<u>Do Not Disturb</u>	
A REVIEW OF MANAGEMENT STRATEGIES FOR ACUTE AGITATION AND AGGRESSION TAYLOR STECKLER, PHARMD	

Disclosu	ures
Dr. Steckler disclose.	does not have any actual or potential conflicts of interest to
Off-label use	e of medication will be discussed throughout.
informational p advice on any p	ion includes information about legal issues. Such materials are for purposes only and are not intended, and should not be taken, as legal particular set of facts or circumstances. You should contact an attorney pecific legal problems.

Learning Objectives for Pharmacists

- Apply at least 3 domains of de-escalation when addressing agitated patients
- Understand the difficultly in creating trials to evaluate management strategies
- \bullet Recognize the importance of patient selection in medications for agitation
- Given a patient case, formulate an appropriate treatment plan for acute management of agitation
- Recall the legal considerations when restraining an agitated patient

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- Apply at least 3 domains of de-escalation when addressing agitated patients
- Discuss the importance of targeting agitation treatment towards the underlying cause
- Recognize the antipsychotics, benzodiazepines, and anesthetics commonly used in the management of agitation
- Recall the legal considerations when restraining an agitated patient

Definitions

- <u>Agitation:</u> a state of excessive psychomotor activity accompanied by increased tension and irritability
- <u>Aggression</u>: hostile, injurious, or destructive behavior or outlook especially when caused by frustration
- <u>Delirium:</u> a mental disturbance characterized by confusion, disordered speech, and hallucinations
- <u>Sundowning</u>: a state of increased agitation, confusion, disorientation, and anxiety that typically occurs in the late afternoon or evening in some individuals affected with dementia

Merriam-Webster, Inc. 2018. Journal of Psychiatric Practice. 2005;11 [Suppl 1]:1–108 Lancet. 2014; 383(9920): 911–922.

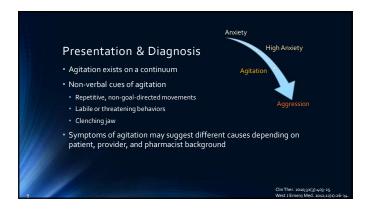
Agitation

- Behavioral emergency
- Requires immediate intervention to mitigate harm to the patient and surrounding individuals
- Agitation is relatively common in the healthcare setting
- Patient illness
- Prolonged waiting times
- Confusion and frustration about patient health
- Availability of medications

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Epidemiology Of healthcare providers are the victim of violence in their career Of emergency department nurses are verbally or physically threatened weekly Of hospitalized seniors develop delirium 1.7 million ED visits per year in the US involving agitated patients 4-8% of patients who present to psychiatric emergency departments are armed Eur J Emerg Med. 2003;2(6):361-4. Lancet. 2004;3(6):361-4. Lancet. 2004;3(6):361-4.

Risk Factors • History of violence or aggression • Impulsiveness or hostility • Prolonged hospitalization • Non-voluntary admission • Aggressor and victim same gender • Alcohol or drug misuse • Younger age • Suicidal risk



Agitation Assessment No standard tool for assessment Most validated in psychiatric or correctional settings Varying level of predictive ability Most clinicians don't need or use a tool May be used to identify patients for early intervention (i.e. de-escalation) Aggressive Behavior Scale Brief Psychiatric Rating Scale Chical Ghavior Rating S

Preparation and Prevention Staff training Annual behavioral emergency training for highest-risk staff Self-reflection on recognizing one's emotions, nonverbal behavior, and limits in dealing with agitated patients Creation of a de-escalation team, where possible (i.e. code green team) Physical environment Movable furniture = flexible and equal access to exits for both patients and staff Avoid extremes in sound, wall color, and temperature Limit access to objects that may be thrown or used a weapon Be capable of creating a quiet room with low lighting

Management Outline • Goal: calm the patient to facilitate assessment and safety 1. Verbal de-escalation 2. Pharmaceutical management 3. Physical restraint • Historically, management has involved seclusion or restraints • Current emphasis on non-coercive approaches, if possible • Enhances relationship with patient • Shorten hospital length of stay

Avoid unintended consequences (e.g. adverse drug reactions, legal ramifications)

Verbal De-Escalation	
13 Throughout West J	Energ Med. 2012;15(1):17-25.

