹
- IM lorazepam
 - 1 mg and 2 mg doses commonly used in geriatric and nongeriatric patients, respectively

¹Baldessarini RJ. Washington, DC: APA; 1980. Task Force Report 18. FDA. *Intramuscular olanzapine for the rapid control of agitation*. Rockville, Maryland: US Dept of Health and Human Services; Feb 12, 2001. NDA 21-253.

Speed of Action



- IV diazepam and midazolam fastest (5 minutes)
- IV lorazepam faster than IM (5-10 minutes) and IM=PO (about 20-30 minutes).
- Haloperidol IM or IV works in 10-15 minutes and is faster than PO (about 45-1hr).
- Risperidone PO is slightly faster than haloperidol PO (about 30-45 mins)
- Liquids may be somewhat faster than po. Risperidone is the only liquid (about 20-25 mins)

Michael Allen. 2000

Drug		Tmax (hours)
Risperidone	Oral	1.00
	Liquid	1.0
Olanzapine	Oral	6.0
	Disintegrating Tab	6.0
	Intramuscular	0.25
Ziprasidone	Oral	6.00-8.00
	Injectable	0.5-0.75
Quetiapine		1.50
Haloperidol		5.00

QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients

- Electrocardiograms were obtained from 101 healthy reference individuals and 495 psychiatric patients in various inpatient and community settings.
- Abnormal QTc was defined from the healthy reference group as more than 456 ms and was present in 8% (40 of 495) of patients.
- Age over 65 years (odds ratio 3.0 [95% CI 1.1-8.3]), use of tricyclic antidepressants (4.4 [1.6-12.1]), thioridazine (5.4 [2.0-13.7]), and droperidol (6.7 [1.8-24.8]) were robust predictors of QTc lengthening, as was antipsychotic dose (high dose 5.3 [1.2-24.4]; very high dose 8.2 [1.5-43.6]).

Reilly, J. G.; Aysc, S. A.; Ferrier, I. N.; Jones, S. J.; Thomas, S. H. *QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients* (2000) *Lancet* 355

Cardiac Repolarization (2/2)

	Ziprasidone	Risperidone	Olanzapine	Quetiapine	Thioridazine	Haloperidol
Dosages Range (mg/day)	40-160	2-6	5-20	50-750	50-300	2-15
QTc Baseline	389.4± 6.5	387.7± 6.1	387.6± 8.4	386.8± 7.1	388.2± 6.0	383.3± 5.9
Mean Change	15.9± 5.3	3.9± 3.6	1.7± 5.4	5.7± 4.0	30.1± 5.4	7.1± 5.3
Steady State	4.2± 1.3	1.0± 1.7	0.5± 1.4	1.5± 1.0	7.8± 1.4	1.9± 1.4
% Change						
Mean Change	16.6± 6.0	2.6± 7.2	3.0± 5.0	8.0± 4.7	29.6± 6.2	13.3± 5.8
Inhibitor Present	4.4± 1.6	0.7± 1.9	0.8± 1.3	2.1± 1.2	7.7± 1.6	3.5± 1.6
% Change						

Pfizer. FDA Psychopharmacological Drug Advisory Committee: briefing document for Zeldox Capsules (ziprasidone HCL), 200 Jul 19.

Thioridazine

- The study examined administrative records (including all prescriptions) from three regions in the United States, comparing the incidence of cardiac arrest and ventricular arrhythmias and all cause mortality in patients with schizophrenia treated with an antipsychotic with that in two other cohorts, one with patients of glaucoma and one with patients of psoriasis.
- The findings confirm that all cause mortality in schizophrenia is relatively high.
- A dose-response relation could be identified only for thioridazine: the risk ratio for cardiac arrest and ventricular arrhythmias between the highest and the lowest doses was 2.5. In other words, the risk is greater with doses of thioridazine above 100 mg per day than with equivalent doses of haloperidol (3 mg or more).

