Evidence review of sedation for acute agitation or aggression in the ED

Richard Paoloni
Concord Hospital
My take on this talk

• De-escalation techniques have not worked
• Oral medication has been offered & refused
• The senior ED MO has determined that parenteral sedation is required

• Not being covered in this talk:
  – Legal considerations were expertly covered last year by Sanj Fernando (& friends) at this meeting
  – ‘Take down’ training & safe assessment rooms are whole discussions in themselves
What I have been doing?

- My ‘not particularly evidence based’ approach

<table>
<thead>
<tr>
<th>Clinical Situation</th>
<th>Medication regime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychotic agitation</td>
<td>Haloperidol &amp; Diazepam (5 - 10 mg of each)</td>
</tr>
<tr>
<td>Aggression NOS</td>
<td>Droperidol &amp; Diazepam (5 - 10 mg of each)</td>
</tr>
<tr>
<td>Elderly pt with agitation</td>
<td>Very small doses of either olanzapine or resperidone</td>
</tr>
</tbody>
</table>
What NSW Health suggests

- GL2015_007  Management of patients with Acute Severe Behavioural Disturbance in Emergency Departments
  - Psychosis is not distinguished from Aggression NOS

<table>
<thead>
<tr>
<th>Clinical Situation</th>
<th>Medication Regime</th>
</tr>
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<tbody>
<tr>
<td>Aggression NOS</td>
<td>Droperidol 10mg IM, repeat if necessary</td>
</tr>
<tr>
<td></td>
<td>- Then either midazolam, diazepam, or ketamine</td>
</tr>
</tbody>
</table>

- Elderly pts → not included in guideline!

- Refers to NSW Handbook “Assessment and Management of People with Behavioural and Psychological Symptoms of Dementia (BPSD)”, which is actually produced by the Royal Australian & NZ College of Psychiatrists

<table>
<thead>
<tr>
<th>Clinical Situation</th>
<th>Medication Regime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggression / agitation in Dementia</td>
<td>Olanzapine 2.5mg, can be repeated (max 7.5 mg)</td>
</tr>
<tr>
<td></td>
<td>- DO NOT use if delirious → seek specialist advice</td>
</tr>
</tbody>
</table>
Evidence cited in NSW Guideline in relation to choice of sedative agent

- RCT of IM Droperidol vs Midazolam for Violence and Acute Behavioural Disturbance: The DORM study

- The Safety & Effectiveness of Droperidol for Sedation of Acute Behavioural Disturbance in the ED.

- RCT comparing IV midazolam & droperidol for sedation of the acutely agitated patient in the ED
What CCMH suggests

<table>
<thead>
<tr>
<th>Psychotic agitation Rx (IM)</th>
<th>Medication Regime</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; Line</td>
<td>Lorazepam 1-2 mg or Midazolam 5-10 mg</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; Line</td>
<td>Ziprasidone 10-20 mg or Olanzapine 10mg</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; Line</td>
<td>Haloperidol IM 5-10 mg or Zuclopenthixol 50mg</td>
</tr>
</tbody>
</table>

CCMH is the Concord Centre for Mental Health

This is the ‘old’ Rozelle Hospital which was transferred to Concord in approximately 2007 and is one of the largest mental health inpatient units in the State, with 173 overnight inpatient beds.

CCMH has its own ‘admission office’ which accepts primary mental health referrals for assessment 24/7 (referred by self or family, GP, police or ambulance). Patients requiring mental health assessments can be re-directed from ED triage.

CCMH provides mental health consultations to Concord ED.
Few answers .. Lots of questions

• My ‘anecdotal’ approach:
  – Am I out of step with the evidence or common practice?
  – Does no-one want to help me work out what to do with old people with agitated delirium?

• NSW Health Guidelines:
  – Should we treat psychotic agitation and non-specific aggression the same way?
  – Three studies cited... all Australian (not that we are xenophobic, or anything) ... all about droperidol ... is that it? ... Are there no other options worth considering? ... Is the rest of the world disinterested in this issue?