Verbal De-Escalation Principles Reasons to start with non-coercive approach Physical force reinforces idea that violence is necessary to resolve conflict Physically restrained patients are more likely to be admitted and have longer length of stay Patients and staff are less likely to be injured TIC and CMS consider low restraint rates a key quality indicator Main objectives of de-escalation Ensure safety of patient, staff, and others nearby Help the patient to manage emotions and control behavior Avoid coercive actions that may escalate agitation Avoid oser frestraint

Verbal De-Escalation Principles • Three-step approach 1. Verbally engage the patient 2. Create a collaborative relationship 3. Verbally de-escalate the patient out of the agitated state • Typically involves a verbal communication loop • May have to repeat several times until your message is heard • Young, inexperienced clinicians often give up too early • Taking time to de-escalate appropriately is less time consuming because restrained patients will require closer monitoring (i.e. more nursing involvement)

Respect personal space	6. Listen closely to what the patient is saying
2. Do not be provocative	7. Agree or agree to disagree
3. Establish verbal contact	8. Lay down the law and set clear limits
4. Be concise	9. Offer choices and optimism
5. Identify wants and feelings	10.Debrief the patient and staff

1. Respect Personal Space Maintain ≥ a arm's length distance from the patient Allow clear paths of exit for yourself and patient Especially important for patients with history of trauma **New John Common Common

3. Establish Verbal Contact • The first person to encounter the patient should attempt deescalation • Introduce yourself and orient the patient • Wait for understanding and repeat as needed to ensure the patient hears what you are saying

10 Domains of De-Escalation 5. Identify Wants and Feelings • Ask the patient for their request, whether or not it can be granted • Use "free information" from the patient's nonverbal cues, past encounters, and seemingly trivial statements 6. Listen Closely to the Patient • Use active listening to repeat and summarize • Use Miller's Law • Assume they are speaking the truth • Try to understand how it could be true to them

7. Agree or Agree to Disagree • Use fogging to find something about the patient's position to agree about • Agree with the truth • Agree with the odds • Agree to disagree 8. Lay Down the Law; Set Limits • Explain what behaviors are acceptable and injury to anyone is not acceptable • Teach the patient how to stay in control

9. Offer Choices and Optimism Patients may feel their only options are fight or flight, so giving choices can empower May offer trivial things perceived as acts of kindness (e.g. food, blankets, phone access) Broach the subject of medications 10. Debrief the Patient and Staff Explain to the patient why further intervention was necessary Teach how to more appropriately respond next time Huddle with staff to identify successes and areas for improvement

	Case #1
me the	G is a 37 year old male who presents to your pharmacy to pick up a dication. After briefly talking to you, it is discovered that insurance denied claim for his expensive medication. He becomes visibly upset and starts ing and wringing his hands, what would be the most appropriate action?
A.	Go block his path and let him know aggression will not be tolerated
	Call over the other two technicians for assistance
	Keep talking with him and ask what he would like you to do
	Grab the secret vial of haloperidol from your lab coat and give 5 mg IM STAT

Pharmaceutical Management of Agitation

Evidence Base

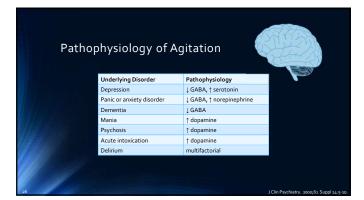
- Most studies are small, from single-sites, and in patients with pre-existing psychiatric diagnoses
- Lack of high-quality studies on management of agitation
- Practical difficulties
- Challenging to obtain consent in an agitated patient
 Unable to predict when agitation will occur (i.e. cannot pre-enroll patients)