BMJ 2002;325:1253-1254 (30 November)

Thioridazine and Sudden Unexplained Death in Psychiatric In-Patients

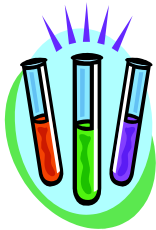
- Reilly and others in England used a case-control method to study the association of antipsychotic drugs and sudden unexplained death.¹
- Medical records from five large psychiatric hospitals identified psychiatric inpatients who had died suddenly during a 12-year period. For each case, two surviving controls—matched for age, gender, and mental disorder—were chosen.
- There were 1350 deaths during the study period, 69 unexplained. Only thioridazine (Mellaril and others) was statistically associated with an increased chance of sudden death, and higher doses might have caused greater risk (adjusted odds ratio 5.3, $P = .004$). The primary cause of thioridazine-related death appeared to be torsades de pointes. Hypertension and ischemic heart disease also increased the likelihood of sudden death.

Reilly JG, Ayis SA, Ferrier IN, Jones SJ, Thomas SHL: Thioridazine and sudden unexplained death in psychiatric in-patients. *Br J Psychiatry* 2002;180:515-522.
Ray WA, Meador KG: Antipsychotics and sudden death: Is thioridazine the only bad actor? *Br J Psychiatry* 2002;180:483-484.

Antipsychotic Drugs: Prolonged QTc Interval, Torsade de Pointes, and Sudden Death

- All drugs that cause torsade de pointes prolong the QTc interval and bind to the potassium rectifier channel, but the relationships are not precise.
- Although sudden unexpected death occurs almost twice as often in populations treated with antipsychotics as in normal populations, there are still only 10-15 such events in 10,000 person-years of observation.
- Although pimozone, sertindole, droperidol, and haloperidol have been documented to cause torsade de pointes and sudden death, the most marked risk is with thioridazine.
- There is no association with olanzapine, quetiapine, or risperidone. Ziprasidone does prolong the QT interval, but there is no evidence to suggest that this leads to torsade de pointes or sudden death.

Glassman AH, Bigger JT Jr. Antipsychotic drugs: prolonged QTc interval, torsade de pointes, and sudden death. *Am J Psychiatry* 2001 Nov;158(11):1774-82



Psychopharmacologic Tools for Treating the Acutely Agitated Patient



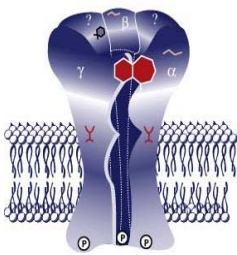
Psychopharmacologic Tools: Benzodiazepines

Mechanisms of action

- Stereospecific binding to unique receptors on GABA-receptor macromolecular complex
- Potentiation of inhibitory effects of GABA at GABA-A receptors
- Higher concentration of benzodiazepine receptors in phylogenetically newer areas (neocortex, limbic areas)
- At least 2 subtypes of benzodiazepine receptors in brain:
 - **Peripheral** (more highly concentrated in cerebellum)
 - **Neuronal** (mainly in cortex and limbic areas)



Psychopharmacologic Tools: Benzodiazepines



Schematic representation of the gamma-aminobutyric acid (GABA_A) receptor. The functional receptor consists of five proteins, or subunits—most likely two α subunits, one β subunit, and two γ subunits. (Question marks indicate that the identity of these subunits has not been confirmed.) The proposed binding sites for GABA (α and β subunits), benzodiazepines (adjacent α and γ subunits), barbiturates (unidentified subunit), and alcohol (α , β , and γ subunits) are indicated. P's represent phosphate groups attached to the receptor that regulate the receptor's activity and sensitivity to alcohol.



Psychopharmacologic Tools: Benzodiazepines

Pharmacodynamics depend on several factors including:

- pharmacokinetic half-life
- affinity for benzodiazepine receptor
- lipid solubility



Psychopharmacologic Tools: Benzodiazepines

Absorption.

- Clinical effects within 1hr, peak within 1-4hrs (*oral ingestion*).
- **High bioavailability** (eg, orally administered diazepam= 94%).
- **Food /antacids slow rate** of absorption, decrease peak plasma levels, but do not alter total amount drug absorbed.
- **Intravenously, all benzodiazepines are quite lipophilic** and generally yield clinical effects within a minute.

Lipophilic spectrum.

Lorazepam [Ativan]: **low**  diazepam: **high**.

Differences may be important in respiratory depression.