• CCMH guidelines:
  – What on earth is ziprasidone? ... let alone Zuclopenthixol !!
Evidence for sedation in psychosis

• Sedation for aeromedical retrieval:
  – Consensus based clinical guideline developed in WA, due to ‘scant literature’ being available
    • Clonazepam 1-2mg and/or Haloperidol 2.5-5mg
      – If clonazepam not stocked, Diazepam 10-20mg
    • If required, Midazolam 2.5-5mg
      – Add maxalon and ranitidine
  – Queensland article on 18 pts given Ketamine
    • Given if first line agents (Benzodiazepine and/or Antipsychotic) had failed to control agitation
    • All effectively sedated, no significant adverse events

Balaratnasingam S. A new clinical guideline to improve sedation safety in patients transferred under the Mental Health Act from remote parts of Western Australia. Australian Psychiatry 2014; 22(6): 564-568
Evidence for sedation in psychosis

- **DROPERIDOL:**
  - Cochrane review 2012 (3 included studies):
    - Superior to placebo three minutes after injection (n=41)
    - Not statistically better than haloperidol for rescue medication needed at 30 minutes
  - RCT of *Droperidol vs Haloperidol* (2015):
    - IM doses of 10mg in a psychiatric ICU (single blind RCT)
    - Primary outcome = time to sedation within 120 minutes
    - 584 pts identified → 228 randomised → 92% sedated in 120 mins
      - Exclusions: 115 previously recruited, 128 clinicians gave droperidol, 48 clinicians gave other medication, 65 wrong dose (not 10mg)
    - No difference in median sedation time (haloperidol 20 min, droperidol 25 min)
    - Additional sedation more often with haloperidol (13% vs 5%, p=0.06) but less adverse effects (1% vs 5%, p=0.12).
      - Adverse events = hypotension (5), desaturation (1), EPS (1), oversedation (1).
      - Note: Two haloperidol pts and 6 droperidol patients also received midazolam
    - Eight staff injuries occurred !!

Rathbone J, Mandriota-Carpenter SL, Cure SJ. Droperidol for acute psychosis. Cochrane Database of Systematic Reviews 2012
Evidence for sedation in psychosis

- **HALOPERIDOL:**
  - Cochrane review 2011 (32 included studies):
    - Superior to placebo
    - Vs olanzapine (4 studies, n=631):
      - Olanzapine superior in terms of adequate sedation at two hours
      - No difference in need for repeat sedation or rate of adverse events
    - Vs Ziprasidone (3 studies, n=739):
      - No difference in sedative outcomes at 2 hrs, more side effects with haloperidol at 72 hours
    - Vs Haloperidol + Lorazepam (2 studies, n=113):
      - More sedation at 30 mins / 60 minutes & more people asleep at 3 hrs with combination Rx
    - Vs Haloperidol + Promethazine (one study, n=316):
      - Combination superior at 20 mins, 40 mins, 60 mins, & 120 mins.
      - Significantly more side effects (particularly dystonia) in the haloperidol alone group
  - Authors’ conclusion → best evidence is probably for the use of haloperidol with promethazine

Powney MJ, Adams CE, Jones H. Haloperidol for psychosis-induced aggression or agitation. Cochrane Database of Systematic Reviews 2011
Evidence for sedation in psychosis

- **HALOPERIDOL PLUS PROMETHAZINE:**
  - Cochrane review 2008 (4 studies, n=1117):
    - Vs **benzodiazepines**:
      - Midazolam appears more swiftly sedating than lorazepam, but higher risk of respiratory depression
      - Difficult to assess against H+P due to variable %sedation in H+P group in the two large studies (67% vs 95% sedated at 30 mins); sedation achieved in 90% at 2 hours
    - Vs **Olanzapine** (n=300):
      - 90% tranquil or sleep in 15 mins in both groups, but 43% given olanzapine needed rescue Rx within 4 hours (vs 21%)
      - Low side effect rates in both groups (not significant)
  - **Authors’ conclusions**:
    - All evaluated treatments effective
    - Benzodiazepines have potential for respiratory depression
    - Haloperidol used alone is at such risk of preventable side effects that this type of use should be avoided
    - IM olanzapine is valuable but its duration of action is short and re-injection is frequently needed
    - H+P used in two diverse situations (Brazil, India) has much evidence to support its swift & safe effects

