Psychopharmacology in the Emergency Room

Michael D. Jibson, M.D., Ph.D.
Professor of Psychiatry
University of Michigan

Disclosure

In the past 12 months I received $3,500 in royalties from *Up-to-Date* for chapters on antipsychotics and psychosis.

Learning Objectives

- Identify the goals and limitations of emergency room medication treatment
- Recognize the symptoms, underlying causes, and treatments of acute agitation
- Understand the advantages and disadvantages of oral and injectable administration of medications for acute agitation

Learning Objectives

- Recognized the advantages and disadvantages of the different antipsychotics for acute agitation
- Identify the symptoms of and treatments for acute dystonia and neuroleptic malignant syndrome (NMS)

Outline

- Appropriate targets for emergency room medication
- Acute agitation
  - Clinical description
  - Underlying causes
  - Goals of treatment
  - Medications
    - PO antipsychotics
    - IM antipsychotics
    - Benzodiazepines
  - Treatment selection

Outline

- Acute anxiety
  - Diagnosis
  - Treatment
- Acute dystonic reactions
  - Diagnosis
  - Treatment
- Neuroleptic malignant syndrome
  - Diagnosis
  - Treatment

Pretest

1. Which of the following conditions is LEAST likely to benefit from emergency room medication?
   a. Acute anxiety
   b. Acute agitation
   c. Acute suicidality
   d. Chronic hallucinations
   e. Alcohol withdrawal

Pretest

2. Which of the following is the most important goal of emergency room medication treatment?
   a. Rapid diagnosis of underlying disorder
   b. Establishment of patient and staff safety
   c. Rapid control of psychotic symptoms
   d. Reduction of suicidal ideation
   e. Disposition to appropriate follow-up care

Pretest

3. Compared to standard tablets of antipsychotics, orally disintegrating tablets have which of the following advantages?
   a. More rapid onset of action
   b. Greater bioavailability
   c. Significant transmucosal (eg, sublingual) absorption
   d. Greater ease of administration
   e. More appropriate dose strengths

Pretest

4. Compared to haloperidol, injectable atypical antipsychotics have which of the following advantages?
   a. Greater efficacy
   b. Better EPS profile
   c. Greater cost-effectiveness
   d. More rapid onset of action
   e. Greater convenience of administration

Pretest

5. Benzodiazepines are identical to one another in which of the following characteristics?

   a. Onset of action

   b. Route of administration

   c. Route of metabolism

   d. Duration of action

   e. Clinical efficacy

Treatment Principles

- Patient and staff safety are the highest priorities
- Pharmacologic interventions in the emergency room are limited to specific situations and target symptoms
- Treatment selection is based on:
  - target symptoms
  - underlying pathology
  - preferred route of administration

Emergency Pharmacology

Likely to benefit from emergency medications

- Psychotic agitation
- Acute anxiety
- Alcohol/sedative/hypnotic withdrawal
- Acute dystonic reaction

Emergency Pharmacology

Unlikely to benefit from emergency medications

- Major depression
- Suicidality
- Other drug withdrawal

Evaluation and Treatment of Acute Agitation

Agitation

Acute state of

- Anxiety
- Heightened arousal
- Increased motor activity

Agitation

May include

- Lack of cooperation
- Attempts to elope
- Hostility
- Aggression

Agitation

May be caused by

- Drug or alcohol intoxication
- Alcohol or sedative withdrawal
- Personality disorders
- Mood disorders
- Psychotic disorders
- Delirium
- Hypoxia
- Cognitive impairment

Agitation

May occur in conjunction with psychosis

- Mania
- Disturbing content of delusions or hallucinations
- Thought disorganization
- Intrusion of law enforcement or mental health workers
- Akathisia

Agitation

May include aggression related to

- More severe pathology
- Persecutory delusions
- Thought disorganization
- Command hallucinations

Treatment

Goals

- Maintain patient and staff safety
- Identify and address underlying pathology
  - Reduce psychosis
  - Reduce mania
  - Improve cognition
  - Treat medical problems

Treatment

Essential Resources

- Adequate staff
- Verbal de-escalation
- Medication
- Room seclusion
- Physical restraints