- Ethical difficulties
 Delaying treatment to obtain consent places patient and others at risk of harm
 If consent obtained, was patient competent enough to understand its meaning
- Body of evidence continues to grow

When to Use Pharmacotherapy

- Failure of verbal de-escalation
- Immediate threat to patient, staff, or others
- Patient cannot be evaluated
- Goals:
- Calm the patient without over-sedating
- Enhance safety
- Facilitate timely diagnosis and treatment
- Target the underlying cause of the agitation
- NOT used for punishment or staff convenience





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- Targeted towards underlying cause
- Easy preparation and administration
- No associated pain or need for restraint
- Rapid onset
- Minimal PK or PD variability between patients
- Sufficient duration of action to enable triage and assessment
- Minimally sedating
- Low risk of adverse drug reactions or drug-drug interactions

lin Ther 2010;22(2):402-:

Oral vs. Parenteral Therapy

- Oral
- Patients may refuse or cheek tablets
- Longer onset of action
- Parenteral
- Higher risk of adverse events
- More involved preparation for administration (e.g. IV line, syringe/needle prep)
- Compromises relationship with the patient
- Risk of needle-stick injuries

First Generation Antipsychotics (FGA)

- <u>Mechanism</u>: dopamine (D2) antagonist → reduction in underlying psychotic symptoms
- <u>Adverse Drug Reactions (ADRs):</u> anticholinergic effects, extrapyramidal reactions, sedation, and prolonged QTc
- Phenothiazines (e.g. chlorpromazine) are not preferred due to more frequent ADRs: hypotension, anticholinergic effects, lowered seizure threshold
- Butyrophenones (e.g. haloperidol, droperidol) are more often used due to higher potency and D2-selectivity, fewer drug interactions, and lower risk of ADRs

Haloperidol and Droperidol

- QTc prolongation, Torsades de Pointes
- Highest risk with higher doses and IV administration
- Haloperidol not approved for IV administration and typically requires EKG monitoring while administering
- Acute extrapyramidal side effects
- Lower risk of EPS when co-administered with lorazepam or promethazine
 Often done in practice to limit doses of both agents
- Increases risk of drug interactions • Droperidol is less frequently used due to cardiovascular risk and no PO availability
- Only approved for post-operative nausea and vomiting

Second Generation Antipsychotics (SGA)

- <u>Mechanism:</u> dopamine (D2) and serotonin (5-HT2a) antagonists with actions at other receptors
- <u>ADRs:</u> metabolic effects, hypotension, sedation, anticholinergic effects, and extrapyramidal effects
- Route of administration does not impact efficacy, only onset of action
- IM or PO: olanzapine, ziprasidone
- PO only: risperidone, quetiapine, aripiprazole
- Systematic reviews suggest most SGAs are equally effective, with a few exceptions
- · Aripiprazole appears slightly less effective
- Quetiapine has a higher risk of orthostatic hypotension

West | Emera Med 2012:12(1):26-:

FGA vs. SGA

- Numerous studies and reviews support SGAs as being as effective as haloperidol
- The American Association of Emergency Psychiatry (AAEP) recommends use of SGAs over FGAs in most situations where an antipsychotic is indicated
- Highly efficacious
- Lower EPS risk
- Subjectively preferred by patients
- Haloperidol is still preferred in alcohol intoxication

West J Emerg Med. 2012;13(1):26-3

Study: SGA vs. FGA Population Patients admitted to psychiatry emergency service with agitation and acute psychosis and requiring medications (n=201) Treatments Oral haloperidol, risperidone, olanzapine, or quetiapine for 72 hours Randomized, doses determined by treating physician, multiple doses (over 72 hours) Assessment Tools Oral haloperidol, risperidone, olanzapine, or quetiapine for 73 hours (over 72 hours) Assessment Tools Oral Prefer Psychiatric Rating Scale Oral Prefer Psychiatric Rating Scale Oral Psychiatric Rating Psychiatri