Evidence for sedation in psychosis

**BENZODIAZEPINES:**

- Cochrane review 2012 (21 trials, n=1968):
  - More participants receiving combined benzodiazepines and haloperidol had NOT improved by medium term (1-48 hrs) when compared to those receiving olanzapine or ziprasidone

- Authors’ conclusions:
  - Adding a benzodiazepine to other drugs does not seem to confer clear advantage and has potential for adding unnecessary adverse effects

Gillies D, Sampson S, Beck A, Rathbone J. Benzodiazepines for psychosis-induced aggression or agitation. Cochrane Database of Systematic Reviews 2013
Evidence for sedation in psychosis

**OLANZAPINE:**

- Cochrane review 2009 (4 studies)
  - Vs placebo → effective
  - Vs haloperidol → as effective at 2 hours, no difference in rescue Rx, less akathisia and EPS
  - Vs lorazepam IM → as effective at 2 hours, less emergent side effects, no difference in anticholinergic Rx
  - Authors’ conclusions note that all included studies of olanzapine are funded by a company with a pecunary interest in the result, however, olanzapine is probably valuable and fewer movement disorders than haloperidol

Belgamwar RB, Fenton M. Olanzapine IM or velotab for acutely disturbed / agitated people with suspected serious mental illness. Cochrane Database of Systematic Reviews 2009
Evidence for sedation in psychosis

• **ZIPRASIDONE:**
  - The first atypical antipsychotic available in both IM and oral formulations
  - Two double-blind, RCT, dose finding studies (2 vs 10, 2 vs 20mg)
    - Both 20mg & 10mg superior to 2mg at 2 & 4 hrs, one akathisia
    - Caused calming without excessive sedation
  - Vs haloperidol → ziprasidone a more effective antipsychotic within 3 days of treatment and lower side effect profile

Evidence for sedation in psychosis

- **MISCELLANEOUS:**

  - Multidrug trial *(olanzapine, ziprasidone, H+P, H+midaz, H alone)* (n=150)
    - Double blind RCT, all medications produced a calming effect within 1 hour
      - Olanzapine showed greatest improvement in 1 hr, followed by ziprasidone & haloperidol alone
      - 70% of patients receiving H + midaz needed mechanical restraint 1-12 hours after Rx
      - This group also had a higher need for rescue medication and highest rate of excessive sedation

  - **Quetiapine** 100-200mg IM
    - 40% of patients developed orthostatic hypotension
      - 25% of these symptomatic from hypotension

  - **Valproic acid IV** (one study, n=80)
    - Compared against haloperidol in double-blind RCT
    - Similar efficacy at 30 mins but better side effect profile
      - 36% of haloperidol group deeply sedated (vs 2.5%) & 9% EPS
    - Mean dose of valproate ≈ 1.5 g

