ACUTE PSYCHOSIS MANAGEMENT

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OBJECTIVES

To be able to identify and prescribe appropriate treatment regimens to manage acute psychosis

To be able to identify specific patient factors that influence treatment decisions relating to the management of acute psychosis

To apply information learned to patient cases

CASE #1

JB is a 23 year old male who presents to the Emergency department with altered mental status. EMS reports that patient had a witnessed seizure at the scene

- S/Sx: agitated, disoriented to time and place, and is having difficulty carrying a conversation
- PE: diaphoretic, tremor present
- PMH is significant for obesity, type II diabetes, and major depressive disorder.
- Social History: Drinks "socially" and uses marijuana occasionally
- Friend in room identified as JB's fraternity brother reports that JB started studying for exams yesterday and swore off alcohol for the week but that he normally drinks heavily and frequently binge drinks

ACUTE ALCOHOL WITHDRAWAL MANAGEMENT

Psychosis Management

- Benzodiazepines are the treatment of choice

Seizure Management

- Lorazepam 0.1 mg/kg (Max: 4 mg/dose) should be given at the time of seizure and repeated as needed Q 5-10 minutes

Other Management

- Thiamine 100 mg IV daily for 3-5 days
  - Traditionally given prior to glucose
- Folic acid 1 mg
- Phenobarbital 10-15 mg/kg IV, propofol, ketamine
  - For benzodiazepine resistant patients

Kattimani S, Bharadwaj B. Clinical management of alcohol withdrawal: A systematic review. *Industrial Psychiatry Journal*. 2013;22(2):100-108.
D. Long et al. *American Journal of Emergency Medicine* 35 (2017) 1005–1011

BENZODIAZEPINES

	Lorazepam (IV)	Midazolam (IV)	Diazepam (IV)	Chlordiazepoxide (PO)
Dose, IV (= 1 std drink)	2-4 mg (Max 8-16 mg/dose)	0.2 mg/kg (Max 10 mg/dose)	5 mg (Max 10 mg/dose)	25 mg (Max 300 mg/day)
Onset	< 10 min	15 min (IM) 3-5 min (IV)	1-3 min	0.5 – 2 h
Half Life	~14 h (IV)	~3 h	33-45 h	24-48 h
Elimination	Renal	Hepatic	Hepatic	Hepatic
Active Metabolites	No	Yes	Yes	Yes
Preparations	PO, SL, IM, IV	PO, IV, IM	PO, IV	PO only
Special Considerations	- Ideal for patients with co-morbidities - Highly viscous – longer IM onset	- Preferred for IM	- Long half life gives better PK profile -Highly lipophilic	- Long half life gives better PK profile in patients without co-morbidities

Holbrook AM, Crowther R, Lotter A, Cheng C, King D. Meta-analysis of benzodiazepine use in the treatment of acute alcohol withdrawal. *CMAJ: Canadian Medical Association Journal*. 1999;160(5):649-655.
Amato L, Minozzi S, Vecchi S, Davoli M. Benzodiazepines for alcohol withdrawal. *Cochrane Database of Systematic Reviews* 2010, Issue 3. Art. No.: CD005063.

BENZODIAZEPINE DOSING STRATEGY

	Symptom Monitored Loading Dose	Fixed Dose	Symptom Triggered
Dosing Strategy	20 mg diazepam given Q 1-2h until CIWA scores are < 10	~5 mg diazepam per drink in 4 doses -DOC: Chlordiazepoxide, diazepam	CIWA score is assessed Q 1-2 h BZDs once over a certain threshold
Advantages	Combines advantages of other dosing strategies	Less monitoring May be used in less responsive patients	Decreased required BZD dose Shorter withdrawal treatment
Disadvantages		Prolonged withdrawal treatment	Cannot be used for all patients
Patient Factors	Best for patients with history of complicated withdrawal, seizures		Not for use in patients with withdrawal seizures, DT, nonverbal

DOC: Drug of Choice

Kattimani S, Bharadwaj B. Clinical management of alcohol withdrawal: A systematic review. *Industrial Psychiatry Journal*. 2013;22(2):100-108.

