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

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

Phase 2: Treat Core Psychotic Symptoms
Expert Consensus: How to Choose a Medication

Most important factors to consider:
- Availability of I.M. formulation
- Speed of onset
- History of medication response
- History of noncompliance and availability of a depot formulation

Other factors to consider:
- Producing clinically useful sedation
- Limited liability for causing intolerable or dangerous side effects
- Patient preference
- Availability of liquid formulation

**Bold italics = factors of choice**

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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

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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

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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.

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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

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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%
**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


**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 20-35 mins)

**Cardiac Repolarization (2/2)**

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<td>Quetiapine</td>
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</tr>
<tr>
<td>Haloperidol</td>
<td>5.00</td>
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</table>

**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 [1.2-19.0]; very high dose 8.2 [1.5-43.6]).


**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.


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 pimozide, sertraline, 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.


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

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.

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
• 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

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]

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

Benefits.
• Manage behavior
• Especially useful in treatment of delirium due to alcohol/sedative withdrawal.
• May be especially effective in tandem w/ neuroleptics, particularly haloperidol.
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<0.03). The significant heart rate increase and HPV decreases demonstrate vagolytic effects of LZ in healthy subjects during 24 hours of normal physiologic activity.

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.

Hazardous Benzodiazepine: Regimens in the Elderly

- Objective: Which benzo characteristics are most associated with hip fracture.
- 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.

IM Haloperidol, Lorazepam or Both?

- 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.

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**

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**Thiothixene vs. Haloperidol**

- Thiothixene has greater efficacy than other major tranquilizers and is comparable to haloperidol (both in combination with lorazepam).
- Thiothixene has slower onset of action than loxapine.
- 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.)

**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.

**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.

**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.
**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

**Olanzapine**

IM had greater speed of action and effectiveness compared with haloperidol.

Oral: Four to six hours to peak plasma concentration

• Same with Zydis 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

**Aripiprazole**

Limited experience in acute agitation

Dose response is not clear

May cause increased agitation

**Standard Dosing of Novel Antipsychotics**

<table>
<thead>
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<th>Drug Name (Trade Name)</th>
<th>Normal Adult Dose Range</th>
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<td>Clozapine (Clozaril)</td>
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<td>Risperidone (Risperdal)</td>
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<td>Olanzapine (Zyprexa)</td>
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<td>Quetiapine (Seroquel)</td>
<td>300 to 750 mg PO (in divided doses)</td>
<td>AstraZeneca</td>
</tr>
<tr>
<td>Ziprasidone (Geodone)</td>
<td>40 to 160 mg PO (in divided doses)</td>
<td>Pfizer, Inc</td>
</tr>
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</table>

**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, dyskinesia, 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.


**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.

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.

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

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.

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.

A Pharmacologic Treatment Algorithm for Agitation and Violence

McElroy Algorithm for Agitation

- Select an effective agent:
  - Effective Syndrome
  - No Effective Syndrome

- Antidepressants
  - SSRIs
  - Other antidepressants

- Mood Stabilizers
  - Lithium or Divalproex

- Antipsychotics
  - Other antiepileptics

- Atypical Antipsychotics

- Other Antidepressants

- SSRI's

- Lamotrigine


- Breastfeeding
- Pregnancy
- Clozapine
- ziprasidone


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.


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.


Depression and Anger Attacks

Anger attacks:
• Found to be more common in depressed patients (48%), than unscreened 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.


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


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.

Double Blind and Placebo-Controlled Studies on Impulsivity

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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.


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.


Anticonvulsants: Lithium

- Demonstrated effective in control of aggressive behaviors in aggressive prisoners and mentally retarded patients.
- Clinical effects: reduce frequency and severity of both hetero and auto aggressive outbursts.
- Mixed results in chronically psychotic patients.
- No adverse effects. 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 disorder.


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


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.


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%.


Other Options

- Fluoxetine open trial in refractory borderline patients (n=5) demonstrated efficacy in treating impulsive aggression ⁵
- 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 hallucinations ⁶