Evidence for sedation in aggression NOS

- Sedation for pre-hospital transport:
  - IM droperidol 5mg under EMS physician order for extreme combativeness (n=53)
    - Five point agitation scale (5 = continuous, vigorous fighting against restraints), mean pre-drug score 4.7
      Decreased to 3.9 after 5 mins, 3.3 after 10 mins, 2.8 at hospital
    - One pt obtunded and required supplemental oxygen, sedation ineffective in 7 pts (15%)
  - Retrospective review of prehospital haloperidol (n=314) & droperidol (n=218)
    - Mean doses were haloperidol 7.9 mg (median 10mg) and droperidol 2.9 mg (median 2.5)
    - Haloperidol IM in 92%, droperidol in 61% - otherwise given IV, no differences in QTc on first ED ECG or rescue Rx in ED
    - One patient with a history of congenital heart disease given droperidol suffered a cardiopulmonary arrest and was resuscitated (ROSC after 1 minute of CPR) with neurologically intact survival
  - Retrospective review of prehospital IM ketamine 4 mg/kg (n=52)
    - 50% were given IM or IV midazolam (2.5 mg) once control established to mitigate emergence reactions
    - 50 of 52 pts rapidly sedated (2 mins), three cases (6%) of significant respiratory depression → one BVM and two ETT
  - ED experience with patients treated with pre-hospital ketamine (n=12)
    - On arrival 5 unrousable, 1 deeply sedated, 4 moderately sedated, two lightly sedated
    - Three hypoxic (1 pre, 2 in ED) → 2 ETT (recurrent laryngospasm, intracranial bleed)
    - 30% emergency reactions, 50% required additional sedation

Evidence for sedation in aggression NOS

- **Droperidol** (efficacy):
  - IV vs lorazepam (n=202)
    - Sedation scores every 5 mins, 72% pts amphetamines / 14% cocaine, 50% ETOH
    - Similar sedation at 5 minutes, droperidol more sedating at 10-60 mins, more repeat doses of lorazepam at 30 minutes, few side effects
  - Double blind RCT of IM droperidol (5), ziprasidone (20), midazolam (5) (n=144)
    - Adequate sedation at 15 mins midazolam, 30 mins for droperidol & ziprasidone
    - Rescue sedation – 50% midazolam, 10-15% droperidol & ziprasidone
    - Respiratory depression needing supplemental O2 (15% in all groups), no ETT
  - Double blind RCT of IV droperidol vs midazolam (n=153) 5 mg every 5 min til sedated
    - No difference in time to sedation (median 6.5 midaz, 8 mins droperidol)
    - Although at 5 minutes 45% midaz pts adequately sedated vs 17% droperidol (p<0.001)
    - At 10 minutes 55% of both groups adequately sedated
    - Similar adverse event rates in both groups; three airway interventions (1 ETT, all with midazolam)

Evidence for sedation in aggression NOS

- **Droperidol (safety):**
  - Prospective study of patients given droperidol (10-20mg) and Holter monitored
    - 46 pts, four pts had abnormal QT (10%), three had QTc >500 but only one c/w droperidol timing
  - Retrospective review of IM or IV droperidol used in ED → further examined high risk pts (head injury, ETOH or cocaine, remote or recent seizures)
    - 2468 pts aged 20 mths to 98 yrs, 1357 Rx for agitation (1310 for pain)
    - 945 pts high risk → mean dose 4.1 mg
      - Transient hypotension (10%), with 25% receiving IV fluids
      - Respiratory depression (2), seizures (3), cardiac arrest (1)
  - Review of literature regarding droperidol & dysrhythmia ‘done before the FDA’s very recent and peremptory warning about droperidol’, as well as their own experience in using droperidol in a busy psychiatric emergency department.

Chase PB, Biros MH. A retrospective review of the use and safety of droperidol in a large, high risk, inner city ED patient population. Acad Emerg Med 2002; 9: 1402-1410
Evidence for sedation in aggression NOS

- Other agents:
  - Double blind RCT of IM midazolam (5), lorazepam (2), haloperidol (2) (n=111)
    - Mean time to sedation: midaz 18 mins, haloperidol 28 mins, lorazepam 32 mins (p<0.05)
    - Mean time to arousal: midaz 82 mins, haloperidol 127 mins, lorazepam 218 mins (p<0.05)
    - No difference in vital sign changes, no adverse events
    - Authors’ conclusion: Midaz shorter time to sedation and more rapid time to arousal, efficacies of all drugs appear similar