Psychopharmacologic Tools: Benzodiazepines

- Intramuscular injection often results in unpredictable and erratic absorption except w/ lorazepam which is the most reliably absorbed intramuscular benzodiazepine
- Benzodiazepine absorption more rapid via deltoid injection vs. gluteal or vastus lateralis



Psychopharmacologic Tools: Benzodiazepines

Entry into nervous system

- Pass through blood-brain barrier by passive diffusion



Directly proportional

- Once equilibrium reached, disappearance from brain occurs at same rate as disappearance in plasma
- Highly lipophilic drugs (eg, diazepam) rapidly distributed to all tissue
- Hence, single dose lorazepam will have longer effect than comparable dose of diazepam, despite shorter elimination half-life



Psychopharmacologic Tools: Benzodiazepines

Metabolism

- Benzodiazepines are metabolized in liver by oxidation, conjugation or nitro-reduction reactions
- Oxidized benzodiazepines are frequently converted into 1+ active metabolites, less likely to be cleared effectively by patients w/ hepatocellular disease
- 3-hydroxy benzodiazepines (eg, lorazepam) are conjugated in liver w/ glucuronic acid, yielding greater clearance

Benzodiazepines: Focus on Lorazepam

- Lorazepam, the only benzodiazepine that is reliably absorbed when administered intramuscularly, remains a rational choice when treating an acute episode of agitation, especially when the etiology is not clear, such as when a patient with a history of schizophrenia may actually be withdrawing from alcohol.[10-12]

10. Salonen C. Use of benzodiazepines to control disruptive behavior in inpatients. *J Clin Psychiatry*. 1988;49(suppl):13-15.
11. Greenblatt DJ, Shader RI, Franke K, et al. Pharmacokinetics and bioavailability of intravenous, intramuscular, and oral lorazepam in humans. *J Pharm Sci*. 1979;68:37-43.
12. Greenblatt DJ, Divall M, Hammett JS, Shader RI. Pharmacokinetic comparison of sublingual lorazepam with intravenous, intramuscular, and oral lorazepam. *J Pharm Sci*. 1982;71:248-252.

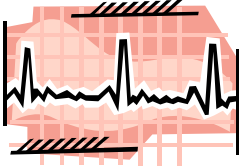


Psychopharmacologic Tools: Benzodiazepines

- Benefits.**
- **Manage behavior**
 -
• **Especially useful in treatment of delirium due to alcohol /sedative withdrawal.**
 - **May be especially effective in tandem w/ neuroleptics, particularly haloperidol.**

- Risks**
- **But may worsen confusion**
 - **Should not be hepatically metabolized via oxidation**
 - **Benzodiazepine withdrawal in elderly may cause confusional states**
 - **Chronic benzodiazepine use in animal models increases aggression**

Cardiac Effects of Lorazepam



- Benzodiazepines are frequently administered postmyocardial infarction, but their effect on heart period variability (HPV), a prognostic index of sudden arrhythmogenic death is unclear.
- LZ increased mean heart rate by 8% ($p < .002$), decreased the standard deviation of R-R intervals by 9% ($p < .05$), decreased the percent differences between adjacent normal R-R intervals > 50 msec by 30% ($p < .03$). The significant heart rate increase and HPV decreases demonstrate vagolytic effects of LZ in healthy subjects during 24 hours of normal physiologic activity.

Journal of Clinical Psychopharmacology 16(6): 449-453 (Vogel et. al.)

Benzodiazepines and Behavioral Disinhibition



- 18-month, retrospective record review of direct and indirect measures of behavioral dyscontrol in 323 psychiatric inpatients (108 taking alprazolam, 111 taking clonazepam, 104 taking no benzodiazepines).
- No differences in self-injury, staff or patient assault, need for seclusion or restraint, need for closer observation, or reduction in privileges.
- **Anecdotal reports of disinhibition do not represent a large-scale problem.**

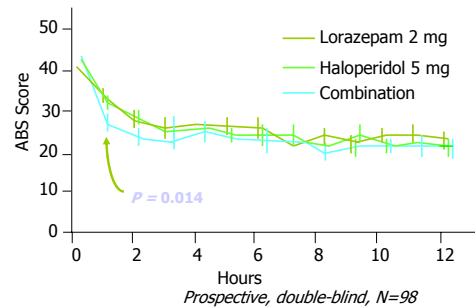
Rothschild AJ et al. Comparison of the frequency of behavioral disinhibition on alprazolam, clonazepam, or no benzodiazepine in hospitalized psychiatric patients. J Clin Psychopharmacol. 2000; 20:7-11

Hazardous Benzodiazepine: Regimens in the Elderly

- **Objective:** Which benzo characteristics are most associated with hip fracture.
- **Method:** Analysis of health care utilization data for hip fracture patients and comparison patients matched for age and gender.
- **Results:** All benzo doses ≥ 3 mg/day in diazepam equivalents significantly increased the adjusted risk of hip fracture by 50%. Risks were significantly greater in the first 2 weeks of treatment as well as after more than 1 month of continuous use, but not fore 2-4 weeks of use.