	Case #2
	GR is a 54 year old female who is admitted to your inpatient psychiatry unit for acute worsening of her schizophrenia. She is becoming more agitated and the treating physician fears for the safety of the other patients. Which of the following would be the best medication to reduce her agitation?
	A. Haloperidol, PO
	B. Haloperidol, IM
	C. Risperidone, PO
	D. Aripiprazole, PO
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Benzodiazepines	
 <u>Mechanism</u>: Activates benzodiazepine receptors on GABA-/ receptors → enhanced inhibitory effects of GABA 	A
<u>ADRs:</u> sedation, respiratory depression, hypotension	
Lorazepam and midazolam are best studied	
ACEP guidelines state benzodiazepines are as effective as h	aloperidol
	West J Emerg Med. 2012;13(1):26-34.
35	Ann Emerg Med. 2006:47(1):79-99.



Stud	y: Benzodiazepine vs. FGA
Population	Patients presenting to one of five emergency departments with psychosis and behavioral dyscontrol requiring pharmacologic intervention (n=98)
Treatments	Lorazepam 2 mg IM, haloperidol 5 mg IM, or a combination Randomized, double blind; multiple doses (up to 6 over 12 hours)
Assessment Tools	o Brief Psychiatric Rating Scale (BPRS) o Agitated Behavior Scale (ABS) o Clinical Global Impression Scale (CGIS)
Findings	Efficacy: Patients who received combination therapy had more improved ABS and BPRS scores at a and 2 hours versus monotherapy. There was no significant difference between monotherapy groups. Safety: Patients who received haloperidol spent less time asleep versus the lorazepam or combination group. EPS were more common in the haloperidol group.
Conclusions	Repeated doses of lorazepam and haloperidol are equally effective Combination of lorazepam and haloperidol is more effective than either alone
	Am J Emerg Med 1997;

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Cor	nbo Therapy
	nbination of an antipsychotic and benzodiazepine may be more ective than either alone
• Re	educed doses of either agent = less risk of ADRs
• Us	sing multiple agents = higher risk of drug interactions
B ₅₂	is a commonly used IM example
• Be	enadryl (diphenhydramine; often 50 mg)
• Ha	aloperidol 5 mg
• Lo	orazepam 2 mg
Avo	id use of IM olanzapine with a IM/IV benzodiazepine

Ketamine

- $\underline{\text{Mechanism:}}$ glutaminergic NMDA receptor antagonist \Rightarrow dissociated state with analgesia and amnesia
- <u>ADRs:</u> emergence reactions, tachycardia, and hypertension
- Avoid in elderly or those with heart disease or risk for heart disease
- Avoid in schizophrenia as it can worsen symptoms
- Emerging therapy; not widely used
- May be used as a second-line option, especially in patients with excited delirium secondary to drug abuse

Ann Emerg Med. 2017;69(4):480-49

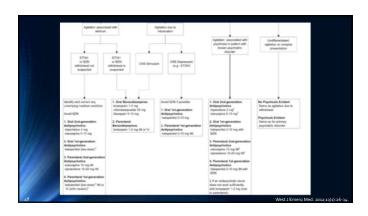
Study: Ketamine vs. FGA vs. Benzodiazepine Population Acutely agitated patients presenting to one emergency department who required chemical sedation for acute agitation (n=98) Treatments O Ketamine, haloperidol, midazolam, lorazepam, or benzodiazepine + haloperidol Observational study, single dose Assessment Tool Six-point sedation scale (used to monitor changes in agitation in ED patients) Findings Efficacy: At 5, 10, and 13 minutes more patients who received ketamine were no longer agitated compared to all other medication groups. Safety: inadequately powered to assess Conclusion Ketamine is faster at controlling agitation than FGAs or benzodiazepines

