The Agitated Patient in the ED

Updates and Revisits
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“Rough” Learning Objectives

• Review literature related to agitated patient management in the ED from 2013/2014
• Discuss novel medications or delivery methods
• Review mainstays of ED treatment
• Discuss EM myths versus realities for certain medications
• Finish this presentation early
What’s new for 2014?

• Difficult search…
  – Psychosis
  – Agitation
  – ED

• Not too much new (shocking!)
Still using the tried and true?


Wilson MP¹, Minassian A², Bahramzi M³, Campillo A³, Vilke GM¹.

- Looked at SGA use versus older medications
- Two academic centers, 1680 patients
  - Those received SGAs, minority of patients
  - No change from benzos and FGAs over time
  - 21% received benzodiazepines along with SGA
  - Increased administration with ETOH presence
Benzodiazepines still working?

Cochrane suggests data quality of studies prohibits conclusion to be made

All FGA/SGA trials compare efficacy to benzodiazepines

Benzos are always non-inferior on basis of “lack of noted effect”

Re-dosing more common than antipsychotics
Benzodiazepines still safer?

Treatment of Agitation in the Emergency Department: Benzodiazepines Could Be Safer than Antipsychotics in Some Cases of Insufficient Medical Data.

Rolland B, Debien C, Vaiva G.
Any practice guidelines?

• All are very dated
• Guidelines.gov
  – Clinical practice documents, no specifics
  – Risperidone, Aripiprazole (young people)
• “NICE” guidelines from UK, 2005
  – Rapid “tranquilisation”
  – Haldol and lorazepam
  – Olanzapine
Appendix A. Tables of FDA-Approved Indications for First- and Second-Generation Antipsychotics

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Indications</th>
<th>Age Group for Which Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>Schizophrenia</td>
<td>Adults and children (1–12 years)</td>
</tr>
<tr>
<td></td>
<td>Bipolar disorder (mania)</td>
<td></td>
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<tr>
<td></td>
<td>Hyperactivity</td>
<td></td>
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<td></td>
<td>Severe behavioral problems</td>
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<tr>
<td>Droperidol</td>
<td>Agitation</td>
<td>Adults and children</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>Psychotic disorders</td>
<td>Adults</td>
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<tr>
<td></td>
<td>Schizophrenia</td>
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<tr>
<td>Haloperidol</td>
<td>Tourette syndrome</td>
<td>Adults</td>
</tr>
<tr>
<td></td>
<td>Hyperactivity</td>
<td></td>
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<tr>
<td></td>
<td>Severe childhood behavioral problems</td>
<td></td>
</tr>
<tr>
<td>Loxapine</td>
<td>Schizophrenia</td>
<td>Adults and children ≥12 years</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>Schizophrenia</td>
<td>Adults and children ≥12 years</td>
</tr>
<tr>
<td>Pimozide</td>
<td>Tourette syndrome</td>
<td>Adults and children ≥12 years</td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td>Schizophrenia</td>
<td>Adults and children &gt;2 years and &gt;20 pounds</td>
</tr>
<tr>
<td></td>
<td>Generalized nonpsychotic anxiety</td>
<td>Adults</td>
</tr>
<tr>
<td>Thiothixene</td>
<td>Schizophrenia</td>
<td>Adults and children ≥12 years</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>Schizophrenia</td>
<td>Adults</td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td>Schizophrenia</td>
<td>Adults and children ≥6 years</td>
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<td></td>
<td>Generalized nonpsychotic anxiety</td>
<td>Adults</td>
</tr>
<tr>
<td>Generic Name</td>
<td>Indications</td>
<td>Age Group for Which Approved</td>
</tr>
<tr>
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<tr>
<td>Aripiprazole</td>
<td>Adjunctive treatment of major depressive disorder</td>
<td>Adults</td>
</tr>
<tr>
<td></td>
<td>Irritability Associated with autistic disorder</td>
<td>Children (6–17 years)</td>
</tr>
<tr>
<td></td>
<td>Acute treatment of agitation</td>
<td>Adults</td>
</tr>
<tr>
<td>Asenapine</td>
<td>Acute schizophrenia</td>
<td>Adults</td>
</tr>
<tr>
<td></td>
<td>Bipolar disorder type 1 (manic/mixed)</td>
<td>Adults</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Reduce the risk of suicidal behavior in younger patients with schizophrenia.</td>
<td>Adults</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>Acute schizophrenia</td>
<td>Adults</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Schizophrenia</td>
<td>Adults and adolescents (13–17 years)</td>
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<tr>
<td></td>
<td>Bipolar disorder (manic/mixed)</td>
<td>Adults and adolescents (13–17 years)</td>
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<td></td>
<td>Treatment resistant depression</td>
<td>Adults</td>
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<tr>
<td></td>
<td>Agitation associated with schizophrenia and bipolar I mania</td>
<td>Adults</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>Schizophrenia</td>
<td>Adults and adolescents (13–17 years)</td>
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<tr>
<td></td>
<td>Schizoaffective disorder</td>
<td>Adults and adolescents (13–17 years)</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Schizophrenia</td>
<td>Adults and adolescents (13–17 years)</td>
</tr>
<tr>
<td></td>
<td>Bipolar disorder (acute manic)</td>
<td>Adults, children, and adolescents (10–17 years)</td>
</tr>
<tr>
<td></td>
<td>Bipolar disorder (depression)</td>
<td>Adults</td>
</tr>
<tr>
<td></td>
<td>Bipolar disorder (maintenance)</td>
<td>Adults</td>
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<td></td>
<td>Adjunctive therapy for major depressive disorder</td>
<td>Adults and adolescents (13–17 years)</td>
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<tr>
<td>Risperidone</td>
<td>Schizophrenia</td>
<td>Adults and adolescents (13–17 years)</td>
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<td>Adults and adolescents (10–17 years)</td>
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<td></td>
<td>Irritability associated with autism</td>
<td>Children (5–16 years)</td>
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<tr>
<td>Ziprasidone</td>
<td>Bipolar disorder (manic/mixed)</td>
<td>Adults</td>
</tr>
<tr>
<td></td>
<td>Bipolar disorder (maintenance)</td>
<td>Adults</td>
</tr>
<tr>
<td></td>
<td>Acute agitation in patients with schizophrenia</td>
<td>Adults</td>
</tr>
</tbody>
</table>
Choice of Antipsychotic Concerns