- IV midazolam plus either droperidol or olanzapine (n=336)
  - Double-blind, placebo controlled RCT of saline, droperidol (5) or olanzapine (5) bolus then incremental boluses of IV midazolam (2.5 – 5mg) until sedation achieved.
  - Combination therapy ➔ median time to sedation 4-5 minutes faster meaning that, at any point, pts were 1.6 times more likely to be sedated, resulted in less rescue or alternative drug Rx after initial sedation
  - Adverse event profiles and LOS did not differ between groups but was relatively high (8-15%)
    - Airway obstruction 3-4% (highest in midaz only group) and oxygen desaturation (5-8%, lower in olanzapine group), requiring jaw thrust or lateral positioning +/- supplemental oxygen
    - Hypotension requiring IV fluids (3-5%, lower in olanzapine group)

Evidence for sedation in aggression NOS

- Safety in chemical sedation:
  - 50 pts (18+ yrs of age), chemical sedation for psychomotor agitation & violent behaviour, SpO2 and ETCO2 recorded every 5 mins
    - Sedation agents not standardised – most commonly haloperidol (IV if possible, 2.5 to 10mg) and lorazepam (IV if possible, doses up to 2mg)
    - 28 pts developed respiratory depression (ETCO2 >50, 10% change from baseline, loss of waveform 15 seconds) at least once during chemical restraint
    - 21 pts had at least one hypoxic event (SpO2 <93% for >15 seconds), with 19 of these having preceding respiratory depression (90% predictive)
    - 5 pts received respiratory interventions (airway repositioning 2, verbal stimulation 3)
    - Few of these events were recognised by their treating physicians

Evidence: Sedation in elderly

- **Double blind RCT** of IM olanzapine (2.5mg or 5mg) vs lorazepam (1mg) vs placebo
  - Pts with Alzheimers or vascular dementia and agitation
  - All active groups superior to placebo at 2 hours, both olanzapine groups still superior at 24 hours (lorazepam not), no difference in sFx between groups (~10% of pts, most common were accidental injury, abnormal ECG, headache and somnolence)

- **IM olanzapine (2.5 mg) vs lorazepam (1mg) vs placebo** [Company run]
  - Pts with Alzheimers or vascular or mixed dementia
  - Both active arms superior to placebo for sedation over the first 2 hours, olanzapine faster to ‘calm’ state but overall rate similar

- **IM ziprasidone** 10-20mg, repeated at 12 hours if needed, for pts 60+ yrs admitted to psychogeriatric ward for acute psychotic agitation (n=21, aged 60-81 yrs)
  - Good efficacy in reducing agitation
  - Documented sFx – one male urinary retention, one report each of transient blurred vision and sedation

- **Retrospective chart review** of pts with delirium treated with haloperidol for agitation (n=56, mean age 83 yrs)
  - Recommended initial dose (0.5 mg) used in 36%, 1mg dose used in 27%, doses >1 mg used in 38%
  - Approximately 30% also given lorazepam in mean doses of 0.4 mg
  - No difference in efficacy between low and high doses, relative risk of sedation significantly greater with higher doses (11 vs 3%)

Summing Up

• So what does it all mean ??

• What drug should I use next time ??
## Sedation for psychosis

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>Efficacy (highest to lowest)</th>
<th>Safety (highest to lowest)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intramuscular</td>
<td><strong>Midazolam</strong></td>
<td><strong>Ziprasidone</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Haloperidol + Promethazine</strong></td>
<td><strong>Haloperidol + Promethazine</strong></td>
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<td></td>
<td><strong>Olanzapine</strong></td>
<td><strong>Olanzapine</strong></td>
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<tr>
<td></td>
<td><strong>Haloperidol + Benzo</strong> (Midazolam / Lorazepam)</td>
<td><strong>Haloperidol + Lorazepam</strong></td>
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<tr>
<td></td>
<td><strong>Droperidol / Haloperidol / Ziprasidone</strong></td>
<td><strong>Haloperidol</strong></td>
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<tr>
<td></td>
<td><strong>Lorazepam</strong></td>
<td><strong>Droperidol</strong></td>
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<tr>
<td></td>
<td><em>(ALL are fairly effective)</em></td>
<td><strong>Lorazepam</strong></td>
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<td></td>
<td></td>
<td><strong>Haloperidol + Midazolam</strong></td>
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<tr>
<td></td>
<td></td>
<td><strong>Midazolam</strong></td>
</tr>
<tr>
<td>Intravenous</td>
<td><strong>Haloperidol / (Valproate)</strong></td>
<td><strong>Sodium valproate</strong></td>
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<td></td>
<td></td>
<td><strong>Haloperidol</strong></td>
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</tbody>
</table>
# Sedation for aggression NOS