Wang, Bohn, et al. Am J Psychiatry 158:6, June 2001.

IM Haloperidol, Lorazepam or Both?



Battaglia J et al. Am J Emerg Med. 1997;15:335-340.



Typical Antipsychotics

- **Traditional approach:** use high potency non-phenothiazine neuroleptics.
- **Haloperidol** most often recommended due to sedating potential and limited anticholinergic effects.
- **Fluphenazine (Prolixin)** similar EPS, though less anticholinergic and decreased effect on seizure threshold.

Dose Response Curve with Haloperidol

- Dose of 10 mg of haloperidol yields all of the ~40% of BPRS improvement that you see in patients who are acutely psychotic
- This is based on 3 studies with multiple doses
- In these studies 10 mg = 14, 33 or 41 in improvement
- Highest improvement was 13 mg

Michael Allen. 1999

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- **Highest improvement was 13 mg**

Michael Allen, 1999

Thiothixene vs. Haloperidol

- Thiothixene has greater efficacy than other major tranquilizers and is comparable to haloperidol (both in combination with lorazepam).¹
- Thiothixene has slower onset of action than loxapine.²
- Loxapine and perphenazine have been reported to have similar efficacy in acute psychosis. (Some have noted that perphenazine may have less efficacy for chronic symptoms. 3, 4

1. Neborsky R. Arch Gen Psychiatry. 1981 1:38 (2): 195-199.
2. Dubin WR, Weiss KJ. J Clin Psychiatry. 1986. 47(6): 294-297.
3. Lepola U. Acta Psychiatrica Scan. 1989. 50(1): 92-96.
4. Ruensgaard K. Curr Med Res Opin. 1978. 5(8):601-607.



Psychopharmacologic Tools: Droperidol

- About 1.2x more potent than haloperidol.
- A butyrophenone, neuroleptic tranquilizer.
- Not indicated for psychiatric use.
- Onset in 3-10 minutes...peak action within 30 minutes.
- Short half life: duration of sedation is 2-4 hours.
- Slightly more hypotension, may be readily managed with hydration.
- Review of literature suggested more use.¹

H Thomas et al. Ann emergency med Apr 1992; Vol 21, 407-413.

D Classen. Gastroenterol nursing Oct 1992; Vol 15, 81-82.

van Leeuwen AM. J Nerv Ment Dis 1977 Apr;164(4):280-283

1. 17; J Clin Psychiatry 1989 Oct;60(10):664-667 Droperidol: efficacy and side effects in

Atypical Antipsychotics

Advantages

- Effective against positive symptoms, at doses below those associated with side effects
- Head to head studies find either greater effectiveness (clozapine, olanzapine, risperidone) or equal effectiveness (ziprasidone, quetiapine)
- Enhanced patient acceptance and compliance

Disadvantages

- "Typical" side effects at higher doses with some agents
- Cost
- Limited experience with prn or single dose use

Risperidone

Greater effectiveness compared to haloperidol on positive and negative symptoms

Comparably effective when given as a liquid concentrate with adjunctive lorazepam

Quick onset with peak plasma levels occurring in roughly one hour (perhaps slightly faster with oral solution or quicksolv tablets)

Forster, P. Managing the agitated psychotic patient: an update. (In Submission) Emergency Psychiatry. 2002.

Quetiapine (Seroquel)

More effective than haloperidol in controlling agitation

Significant sedation and orthostatic dizziness

Relatively rapid absorption but only a tablet form

Comparable effectiveness found in controlled trials

Forster, P. Managing the agitated psychotic patient: an update. (In Submission) Emergency Psychiatry. 2002.

Ziprasidone

Intramuscular ziprasidone reduced agitation scores significantly compared to haloperidol

Quite sedating in clinical experience

Not approved for use combined with oral

Roughly comparable to haloperidol in effectiveness in controlled trials

More effective in reducing agitation more quickly

Oral reaches peak plasma concentration in 6-8 hours

Intramuscular peak plasma concentration achieved in 30-45 minutes post-injection

Forster, P. Managing the agitated psychotic patient: an update. (In Submission) Emergency Psychiatry. 2002.