Order Sets

Medications

Alcohol Withdrawal Meds - Lorazepam Scheduled

- ○ LORazepam (ATIVAN) tablet
  1 mg, Oral, EVERY 6 HOURS for 30 days, Hold dose if patient is calm/sedate (RASS 0 or -1)
- ○ LORAZEPAM (ATIVAN) IV
  1 mg, Intravenous, EVERY 6 HOURS for 30 days, Hold dose if patient is calm/sedate (RASS 0 or -1)
- ○ LORazepam (ATIVAN) tablet
  2 mg, Oral, EVERY 6 HOURS for 30 days, Hold dose if patient is calm/sedate (RASS 0 to -1)
- ○ LORAZEPAM (ATIVAN) IV
  2 mg, Intravenous, EVERY 6 HOURS for 30 days, Hold dose if patient is calm/sedate (RASS 0 to -1)

Alcohol Withdrawal Medications - Lorazepam Regimen PRN

- ☑ PANEL ALCOHOL WITHDRAWL MEDS - LORAZEPAM REGIMAN PRN

  LORazepam (ATIVAN) 2 mg/mL vial 1 mg
  1 mg, Intravenous, EVERY HOUR AS NEEDED starting Today at 0859 until Fri 10/27 at 0858, For alcohol withdrawal
  CIWA score 8-20

  ⓘ **LORazepam (ATIVAN) 2 mg/mL vial 1 mg**
  - Daily dose of **24 mg (1 mg EVERY HOUR AS NEEDED) exceeds** recommended maximum of **12 mg**, over by **100%**
  - Frequency of **24 doses/day exceeds** recommended maximum of **6 doses/day**

  Or

  LORazepam (ATIVAN) 2 mg/mL vial 2 mg
  2 mg, Intravenous, EVERY HOUR AS NEEDED starting Today at 0859 until Fri 10/27 at 0858, For alcohol withdrawal
  CIWA score 20 or greater

  ⓘ **LORazepam (ATIVAN) 2 mg/mL vial 2 mg**
  - Daily dose of **48 mg (2 mg EVERY HOUR AS NEEDED) exceeds** recommended maximum of **12 mg**, over by **300%**
  - Frequency of **24 doses/day exceeds** recommended maximum of **6 doses/day**

Alcohol Withdrawal Nutrient Regiman (CMC ONLY)

- ☑ therapeutic multivitamin (THERAGRAN) tablet 1 Tab
  1 Tab, Oral, DAILY, 30 doses with the First Dose on Sat 9/30 at 0900, Last dose on Sun 10/29 at 0900
- ☑ folic acid (FOLVITE) tablet 1 mg
  1 mg, Oral, DAILY, 30 doses with the First Dose on Sat 9/30 at 0900, Last dose on Sun 10/29 at 0900
- ☑ thiamine (VITAMIN B1) tablet
  100 mg, Oral, DAILY, 30 doses with the First Dose Today at 0915, Last dose on Thu 10/26 at 0900

CASE #2

CS presents to the ED highly agitated with tachycardia and hypertension. He reports going on a “bender” last night and needing a “little pick me up” this morning and taking cocaine. You determine that he has cocaine toxicity.

The patient receives 2 mg lorazepam and continues to be agitated.

COCAINE INDUCED PSYCHOSIS TREATMENT

1. Benzodiazepines (BZD) – Drug of choice
   - May help reduce cardiovascular symptoms as well as limit agitation.
   - These patients frequently require higher doses of BZD
   - Start with IV or IM BZD given every 5-10 minutes (Dosing on slide 5)

2. Antipsychotics – both typical and atypical have been studied with mixed results
   - Droperidol – 5-10 mg IM every 10-30 min or 2.5-10 mg IV every 5 min (Max 20 mg per episode)
   - Haloperidol – 2-5 mg IM or IV every 4 hours

3. Ketamine
   - May not be ideal for these patients because HR and BP are typically elevated as well

Richards JR, et al. Treatment of cocaine cardiovascular toxicity: a systematic review. *Clinical Toxicology*. 2016 Feb; 54:5, 345-364

CASE #3

TJ is a 30 year old male who presents to the emergency department for ringing in his ears that started after an explosion that he was close to. He is extremely agitated, is lashing out at staff, screaming “they’re trying to kill me,” and is reaching for objects that do not exist.

TJ has a past medical history of multiple traumas, schizoaffective disorder, and hypertension.