Treatment

Medications

- Antipsychotics
  - Oral
  - Injectable
- Benzodiazepines
  - Oral
  - Injectable

Oral Antipsychotics

Preferred Option

- Orally disintegrating tablets

Alternative Options

- Standard tablets
- Liquid concentrate
- Sublingual tablets

Oral Antipsychotics

- Standard tablets
  - Most antipsychotics are available
  - Easy to cheek
- Liquid concentrate
  - Many antipsychotics are available
  - Difficult to administer
- Sublingual tablets
  - Only asenapine (Saphris) is available
  - No data on use for acute agitation

Oral Antipsychotics

Orally Disintegrating Tablets

- Easy to administer
- Noninvasive
- Hard to “cheek”
- NOT absorbed transmucosally
- Same pharmacokinetics as standard tablets

Oral Antipsychotics

Orally Disintegrating Tablets

- Aripiprazole (Abilify Discmelt)
- Olanzapine (Zyprexa Zydis)
- Risperidone (Risperdal M-Tab)

Aripiprazole

Dosing (disintegrating tablets)

- 10-15 mg q 2 hrs
- Average dose: 20 mg/day
- Maximum recommended dose: 30 mg/day
- Supplied in 10 mg and 15 mg tablets

Aripiprazole

Pharmacokinetics (oral)

- 3-5 hr to peak concentration
- 75-hr elimination half-time
- No significant drug interactions
- Pharmacokinetics are identical to standard tablet

Aripiprazole

Short-term Side Effects

- Nausea/vomiting
- Akathisia
- Insomnia

Aripiprazole

Treatment Issues

- Nonsedating
- The combination of a partial agonist with an antagonist (ie, all other antipsychotics) leads to unpredictable receptor activities

Risperidone

Dosing (disintegrating tablets)

- 1-2 mg q 30 min - 2 hrs
- Average dose: 4 mg/day
- Maximum recommended dose: 6 mg/day
- Supplied in 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg tablets

Risperidone

Pharmacokinetics (oral)

- 1.5-hr to peak concentration
- 20-hr elimination half-time
- No significant drug interactions
- Pharmacokinetics are identical to standard tablets

Risperidone

Short-term Side Effects

- Sedation
- Orthostatic hypotension
- Akathisia
- EPS (dose-dependent)

Risperidone

Treatment Issues

- Higher risk of EPS
- Intermediate level of sedation

Olanzapine

Dosing (disintegrating tablets)

- 5-10 mg q 30 min - 2 hrs
- Average dose: 10 mg/day
- Maximum recommended dose: 20 mg/day
- Supplied as 5 mg, 10 mg, 15 mg, and 20 mg tablets

Olanzapine

Pharmacokinetics (oral)

- 5-hr to peak concentration
- 30-hr elimination half-time
- No major drug-drug interactions
- Pharmacokinetics are identical to coated tablets

Olanzapine

Treatment Issues

- More sedating
- More anticholinergic

Injectable Antipsychotics

Intramuscular Injection

- Ensured administration
- Rapid absorption
- Difficult to administer
- Invasive

Injectable Antipsychotic Medications

- Haloperidol (Haldol)
- Aripiprazole (Abilify)
- Olanzapine (Zyprexa)
- Ziprasidone (Geodon)

Haloperidol

Dosing (intramuscular or intravenous injection)

- 5-10 mg q 30 min - q 2 hr
- Average dose: 10 mg/day
- Maximum recommended dose: 20-30 mg/day

Haloperidol

Pharmacokinetics (IM or IV injection)

- IV: 20-30 min to peak concentration
- IM: 30-45 min to peak concentration
- 20-hr elimination half-time
- No major drug-drug interactions

Haloperidol

Short-term Side Effects

- Akathisia
- Acute dystonia
- Extrapyramidal side effects (EPS)
- Sedation
- QT prolongation (IV administration only)

Haloperidol

Treatment Issues

- Multiple routes of administration (IM, IV)
- Low cost
- High risk of side effects
- May require treatment transition

Aripiprazole

Dosing (intramuscular injection)

- 9.75 mg q 2 hrs
- Average dose: 19.5 mg/day
- Maximum recommended dose: 30 mg/day
- Available in 9.75 mg vials

Aripiprazole

Pharmacokinetics (injectable)