Olanzapine

IM had greater speed of action and effectiveness compared with haloperidol

Oral: Four to six hours to peak plasma concentration

•Same with Zydys and pill form

IM: peak plasma concentration as soon as 15-30 minutes post-injection

Excellent studies on its use in both schizophrenia and bipolar agitation

Forster, P. Managing the agitated psychotic patient: an update. (In Submission) Emergency Psychiatry. 2002.

Aripiprazole

Limited experience in acute agitation

Dose response is not clear

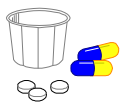
May cause *increased* agitation

Forster, P. Managing the agitated psychotic patient: an update. (In Submission) Emergency Psychiatry. 2002.

Standard Dosing of Novel Antipsychotics

Drug Name (Trade Name)	Normal Adult Dose Range	Pharmaceutical Company
Clozapine (Clozaril)	150 to 900 mg PO	Novartis
Risperidone (Risperdal)	4 to 16 mg PO (in divided doses)	Janssen
Olanzapine (Zyprexa)	5 to 20 mg PO	Eli Lilly and Company
Quetiapine (Seroquel)	300 to 750 mg PO (in divided doses)	AstraZeneca
Ziprasidone (Geodone)	40 to 160 mg PO (in divided doses)	Pfizer, Inc

Physicians' Desk Reference. Montvale, NJ: Medical Economics CO.; 2002



Delirium: Psychopharmacology

- **Typical antipsychotics:** work quickly, high potency (haloperidol) are safe in fairly high doses and can be given iv. Disadvantages include some anticholinergic potency, dystonia, concern re NMS confusing the picture, akathisia, etcetera. Some evidence suggests lower EPS when administered intravenously.*.
- **Benzodiazepines:** lorazepam is safe (except if given in large single doses) and almost always effective if enough is given. However, withdrawal is associated with worsening delirium, disinhibition often occurs at intermediate doses.
- **Atypical antipsychotics:** appear to be safe, but limited data, may not work as rapidly.
- **Narcotics:** may be used in an ICU setting if staff are very familiar with them.

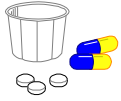
* Menza, et al. J Clin Psychiatry 1987;48:278-80



Delirium: Rapid Control With IV Neuroleptics

- **Intravenous neuroleptic sedation** is established technique for emergency treatment of delirium.
- **Safety and efficacy may be possible at doses far in excess** of those conventionally recommended, and may be necessary for some delirious, medically ill, agitated patients.
- **"Torsades de pointes"** reported with high dose neuroleptics. Estimates of incidence range from 4 out of 1,100 patients to 8 out of 223 patients. There is some evidence associating droperidol and haloperidol with torsades de pointes.

Am J Psychiatry 156:5, May 1999 Supplement. Adams, 1988.

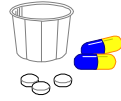


Delirium: Dosing Strategies for Haloperidol

- Several studies suggest **starting at 1-2 mg every 2/4 hours as needed.**
- For elderly patients, **doses as low as 0.25-0.50 mg every 4 hours have been suggested.**
- For severely agitated patients, bolus intravenous dosing exceeding 50 mg, and with daily doses up to 500 mg have been reported with minimal EPS, and minimal effects on heart rate, respiratory rate, blood pressure, and pulmonary artery pressure.*.
- Continuous intravenous infusion has been recommended for patients requiring multiple bolus intravenous injections.
 - Continuous infusion of 5-10 mg/hour after initial bolus dose of 10 mg.

AM J Psychiatry 156:5, May 1999 Supplement

Step TA. The management of depression and anxiety following MI. *MJ Singap J Med*



Delirium: Use of Atypical Antipsychotics

- No published clinical trials exist, however several case reports suggest that risperidone and other atypicals may be especially useful in the elderly and severely ill.
- Two case reports with risperidone.¹
- One case series with olanzapine.²

1. Sipahimalani A, Masand PS. *Ann Clin Psychiatry* 1997 Jun;9(2):105-7; Ravona-Springer, et al. *J Clin Psychopharmacology*. 1998. 18(2):171-2