Medication List: Lisinopril, amlodipine, melatonin, risperidone

PSYCHIATRIC DISORDER RELATED PSYCHOSIS

Pharmacologic Treatment

1. Atypical Antipsychotics
2. Typical antipsychotics
3. Combination therapy of BZD + antipsychotic

ANTIPSYCHOTICS VS BENZODIAZEPINES

Management of Acute Undifferentiated Agitation in the Emergency Department: A Randomized Double Blind Trial of Droperidol, Ziprasidone, and Midazolam

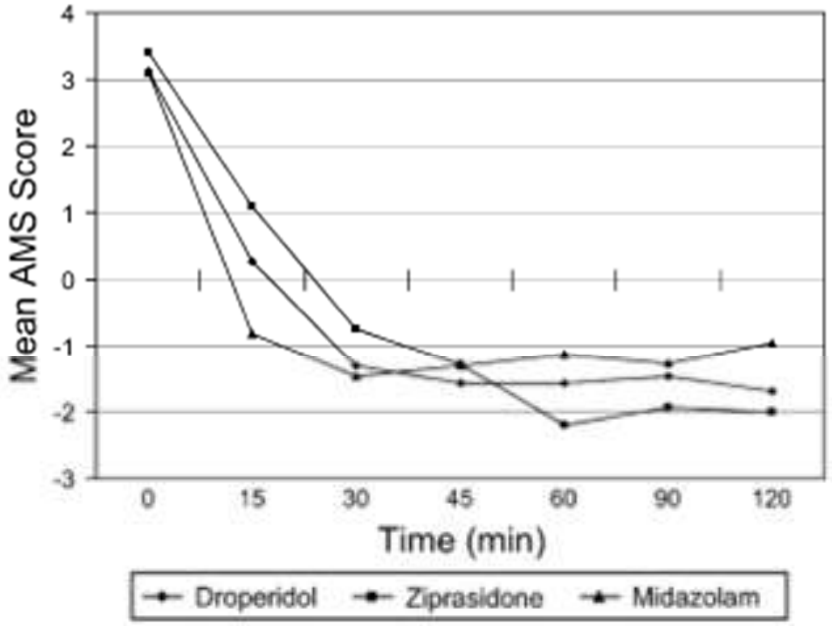


Figure 2. Mean Altered Mental Status Scale scores over time (see also Table 4).

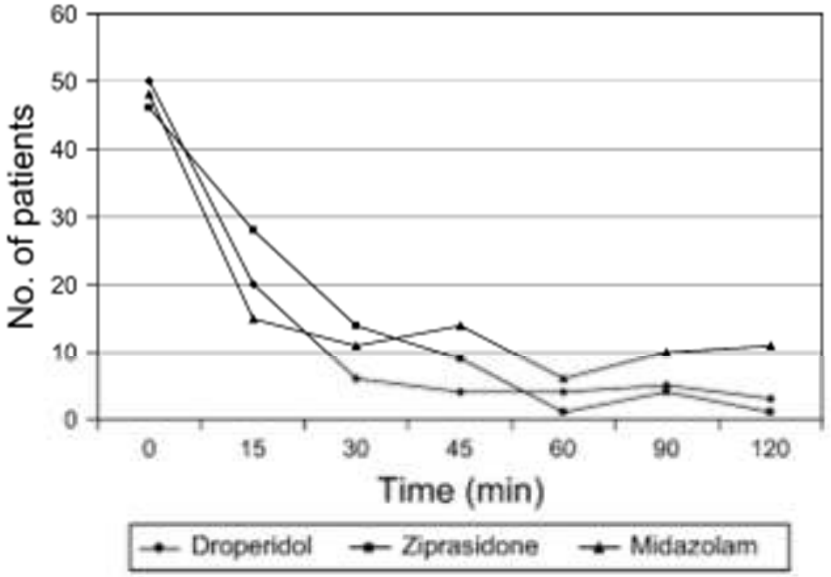


Figure 3. Total number of agitated patients (Altered Mental Status Scale score >0) over time.