- 1-3 hr to peak concentration
- 75-hr elimination half-time
- No major drug-drug interactions

Aripiprazole

Short-term Side Effects

- Nausea/vomiting
- Headache
- Mild sedation

Aripiprazole

Treatment Issues

- Less sedation
- May be administered concurrently with BZDs
- Partial agonist-antagonist combinations lead to unpredictable receptor activities

Olanzapine

Dosing (intramuscular injection)

- 10 mg q 30 min - 2 hrs
- Average dose: 20 mg/day
- Maximum recommended dose: 30 mg/day

Olanzapine

Pharmacokinetics (injectable)

- 15-45 min to peak concentration
- 30-hr elimination half-time
- Possible interaction with IM lorazepam

Olanzapine

Short-term Side Effects

- Sedation
- Orthostatic hypotension
- Anticholinergic effects
- Akathisia

Olanzapine

Treatment Issues

- More sedating
- Unclear if safe with IM lorazepam
  - No controlled studies of safety
  - Few published case reports of problems
  - Most expert guidelines recommend a 1-hr delay between the medications to avoid cardiorespiratory depression

Ziprasidone

Dosing (intramuscular injection)

- Common dose range: 10-40 mg/day q 4 hr
- Average dose: 20 mg/injection
- Maximum recommended dose: 40 mg/day
- Available in 20 mg vials

Ziprasidone

Pharmacokinetics (injectable)

- 1 hr to peak concentration
- 2.5-hr elimination half-time
- Serum levels decreased by carbamazepine

Ziprasidone

Short-term Side Effects

- Somnolence
- Nausea
- Akathisia
- QT prolongation

Ziprasidone

Treatment Issues

- Moderately sedating
- No cardiac problems have been reported

  but

- Avoid use with other agents causing QT prolongation

Benzodiazepines

- Alprazolam (Xanax)
- Chlordiazepoxide (Librium)
- Clonazepam (Klonopin)
- Clorazepate (Tranxene)
- Diazepam (Valium, Dizac)
- Estazolam (ProSom)
- Flurazepam (Dalmane)
- Halazepam (Paxipam)
- Lorazepam (Ativan)
- Midazolam (Versed)
- Oxazepam (Serax)
- Prazepam (Centrax)
- Quazepam (Doral)
- Temazepam (Restoril)
- Triazolam (Halcion)

Benzodiazepines

Differ in

- Potency
- Onset of action
- Duration of action
- Route of administration
- Metabolic pathways

Are identical in

- Efficacy
- Clinical activity
- Pharmacologic activity

Benzodiazepines

Intramuscular

- Lorazepam (Ativan)

Intravenous

- Chlordiazepoxide (Librium)
- Diazepam (Dizac, Valium)
- Lorazepam (Ativan)

Lorazepam

Dosing (oral, intramuscular, intravenous)

- 1-2 mg q 30 min - 2 hr
- Average dose: 2-4 mg/day
- Maximum recommended dose: 12 mg/day

Lorazepam

Pharmacokinetics (Oral)

- 30 min to onset of action
- 2 hr to peak concentration
- 16 hr serum half-time
- No active metabolites
- Metabolism not affected by liver dysfunction

Lorazepam

Pharmacokinetics (IM or IV injection)

- 30 min to peak concentration
- 16 hr serum half-time

Lorazepam

Side Effects

- Sedation
- Disinhibition
- Delirium
- Respiratory depression

Lorazepam

Treatment Issues

- Highly sedating
- Generally well tolerated
- May cause respiratory depression when given IV
- May cause delirium or disinhibition

Treatment Selection for Psychotic Agitation

- FDA studies do not include highly agitated, involuntary patients
- Few studies compare available drugs
- Published studies are small, uncontrolled, and retrospective

Treatment Selection for Psychotic Agitation

Antipsychotics

- All antipsychotics appear comparable in efficacy
- Differences in onset of action have not been demonstrated
- Side effect profiles differ, but are rarely important in the acute phase
- Mode of administration differs

Treatment Selection for Psychotic Agitation

Benzodiazepines

- In the short term, benzodiazepines appear as effective as antipsychotics
- Benzodiazepines are highly sedating
- Lorazepam is the only IM benzodiazepine