An Atypical Treatment for Delirium

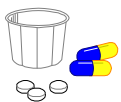
- In this large, open-label, prospective study, researchers identified 154 delirious cancer patients, of whom 52 were excluded because they could not or would not take oral medication, 20 were excluded because they were already taking neuroleptics, and 3 were unable to complete the trial. Olanzapine was given to the remaining 79 patients (mean age, 61; 70% had multiple causes of delirium; 49% female). Delirium was evaluated with a standardized, DSM-IV-based, 10-item rating scale at baseline and at 2-3 days and 4-7 days after treatment began.
- Patients were grouped by degree of delirium (severe or mild-to-moderate). Mean olanzapine dose was 3.0 mg at baseline, 4.6 mg at 2-3 days, and 6.3 mg at 4-7 days. More than 75% of patients achieved complete remission by day 7, particularly those with mild-to-moderate delirium.

Breitbart W et al. An open trial of olanzapine for the treatment of delirium in hospitalized cancer patients. *Psychosomatics* 2002 May/June; 43:175-82.

An Atypical Treatment for Delirium

- Characteristics associated with significantly poorer response to olanzapine were age over 70, hypoactive delirium, history of delirium, and spread of cancer to the CNS. Patients with hypoxic delirium responded to olanzapine, but less so than did those without hypoxic delirium. Sedation occurred in 30% of patients, and olanzapine worsened delirium in 1.3%.
- In this study, olanzapine was useful for treating mild-to-moderate delirium and had few side effects. These results are interesting, but not strong: Because this was an open-label trial without a control group, it is unclear how many patients would have remitted spontaneously.
- The exclusion of so many patients also limits these findings to patients with mild-to-moderate delirium.

Breitbart W et al. An open trial of olanzapine for the treatment of delirium in hospitalized cancer patients. *Psychosomatics* 2002 May/June; 43:175-82.



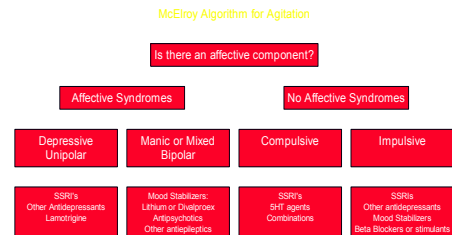
Delirium: Antipsychotics Vs. Benzodiazepines

- Randomized, double-blind study of 244 hospitalized AIDS patients, diagnosed with delirium: chlorpromazine and haloperidol reduced symptoms significantly within two days. Lorazepam did not.
- Average decrease in scores on the delirium rating scale:

Chlorpromazine	8.5.
Haloperidol	8.0.
Lorazepam	1.0.
- No side effects with antipsychotics. Treatment-limiting adverse effects were associated with lorazepam treatment.

Breitbart W, Et al. A double-blind trial of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalized AIDS patients. *Am J psychiatry* 1996; 153:231-237.

A Pharmacologic Treatment Algorithm for Agitation and Violence



J Clinical Psychiatry Monograph 17:2, April 1999, Susan McElroy.



Depression and Anger Attacks

Anger attacks:

- “Sudden intense spells of anger that resemble panic attacks but lack the predominant affects of fear and anxiety associated with panic attacks”.
- Typically occur in situations where an individual feels emotionally trapped.

Fava, et al. J Clin Psychiatry 1999; 60 (Suppl 15): 21-24



Depression and Anger Attacks

Criteria for anger attacks:

- Irritability during previous six months.
- Overreactivity to minor annoyances and anger.
- Occurrence of 1 or more anger attacks during previous month.
- Inappropriate anger and rage during an attack.

Fava, et al. J Clin Psychiatry 1999; 60 (Suppl 15): 21-24



Depression and Anger Attacks

Anger attacks:

- Found to be more common in depressed patients (48%), than unselected volunteers (21%).
- Reported in 56 (44%) of 127 depressed outpatients in one survey, and 64 (39%) of 164 outpatients in another survey.
- Between depressed patients with and without anger attacks, no significant differences were found in lifetime rates of comorbid anxiety disorders, eating disorders, or substance use disorders.

Fava et al., 1991; Fava et al., 1996; Rosenbaum JF, J Clin Psychiatry Monograph 17:2 Apr 1999



SSRI's for Compulsive or Depressive Agitation

Etiology of anger attacks:

- Study found depressed patients with anger attacks to have blunted prolactin response to thyrotropin-releasing hormone (TRH).
- Prolactin response to TRH was significantly increased by eight weeks of fluoxetine treatment.
 - This treatment had no effect on patients without anger attacks.
- Suggests greater central serotonergic dysregulation in patients with anger attacks.