Martel M, Sterzinger A, et al. Acad Emerg Med. 2005;12:1167-1172

COMPARISON OF ANTIPSYCHOTICS

A Naturalistic Comparison Study of the Efficacy and Safety of Intramuscular Olanzapine, Intramuscular Haloperidol, and Intramuscular Levomepromazine in Acute Agitated Patients with Schizophrenia

Outcome	Results
Reduction in PANSS-EC and ACES scores	Olanzapine > Levomepromazine > haloperidol
EPS Symptoms (Dyskinesia, dystonia)	Haloperidol > olanzapine/levomepromazine
Somnolence, dizziness, thirst, akathisia	Olanzapine > haloperiderol

Suzuki H, Gen K, Takahashi Y. Hum Psychopharmacol Clin Exp. 2014

INTRAVENOUS OLANZAPINE

A Large Retrospective Cohort of Patients Receiving Intravenous Olanzapine in the Emergency Department

- Martel M, et al. Acad Emerg Med. 2016;23(1):29-35

Outcome	Incidence
Indication for IV olanzapine	Acute agitation (34.4%) Abdominal Pain (23.1%) Headache (17%) Nausea/Vomiting (15%)
Dose	1.25-10 mg (74.4% received 5 mg)
QTc Prolongation	+ 12 ms (median, measured in 12 patients)
Respiratory Complications	14% (Most cases considered minor) 2.1% - Serious airway complications (1% were intubated)

Drug	Route	Dose	Onset	Half Life	Special Considerations
Typical (First Generation)					
Haloperidol	PO	5 mg	30-60 min	12-36 h	Repeat Q15m PRN
	IM	5 mg	20 min	20 h	IM/IV administration increases EPS side effects Repeat Q1h PRN – once stable dose Q4-8h
	IV	2-5 mg		14-26 h	Repeat Q 15-30 min PRN Not recommended
Chlorpromazine	IM	25 mg IM	15 min	2 h	Repeat 25-50 mg in 1 h – gradually ↑ to max 400 mg/dose Q4-6h Not available in ED pyxis
	PO	25 mg	30-60 min	2 h	Only PO available in ED pyxis
Atypical (Second Generation)					
Olanzapine	IM	5-10 mg IM	15-45 min	~30 h	Do not confuse IM form with olanzapine pamoate (long acting) Do not give IM/IV with CNS depressants 2nd dose 2 h after initial; 3rd dose 4 h after 2nd dose
Risperidone	PO	2 mg	1 h	3-20 h	Not available in ED pyxis
Ziprasidone	PO	20-80 mg BID	6-8 h	7 h	
	IM	10-20 mg IM	30-45 min	2-4 h	Max 40 mg/day IM Dose Q2h if 10 mg or Q4h if 20 mg Takes 2-3 min to reconstitute

ANTIPSYCHOTICS

Drug	EPS / TD	Sedation	Anticholinergic Effects	QTc Prolongation	Metabolic Effects
Typical (First Generation)					
Haloperidol	+++	++	+/-	+	+
Chlorpromazine	+	+++	+++	+	+++
Atypical (Second Generation)					
Olanzapine	+	++	++	+	++++
Risperidone	+++	+	+	+	+++
Ziprasidone	+	+	-	++	+/-

CASE #4

ES is a 75 year old male who presents to the emergency department on December 24 with his neighbor. The neighbor reports that ES has been screaming about seeing 3 “ghosts of Christmas.” In the room ES is noted to be anxious, continually trying to get out of bed, and very grouchy, telling staff to “Go away,” and “I don’t want to be bothered.”

ES has a PMH history significant for epilepsy, osteoarthritis, hyperlipidemia, vascular dementia, and gout. Vital signs are normal and physical exam did not reveal anything significant.

AGITATION TREATMENT IN DEMENTIA PATIENTS

Considerations

- Remember pain management
  - Can use PAINAD scale to assess pain level
- AVOID benzodiazepines - ↓ efficacy and ↑ rates of ADEs
- Chronic agitation: cholinesterase inhibitors, antidepressants (particularly SSRIs), and antipsychotics
  - Anticonvulsants show uncertain benefit.