		Initial Dose (mg)	Tmax (min.)	Repeat Interval (hr.)	Max. daily dose (mg)
	Risperidone	2	60	2	6
PO	Olanzapine	5-10	360	2	20
PO	Haloperidol	2.5-5	30-60	0.25	20
	Lorazepam	2	20-30	2	12
	Ziprasidone	10-20	15	2-4	40
	Olanzapine	10	15-45	0.5	30
	Haloperidol	5	30-60	0.25	20
IM	Lorazepam	2	20-30	2	12
	Ketamine	4-5 (per kg)	15		-
	Droperidol	5-10	30	0.25-0.5	
	Midazolam	2.5-5	30-60		-
	Haloperidol	2-5	15	4	10
IV	Ketamine	1 (per kg)	1-5	0.25	
IV	Droperidol	2.5-10	15	0.1	20
	Midazolam	2.5-5	3-5		

AAEP Guidelines	
43 Throughout, West J Emerg Med. 2012;3(s) 26-34.	
Agitation Due to Intoxication	
 Alcohol Eirst line: Avoid medications, if possible 	
Second line. Haloperidol (best studied), SGAs Other recreational drugs	
Eirst line: Benzodiazepines (for most) Second line: SGA (especially in amphetamine users with psychotic symptoms)	
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Agitation Due to Psychiatric Illness	
First line: SGAs Antipsychotics address the underlying disorder	
 Oral risperidone has best data If IM is required, ziprasidone or olanzapine are preferred 	
<u>Second line:</u> Combination of SGA and benzodiazepine	-

Agitatio	on Due to Deliriu	m
Cause of	Withdrawal (alcohol or benzodiazepine):	Benzodiazepine
Delirium		Clonidine
	Withdrawal (other medication):	Replace the medication
	Acute ingestion (drug or medication):	Avoid any medications
	Lab or vital abnormality:	Correct the underlying cause
	Unknown cause:	SGA
		Haloperidol (second line)

Agitation Due to Unknown or Complex Etiology No psychotic features: Benzodiazepine Psychotic features: SGAs ACEP recommendations Voluntary administration: Benzodiazepine + SGA Involuntary administration: Benzodiazepine or FGA



Case #3
PO'd is a 23 year old male who presents to your emergency department and after 5 minutes in the waiting area he starts screaming "INEBTO SEE A DOCTOR!" and knocking chairs over. There are no ED beds to provide him a room and no indication of what is causing this reaction. After failed attempts at de-escalation, which IM medication would you recommend to assist in calming him and facilitating a diagnosis?
A. Midazolam 10 mg
B. Lorazepam 2 mg
C. Haloperidol 5 mg
D. Olanzapine 10 mg

Case	#4

One hour after receiving two doses of the medication you suggested, PO'd remains agitated and has begun directly threatening the nursing staff. Which of the following is the best option for management of his agitation?

- A. Administer a combination of haloperidol and lorazepam
- B. Give another dose of the same medication
- C. Calmly ask for his demands and his cooperation
- D. Lunge towards him and attempt to subdue him with a half-nelson

Alternative Recommendations

- "A written survey of 61 questions was mailed to 50 experts in the field... the survey sought to define..."
- Level of agitation where emergency intervention is appropriate
- Guiding principles for selecting interventions
- Appropriate physical and medication strategies for a variety of provisional diagnoses and complicating conditions
- All experts have extensive clinical or research experience in agitation
- 48 of 50 experts responded
- Survey items were statements that participants would rate on appropriateness from 1 to 9