Rosenbaum, et al. 1993. Anger attacks in unipolar depression, II: neuroendocrine correlates and changes following treatment. Am J Psychiatry 150:1164-68



SSRI's for Compulsive or Depressive Agitation or Violence

Three studies have demonstrated the responsiveness of anger attacks to SSRI therapy:

- Among patients treated openly with 20 mg/day of fluoxetine, attacks decreased in 24 (71%) of 34 patients¹, and 41 (64%) of 64 patients.²
- Attacks also decreased in 9 (53%) of 17 patients treated with up to 200 mg/day of sertraline, and 12 (57%) of 21 patients treated with up to 300 mg/day of imipramine.³

¹ Fava et al. 1993 Anger attacks in unipolar depression, part 1: clinical correlates and response to fluoxetine treatment. AM J Psychiatry 150:1158-63

² Fava et al. 1996 Fluoxetine treatment of anger attacks: a replication study. Ann Clin Psychiatry 8:7-10

³ Fava et al. 1997 A preliminary study on the efficacy of sertraline and imipramine on anger

SSRI's: Why Don't They Just Put Them in the Water?

- Paroxetine was given to normal subjects.
- It reduced hostility by reducing overall negative affect, while not affecting positive affect.
- It increased social cooperation and affiliative behavior
- SSRI administration has significant and detectable effects on these measures even in the absence of baseline clinical depression or other psychopathology. SSRI administration reduced psychometric assaultiveness relative to placebo
- While collaboratively solving a puzzle, SSRI-treated partners increased suggestions, decreased commands, and decreased unilateral solution attempts

*3/98 Am J Psychiatry. Knutson B et al. Selective alteration of personality and social behavior by serotonergic intervention.

Double Blind and Placebo-Controlled Studies on Impulsivity

Sheard	1976	prisoners	Li>placebo
Campbell	1995	Conduct dis	Li>placebo
Malone	2000	Conduct dis	Li>placebo
Rifkin	1997	Conduct dis	Li=placebo
Tariot	1998	Dementia	Tegretol>pl
Barratt	1997	prisoners	Phenytoin>pl
Donovan	2000	Conduct dis	Divalproex>pl

Moeller et al, *Psych Aspects of Impulsivity, Am J Psych, 158:11, 2001*

Double Blind and Placebo-Controlled Studies on Impulsivity

Greendyke '86	Organic Brain	Propranolol>pl
Greendyke '86	Organic Brain	Pindolol>pl
Brown 1979	Hyperactive	Methylphenidate>pl
Musten 1997	ADHD	Methylphenidate>pl
Malone 1993	ADHD	Methylphenidate>pl
Matier 1992	ADHD	Methylphenidate=pl
Schleifer 1975	Hyperactive	Methylphenidate=pl

Moeller et al, *Psych Aspects of Impulsivity, Am J Psych, 158:11, 2001*

Double Blind and Placebo-Controlled Studies on Impulsivity

Katz	1999	Dementia	Risp>placebo
de Deyn	1999	Dementia	Risp>placebo
McDouglas	98	Autism	Risp>placebo
Findling	2000	Conduct Dis	Risp>placebo
Citrome	2001	Schizophrenia	Risp=Haldol
Citrome	2001	Schizophrenia	Olz=Haldol
Citrome	2001	Schizophrenia	Clozapine>HI

Moeller et al, *Psych Aspects of Impulsivity, Am J Psych, 158:11, 2001*

Aggression and Pharmacology Anticonvulsants: *Phenytoin*

Study of 60 inmates in Texas correctional facility...

- Phenytoin (200q am & 100 q pm) significantly reduced impulsive aggressive acts, but not premeditated aggressive acts.

Aggression and Pharmacology Anticonvulsants: *Divalproex*

Divalproex treatment of identified explosive adolescents with irritable mood swings... A report of 10 cases

- Treatment prevented irritability and resultant explosive aggression.
- Divalproex dosed up to 1000mg qd, blood levels of 45-113.
- None had adverse effects.
- 5/6 who stopped on own got worse and restarted.