PAINAD SCALE

	0	1	2
Breathing (Independent of vocalization)	Normal	Occasional labored breathing; short period of hyperventilation	Noisy labored breathing; long periods of hyperventilation; Cheyene-Stokes respirations
Negative Vocalization	None	Occasional groan; Low level speech with a negative or disappearing quality	Repeated troubled calling out; loud groaning; crying
Facial Expression	Smiling or inexpressive	Sad, frightened, frown	Facial grimacing
Body Language	Relaxed	Tense, distressed pacing, fidgeting	Rigid, fists clenched, knees pulled up, pulling or pushing away, striking out
Consolability	No need to console	Distracted or reassured by voice or touch	Unable to console, distract, or reassure

<u>Scoring:</u>

1-3: Mild pain – provide comfort measures (non-pharmacologic measures, mild analgesics like acetaminophen)

4-6: Moderate pain

7-10: Moderate to severe pain – warrants stronger analgesia (ie opioid) and comfort measures

Warden V, et al. Development and psychometric evaluation of the Pain Assessment in Advanced Dementia (PAINAD) scale. J Am Med Dir Assoc. 2003 Jan-Feb;4(1):9-15

ROLE OF ANTIPSYCHOTICS IN DEMENTIA TREATMENT

- Last line therapy for patients with severe, persistent symptoms of psychosis
- Highly efficacious in this population
- Black box warning for increased mortality in elderly patients with dementia
- Typical antipsychotics have NOT been shown to have the same benefit in this setting as atypical antipsychotics

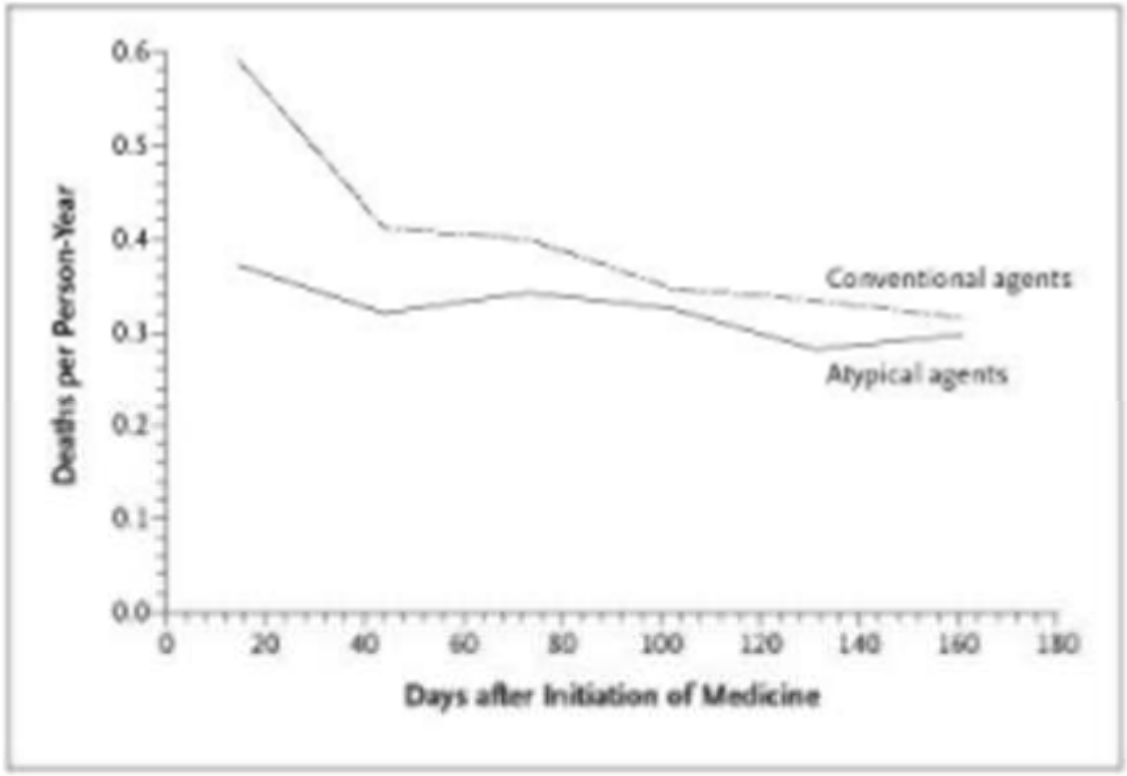
WARNINGS: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS and SUICIDALITY AND ANTIDEPRESSANT DRUGS

See full prescribing information for complete boxed warning.

- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ABILIFY is not approved for the treatment of patients with dementia-related psychosis. (5.1)
- Children, adolescents, and young adults taking antidepressants for major depressive disorder (MDD) and other psychiatric disorders are at increased risk of suicidal thinking and behavior. (5.2)

Gareri P, Segura-García C, Manfredi VGL, et al. Use of atypical antipsychotics in the elderly: a clinical review. *Clinical Interventions in Aging*. 2014;9:1363-1373.

RISK OF DEATH IN ELDERLY USERS OF CONVENTIONAL VS. ATYPICAL ANTIPSYCHOTIC MEDICATIONS



Wang S, et al. NEJM. 2005 Dec; 353:2335-2341

QTC PROLONGATION BY PSYCHOTROPIC DRUGS AND THE RISK OF TORSADE DE POINTES

Wenzel-Seifert K, et al. Dtsch Arztebl Int. 2011 Oct; 108(4):687-693

Drug	QTc Prolongation (Specific increase)	Reported Cases of Torsades de Pointes
Haloperidol	+ (+ 3.8-8.9 ms)	+++
Chlorpromazine	++ (Not reported)	++
Ziprasidone	++ (+ 9.7 ms)	+++
Olanzapine	+ (-4.5 - +8.4 ms)	Not reported
Risperidone	++ (+2-11.6 ms)	+

For QTc
+ Mild prolongation (5-8ms)
++ Moderate prolongation (9-15 ms)
+++ Severe prolongation (≥17 ms)

For Torsades de Pointes
+ Rare cases in combination with other medications
++ Rare cases under monotherapy
+++ Multiple cases reported

ANTIPSYCHOTIC SELECTION IN THE ELDERLY

Scenario	Antipsychotic Choice
Acute Agitation	Olanzapine, risperidone, quetiapine have shown similar efficacy
Prolonged QTc	AVOID ziprasidone, aripiprazole, and haloperidol
Parkinson's Disease	Clozapine and quetiapine

Gareri P, Segura-García C, Manfredi VGL, et al. Use of atypical antipsychotics in the elderly: a clinical review. *Clinical Interventions in Aging*. 2014;9:1363-1373.

CASE #5

KM is an 8yo male who presents to the ED highly agitated. His parents report that he was accidentally left home alone for a while and has been like this ever since they returned home this morning.

- PMH: ADHD, seasonal allergies, asthma
- Home Medications: Albuterol PRN, loratadine, vyvanse, clonidine
- Parents report that no pills are missing from any of the medication bottles in the house

AGITATION MANAGEMENT IN CHILDREN

Always attempt non-pharmacologic interventions first

1. If the patient takes psychotropic medications at home ¼-½ of daily dose should be considered unless toxicity is suspected
2. Select an agent based on underlying etiology
3. Oral medication is preferred over IM or IV

Anxiety	Mania/Psychotic Thoughts	General Agitation
Lorazepam Consider diphenhydramine	Haloperidol Risperidone Olanzapine Ziprasidone	Benzodiazepine or antipsychotic Lorazepam + haloperidol Other AP + BZD after 30m

Marzullo LR. *Ped Emerg Med.* 2014 April;30(4):269-275

BENZODIAZEPINES AND ANTIPSYCHOTICS IN CHILDREN

Drug	Class	Dose	Route	Onset
Lorazepam	Benzodiazepine	0.05-0.1 mg/kg/dose (usually 1-2mg)	PO/IM/IV	5-10 min IM/IV 20-30 min PO
Haloperidol	Typical AP	0.025-0.075 mg/kg/dose (usually 2-10 mg)	PO/IM	20-30 min IM 45-60 min PO
Risperidone	Atypical AP	0.25-2 mg	PO	2 h (Tmax)
Ziprasidone	Atypical AP	10-20 mg (over 12y)	PO/IM	30-45 min
Olanzapine	Atypical AP	2.5-10 mg	PO/IM/ODT	15-30 min

Marzullo LR. *Ped Emerg Med.* 2014 April;30(4):269-275

UNDIFFERENTIATED AGITATION

First, rule out organic causes of agitation

Treat with benzodiazepines or antipsychotics:

- For patients with psychotic symptoms:
  - Start with antipsychotics and follow psychotic disorder pathway

- For patients without psychotic symptoms
  - Start with benzodiazepines and follow withdrawal pathway