<table>
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<tr>
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<tbody>
<tr>
<td>Intramuscular</td>
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</tr>
<tr>
<td></td>
<td>Droperidol / Ziprasidone</td>
<td>Lorazepam</td>
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<tr>
<td></td>
<td>Haloperidol</td>
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<tr>
<td></td>
<td>Lorazepam</td>
<td>Droperidol</td>
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<tr>
<td></td>
<td></td>
<td>Midazolam</td>
</tr>
<tr>
<td>Intravenous</td>
<td>Midazolam + Droperidol / Midazolam + Olanzapine</td>
<td>Lorazepam</td>
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<td></td>
<td>Midazolam</td>
<td>Midazolam + Olanzapine</td>
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<td>Droperidol</td>
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<td>Lorazepam</td>
<td>Midazolam + Droperidol</td>
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<tr>
<td></td>
<td></td>
<td>Midazolam</td>
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</tbody>
</table>
Comments on above tables

- **EFFICACY:**
  - All listed agents are effective, and differences in efficacy are likely minor.
  - Almost certainly midazolam produces fastest sedation but moderate risk of respiratory sFx

- **SAFETY:**
  - Droperidol: overall adverse event rate similar to midazolam, haloperidol & benzodiazepines but most frequent side effect is hypotension (up to 10% of pts), which is potentially problematic if droperidol given IM (no IV access) and two documented cardiac arrests
  - Droperidol adverse event rate is considerably higher than ziprasidone and haloperidol with promethazine (both of which have been studied in significant numbers of patients) and probably olanzapine (less patient numbers in studies & half of studies potentially conflicted)
## Sedation for elderly agitated pts

<table>
<thead>
<tr>
<th>Method</th>
<th>Efficacy (highest to lowest)</th>
<th>Safety (highest to lowest)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intramuscular</td>
<td>Olanzapine (if not delirious)</td>
<td></td>
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<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td>If delirious</td>
<td>??Ziprasidone</td>
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</tr>
<tr>
<td></td>
<td>??Lorazepam</td>
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<tr>
<td></td>
<td>??Haloperidol</td>
<td>Haloperidol</td>
</tr>
<tr>
<td>Clinical Situation</td>
<td>Medication Regime</td>
<td>Comment</td>
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<tr>
<td>-------------------------</td>
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<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Psychosis (IM)</td>
<td>Midazolam, or</td>
<td>Fastest effect, significant side effects (respiratory) but can also be reversed</td>
</tr>
<tr>
<td></td>
<td>Ziprasidone</td>
<td>Good evidence of efficacy (similar to haloperidol / droperidol) but MUCH better safety profile</td>
</tr>
<tr>
<td>Psychosis (IV)</td>
<td>Haloperidol, or (Valproate)</td>
<td>(?Add small dose of promethazine)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Limited information but looks effective &amp; low sFx (watch this space)</td>
</tr>
<tr>
<td>Aggression NOS (IM)</td>
<td>Midazolam, or</td>
<td>(as above)</td>
</tr>
<tr>
<td></td>
<td>Ziprasidone</td>
<td>(as above)</td>
</tr>
<tr>
<td>Aggression NOS (IV)</td>
<td>Midazolam + Olanzapine</td>
<td>Probably same efficacy as midazolam + droperidol, but likely better safety profile</td>
</tr>
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<td>Elderly pts (IM)</td>
<td>Olanzapine</td>
<td>If not delirious</td>
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<td>If delirious; probably MUCH better side effect profile than lorazepam or haloperidol</td>
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