S.J. Donovan, *J clinical psychiatry, 1997; 58:12-15*

Aggression and Pharmacology *Lithium*

- Demonstrated effective in control of aggressive behaviors in aggressive prisoners and mentally retarded patients.
- Clinical effect= reduce frequency and severity of both hetero and auto aggressive outbursts.
- Mixed results in chronically psychotic patients.
- Careful monitoring of blood levels necessary to ensure adequate therapeutic efficacy without toxicity.
- Anti-aggressive effect may be associated with serotonergic effects.
- Lithium effective treatment for severely aggressive children with conduct disorder³.

DJ Pabis, SW Stanislav. *Ann Pharmacotherapy* 1996 mar; 30(3):278-287.

F.Thibaut, L.colonna. *Encephale (France)* 1992 mar; 18(2):193-198.

Aggression and Pharmacology *Lithium*

- The single best medication for controlling violence may be lithium
- Doses that achieve serum levels between 0.6 and 1.0 mEq/L appear to be most effective.

Doug Hughes. *Psychiatric Annals*. 1998

Aggression and Agitation: Pharmacology: *Other Options*

- Clozapine used to treat brain-injured patients (n=9) with psychotic sx, outbursts of rage and refractory aggression... improvement in aggression, despite adverse side effects (2/9 patients in this trial experienced seizures)².



² ML Michaels et al. *J Clin Psychopharmacol* 1993 Jun; 13(3):198-203.

Aggression and Agitation: Pharmacology: *Beta Blockers*

- Adjunctive nadolol useful in acutely aggressive schizophrenic patients by inducing a more rapid & consistent decrease in overall psychiatric symptoms and reducing EPS¹.
- 2 month study of 20 chronically hospitalized aggressive patients with propranolol and stable doses of other medications.
- Researchers attempted to treat each patient with 1,440 mg/day or 20 mg/kg of propranolol (propranolol was not increased if pulse was under 50 or systolic pressure was under 90).
- Seven patients had an improvement over 50%, and five of these had an improvement greater than 75%.

¹ *J Clin. Psychiatry* Oct 1996.

² Silver JM et al. *Propranolol treatment of chronically hospitalized aggressive patients*. *J Clin Neuropsychiatry and Neurosci* 1999 Summer; 11:328-35.



Aggression and Agitation: Pharmacology: *Beta Blockers*

- Beta adrenergic antagonists, have been shown to be highly effective for agitation and aggression in traumatically brain injured.
- After the patient reaches a propranolol dosage of 200 to 300 milligrams per day, peripheral effects seem to taper off.
- 400 to 600 milligrams per day is the usual dosage range.
- Begin with a test dose of 20 milligrams of propranolol per day and watch for hypotension and bradycardia, then increase dosage by 20 milligrams per day every three days.
- It may take six weeks before beneficial effects emerge.
- The effect of beta blockers can be highly dramatic, about 70 percent show a good response based on the Overt Aggression Scale.
- There are case reports and good double-blind studies suggesting that weakly lipophilic beta blockers, such as atenolol, metoprolol, and nadolol also are effective.



Stuart Yudofsky in *Currents in Affective Disorders*. 1999

Aggression and Agitation: Pharmacology: *Other Options*

- Fluoxetine open trial in refractory borderline patients (n=5) demonstrated efficacy in treating impulsive aggression⁵.
- Clonazepam adjunctive treatment of refractory schizophrenia associated with complex partial seizure disorder and postictal violence (also refractory). Treatment resulted in cessation of seizures as well as cessation of violence and hallucinations⁶.

⁵ JR Cornelius. *J Clin Psychopharmacol* 1991 Apr; 11(2): 116-120.

⁶ MM Keats, S Mukherjee. *J Clin Psychiatry* 1988 mar;

Nutritional Supplements Reduce Violence in Prisoners

- In this double-blind, placebo-controlled, randomized trial, researchers examined the effect of nutritional supplements on antisocial behavior in 231 adult male prisoners in Britain.
- Prisoners were randomized to receive either placebo or an over-the-counter multivitamin supplement (similar to Centrum Silver) plus omega-3 and omega-6 fatty acid supplements daily for a minimum of 2 weeks (average, 142 days).
- Reductions from baseline incidents were 7% in the placebo group and 35% in the supplement group, also a significant difference.

Gesch CB et al. *Influence of supplementary vitamins, minerals and essential fatty acids on the antisocial behavior of young adult prisoners: Randomized, placebo-controlled trial*. *Br J Psychiatry* 2002 Jul; 181:22-5.