Journal of Psychiatric Practice. 2005;11 [Suppl 1]:1-10

Alternative Decomposedations (cont.)	
Alternative Recommendations (cont.) • Panel reached consensus on 78% of the items	
Unknown/multifactorial cause: benzodiazepines	
Intoxication: benzodiazepines	
Schizophrenia/mania: olanzapine, risperidone (IM: ziprasidone), or haloperidol + benzodiazepine	
Not a gold standard of evidence	
Results provide evidence of how agitation is managed in practice	
An interesting approach given the paucity of evidence	
Sournal of Psychiatric Practice. 2005;11 (Suppl s):1-108.	
No. of the Control of	
Use of Physical Restraint	
9	
Rationale and Methods of Restraint	
Like pharmacologic restraint, reserved for use in facilitating diagnosis and treatment or preventing injury to self or others	
 Considered a procedure, where each member of the restraint team plays a specific role and the team enters room as one single unit 	
Once patient is restrained, announcing "the crisis is over" is calming	
Close monitoring needed to ensure patient safety and provision of basic human needs	
Remove restraints as soon as possible	

Ethical & Legal Considerations	
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Competence & Consent	
 <u>Competence</u>: the ability of a person to act on his/her own behalf <u>Consent</u>: a voluntary agreement by a competent person to do something proposed by another 	
Considerations in agitation Best to obtain consent if possible, even if from next of kin	
Have another medical professional document agreeance with the decision Document considerations when deeming someone incompetent Courts have supported physician actions without consent when needed to preserve life or health	
preserve life or health	
Duty to Protect	
 Use of restraints takes away a patient's freedom Gives the provider a fiduciary responsibility for all health and welfare of the patient 	
Physically restrained patients require frequent monitoring	
Example: Estate of Doe v. ABC Ambulance 32-year old patient with schizophrenia threatened to kill his psychologist and was	
32-year old patient with schizophrenia threatened to kill his psychologist and was taken to the ED., when informed of his inwoluntary admission, he became violent he was physically restrained, chemically sedated, with a towel placed over his face.	
to prevent spitting it was later noticed that one of his hands was turning blue and was found to have experienced cardiac arrest his estate was awarded \$2 million.	

Battery & False Imprisonment

- Battery: intentional infliction of a harmful or offensive bodily contact
- <u>False Imprisonment:</u> intentional confinement and deprivation of personal liberty, without consent
- Considerations in agitation
- Battery and false imprisonment are applicable if a patient is restrained for convenience, not medical necessity
- Must follow appropriate protocol and document rationale when using restraint

Duty to Warn

- Providers must warn a third party of imminent danger, regardless of obligation to patient confidentiality
- Dictated on a state-by-state basis (lowa: permitted, not required)
- Example: Dorothy McGrath et al. v. Barnes Hospital et al.

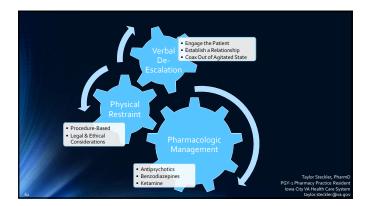
 Patient with paranoid schizophrenia treated as an inpatient repeatedly told hospital workers of thoughts of stabbing his mother with a kitchen knife... the night he was released he stabbed both his parents, killing his father and severely injuring his mother... plaintiff was awarded \$2 million despite his parents' knowledge of his risk of violence

Key Points

- Agitation is a behavioral emergency and exists on a continuum from anxiety to aggression
- Management of agitation should always start with attempts at deescalation, if safe to do so
- Verbal de-escalation aims to engage the patient, establish a relationship, and coax him or her out of the agitated state
- Use of physical or chemical restraint should be done only if needed to enable further diagnostic workup or ensure safety of the patient and others

Key Points

- Antipsychotics are generally preferred in patients intoxicated with alcohol, those with pre-existing psychiatric illness, or if patient is exhibiting psychotic symptoms regardless of etiology
- Benzodiazepines are generally preferred in patients using illicit drugs, withdrawing from alcohol, or with idiopathic or multifactorial agitation with no psychotic symptoms
- Combination therapy with an antipsychotic plus a benzodiazepine may be more safe and effective than monotherapy with either agent
- Ketamine is an emerging treatment option for agitation and evidence for its use continues to accumulate
- Use of restraint can open up healthcare providers to legal action if protocols are not followed and documented



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