Treatment Selection for Psychotic Agitation

- Antipsychotics are essential to treat underlying psychosis or mania
- Antipsychotics may have longer duration of action
- The combination of antipsychotics and benzodiazepines appears more effective than either one alone (but only one major study)

Evaluation and Treatment of Acute Anxiety

Acute Anxiety

Differential Diagnosis

- Panic attack
- Generalized anxiety
- Adjustment disorder
- Posttraumatic stress disorder (PTSD)
- Medical conditions
- Drug intoxication or withdrawal

Acute Anxiety

Treatment

- Benzodiazepines provide optimal short-term treatment for anxiety and panic symptoms
- Benzodiazepines may be used as an interim treatment during titration of other medications for anxiety (e.g., SSRIs, SNRIs).

Acute Dystonic Reaction

Acute Dystonic Reaction

- Intense muscle cramps as side effect of antipsychotic medications
- Highest risk with high potency first generation antipsychotics (e.g., haloperidol, thiothixene, fluphenazine)
- Not specific to any one medication

Acute Dystonic Reaction

- Most common early in treatment or shortly after a dose increase
- Highest incidence is at trough drug level
- May be isolated to specific regions of the body
  - Oculogyric crisis (extraocular muscles)
  - Torticollis (neck)
  - Laryngospasm (throat/larynx) – may be life threatening

Acute Dystonic Reaction

Treatment

- Benztropine (Cogentin)
  - 2 mg IM q 15-30 min up to 8 mg/day
- Diphenhydramine (Benadryl)
  - 50 mg IM q 15-30 min up to 200 mg/day

Neuroleptic Malignant Syndrome

Neuroleptic Malignant Syndrome (NMS)

- Diagnosis (DSM-5)
  - Hyperthermia (>38C) x 2
  - Profuse diaphoresis
  - Generalized rigidity (unresponsive to treatment)
  - Elevated CPK (>4x normal)
  - Early delirium, catatonia, stupor, or coma
  - Autonomic activation (elevated HR, BP, resp)

Neuroleptic Malignant Syndrome (NMS)

- Risk Factors
  - Rapid increase in antipsychotic dose
  - Parenteral administration
  - Dehydration
  - Agitation
  - Mood disorders
  - Neurologic illness
  - Younger or middle ages

Neuroleptic Malignant Syndrome (NMS)

- Risk Factors
  - All antipsychotics carry risk (~0.2%)
  - Risk may be lower with atypicals
  - Risk may be lowest with clozapine (~0.1%)
  - Course with clozapine may be more benign
  - Risk may be increased by concurrent lithium
  - Rechallenge carries a 30% risk of recurrence

Neuroleptic Malignant Syndrome (NMS)

- Natural History (in order of occurrence)
  - Changes in mental status (delirium or catatonia)
  - Temperature elevation/Diaphoresis
  - Autonomic instability
  - Muscle rigidity
  - Myoclonus
  - Elevated CPK
  - Death (20%)

Neuroleptic Malignant Syndrome (NMS)

- Differential Diagnosis
  - CNS infection
  - Severe EPS
  - Lethal catatonia
  - Malignant hyperthermia
  - Status epilepticus
  - Amphetamines/cocaine

Neuroleptic Malignant Syndrome (NMS)

- Treatment Recommendations
  - ECT may be fastest and most effective treatment
  - Conservative treatment (hydration, BZD) take longer to work, but reduce total hospital days
  - Bromocriptine and dantroline work faster, but are associated with more total hospital days

Neuroleptic Malignant Syndrome (NMS)

- Treatment Considerations
  - Do not resume antipsychotic medication until all symptoms have resolved (4-6 weeks)
  - Consider clozapine
  - Titrate antipsychotic slowly
  - Avoid lithium/antipsychotic combination

Post-test

1. Which of the following conditions is LEAST likely to benefit from emergency room medication?
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   b. Acute agitation
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   e. Alcohol withdrawal

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Post-test

5. Benzodiazepines are identical to one another in which of the following characteristics?

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   b. Route of administration

   c. Route of metabolism

   d. Duration of action

   e. Clinical efficacy

Pre- and Post-test Answers

1. c
2. b
3. d
4. b
5. e