Wilson MP, Pepper D, Currier GW, Holloman GH, Feifel D. The Psychopharmacology of Agitation: Consensus Statement of the American Association for Emergency Psychiatry Project BETA Psychopharmacology Workgroup. *Western Journal of Emergency Medicine*. 2012;13(1):26-34. doi:10.5811/westjem.2011.9.6866

KETAMINE AS A FIRST-LINE TREATMENT FOR SEVERELY AGITATED EMERGENCY DEPARTMENT PATIENTS

Concluded that using ketamine as a first-line treatment option for severely agitated patients in the ED resulted in significantly fewer agitated patients at 5, 10, and 15 minutes after administration

Table 4
Agitation scores and time until control of agitation.

	n	0 min (mean ± SD)	5 min	10 min	15 min	Time until control (min) (mean ± SD)
Ketamine	24	4.29 (0.91)	1.25 (1.73)	0.71 (1.08)	0.79 (1.14)	6.57 (8.65)
Midazolam	19	4.58 (0.77)	2.90 (1.56)	2.58 (1.54)	1.95 (1.51)	14.95 (10.47)
Lorazepam	33	4.24 (1.06)	2.51 (1.71)	1.85 (1.58)	1.45 (1.52)	17.73 (24.78)
Haloperidol	14	4.29 (0.91)	2.79 (1.63)	2.71 (1.32)	2.14 (1.66)	13.43 (15.36)
Combo	10	4.80 (0.42)	3.60 (1.26)	2.30 (1.83)	1.10 (1.37)	23.30 (25.12)
p-Value		0.386	0.001	<0.001	0.032	0.107

Riddell J, et al. Am J Emerg Med. 2017 Jul;35(7):1000-1004

ALTERNATIVE THERAPY - KETAMINE

Ketamine Use for Acute Agitation in the Emergency Department

- 56.2% - calming medication prior to ketamine
- 62.5% - calming medication within 3 hours of ketamine
- 40.6% - intoxicated with alcohol or another substance
  - Required additional calming medication at a higher rate than other patients

Vital Sign Parameter	Baseline	Avg Highest Increase from Baseline	Avg Lowest Drop from Baseline
Systolic Blood Pressure	131 +/- 20 mmHg	17 +/- 25 mmHg	14 +/- 24 mmHg
Pulse	98 +/- 23 bpm	8 +/- 17 bpm	10 +/- 18 bpm
Oxygen Saturation	98 +/- 2%	1.1 +/- 1.7%	0.6 +/- 2.2%

Hopper AB, Vike GM, et al. J Emerg Med. 2015

KETAMINE FOR AGITATION

	Intramuscular	Intravenous
Dose	4-6 mg/kg	1-2 mg/kg
Onset	3-4 min	< 30 s
Duration	15-30 min	5-10 min

- Side Effects:
  - Increased BP, HR
  - Emergence reactions
- AVOID in schizophrenic patients
  - Has been shown to exacerbate psychotic symptoms

Hopper AB, Vike GM, et al. J Emerg Med. 2015

SUMMARY

Alcohol and/or BZD Withdrawal	Stimulant Intoxication	Cognitive Impairment (Dementia)	Psychiatric Disorder (Bipolar or Schizoaffective)	Psychiatric Disorder (Anxiety or Personality)
1. BZD • Lorazepam • Midazolam • Diazepam (Note: Use antipsychotics for patients with acute EtOH/BZD intoxication)	BZD (Use 1st) • Lorazepam • Midazolam Antipsychotic • Ziprasidone • Olanzapine	Antipsychotic • Olanzapine • Ziprasidone • Haloperidol	1. 2nd generation antipsychotic 2. 1st generation antipsychotic +/- BZD 3. Avoid ketamine	BZD

Vieta et al. Protocol for the Management of Psychiatric Patients with Psychomotor Agitation. *BMC Psychiatry*. 2017; 17:328
Wilson MP, Pepper D, Currier GW, Holloman GH, Feifel D. The Psychopharmacology of Agitation: Consensus Statement of the American Association for Emergency Psychiatry Project BETA Psychopharmacology Workgroup. *Western Journal of Emergency Medicine*. 2012;13(1):26-34. doi:10.5811/westjem.2011.9.6866.

QUESTIONS?