• Extrapyramidal
  – Dystonic, dyskinesia, akinesia
• Cardiovascular
  – Prolonged QTc
• Metabolic
  – Hyperglycemia, dyslipidemia
• Hormonal
  – Plasma prolactin, gynecomastia
• Other
  – Subjective experience (hallucination, etc.)
ED Concerns

• Cardiovascular effects
  – Dreaded QTc prolongation

• CNS depression

• ACUTE dystonia
  – More common in young people/naive population

• What is the reality?
## QT Prolongation

**Table 1. Effects of Orally-Administered Antipsychotics on the QT Interval**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean Increase in QTc (ms)</th>
<th>% of Subjects With &gt; 60 ms Increase in QTc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thioridazine</td>
<td>35.8</td>
<td>29</td>
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<tr>
<td>Ziprasidone</td>
<td>20.6</td>
<td>21</td>
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<tr>
<td>Quetiapine</td>
<td>14.5</td>
<td>11</td>
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<tr>
<td>Risperidone</td>
<td>10.0</td>
<td>4</td>
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<tr>
<td>Olanzapine</td>
<td>6.4</td>
<td>4</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>4.7</td>
<td>4</td>
</tr>
</tbody>
</table>

*Data adapted from the U.S. Food and Drug Administration’s Center for Drug Evaluation and Research, Psychopharmacological Drugs Advisory Committee.*

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**Note:** The table provides the mean increase in QTc (milliseconds) and the percentage of subjects with a QTc increase greater than 60 milliseconds for various antipsychotics. The data is adapted from the U.S. Food and Drug Administration’s Center for Drug Evaluation and Research, Psychopharmacological Drugs Advisory Committee.
QT Prolongation

- 60 patients, average 10.2 years old
  - Aripiprazole or Risperidone oral monotherapy
  - Risperidone, average 12 ms increase
  - Aripiprazole, negligible
QT Prolongation

- 49 patients, mean age 81
- Droperidol (10, 5 or 2.5mg) plus midazolam
- 5mg dose had optimal sedation time
- None had QTc prolongation
CNS depression w/ SGA and ETOH?

- Alcohol was independent risk factor for respiratory depression
- Minimal contribution from adding benzodiazepine
- Effect was of course magnified with either FGA, SGA or benzo


*Intramuscular ziprasidone: influence of alcohol and benzodiazepines on vital signs in the emergency setting.*

Wilson MP, MacDonald K, Vilke GM, Ronquillo L, Feifel D.
Bottom line...

• QTc prolongation
  – Beware combinations with other medications
  – High dose or multi-dose utilization
  – Patients with congenital prolongation
  – Always obtain, compare ECG intervals

• Sedation
  – Dose dependent, polypharmacy enhances
  – Beware concomitant drug/ETOH ingestion
Treatment Options
Classic Combinations

• First generation antipsychotic
  – Haloperidol (Haldol) still considered a mainstay
  – Frequently combined with benzodiazepine
  – Typical sedation times of 10-30 minutes
  – Other various “additions”
  – The “B52”
    • Haldol, 50mg Benadryl, 2mg Lorazepam
  – Droperidol still in use as well
Classic Combinations

• Second generation antipsychotics
  – Classically olanzapine (Zyprexa)
    • PO, IM, depot (Relprevv) and ODT (Zydis) formulations
  – OR ziprasidone (Geodon)
    • PO and IM formulations
  – OR aripiprazole (Abilify) gaining traction
    • PO, IM and ODT (discmelt) formulations

• Others used off label

• Frequently paired with benzodiazepines
Are there differences?

- Multiple studies looking at FGA versus SGA efficacy
  - Few address the ED setting
  - All conclusions are ‘limited’ by unclear clinical outcomes and data extraction
  - If any, olanzapine has hx of higher efficacy by small margin, higher s/e profile however (long term)
A trip down the K-hole?

• Ketamine
  – An old drug with new life
  – Recent flurry of studies disproving old concerns
  – Modulation of NMDA and other receptors
    • Emerging benefits in psychosis, PTSD, etc.
  – No clear clinical trials for ED tranquilization
  – Prehospital use climbing again
Ketamine come back?

- EMS providers recognized independent risk factors for ExDS
- Ketamine used for chemical restraint
- No untoward effects in 2 case reports
  - Suspected problems?
  - Hyperadrenergic state, QTc, electrolytes?
Ketamine Koncerns

• ED still not sure how to receive EMS patients treated with Ketamine

• Unclear data on drug interaction with others
  – Historical reports of bad outcomes with ketamine and PCP or bath salts abuse
  – Interplay with catecholamine release in EdSx
We Still Have Issues

• Few standards of care or policy statements on ED management of agitated patients
• Agreement that patients must be controlled
• Highly comorbid with bad outcomes due to patient population
• Perfect drug still does not exist, most dependent on multi-drug cocktail for adequate response
• More research to be done with Ketamine
Questions?