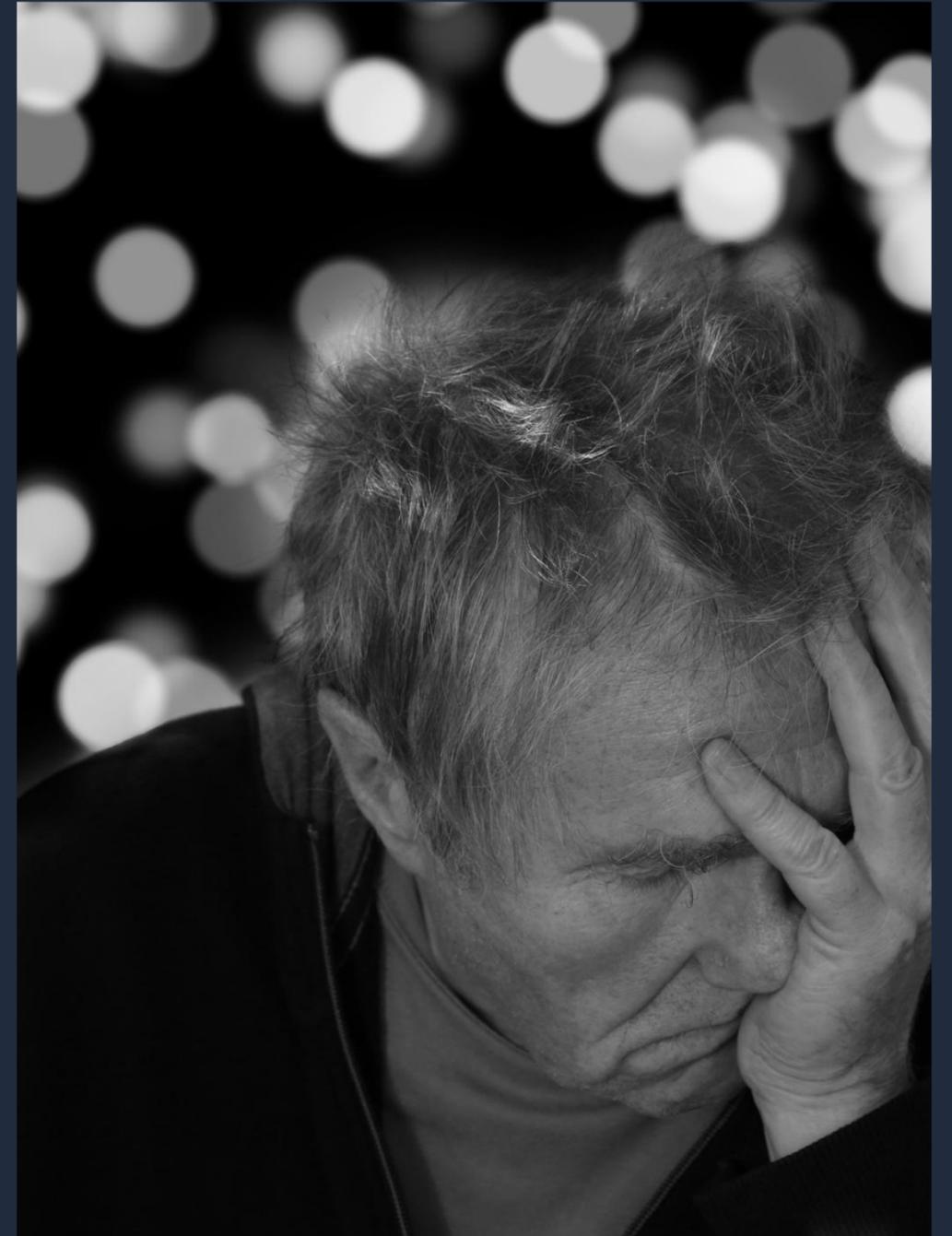


Managing Agitation in the Medical Setting: An Update in Consultation-Liaison Psychiatry

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Disclosures

- Naomi A. Schmelzer, MD, MPH
- I have no financial disclosures or conflicts of interest with the material in this presentation

Objectives:

- To provide an overview of agitation management in the medical setting
- Develop effective strategies for agitation assessment and management
- Explore pharmacological Interventions and updates

Definitions:

Anger – a strong feeling (of resentment, wrath, ire) excited by a real or supposed injury (an emotion)

Aggression – an unprovoked attack or attempt to quarrel or fight (a behavior)

- subtypes: reactive/impulsive, planned/instrumental

Violence – physical force used so as to injure or damage (an extreme behavior)

Agitation – a behavioral syndrome characterized by a state of excessive motor or verbal activity accompanied by heightened arousal and emotional distress

Why is agitation in the hospital problematic?

What is the **impact** of agitation?



- Agitation is **painful**
- It can escalate to **aggression, violence**
- It can disrupt the therapeutic milieu
- It can lead to **adverse events**
- It can interrupt treatment
- It can manifest from markedly different presentations and etiologies
- It can be distressing to patients, caregivers and families
- Compromise patient-staff relationships
- Increase the **length of stay** and **cost** per admission

Epidemiology:

- There is little direct data on the prevalence of agitation in the medical setting or utilization of hospital or ED resources
- In a study (Cots et al) of hospital costs associated with agitation, agitation led to:
 - ↑ increased use of hospital resources by 8%
 - ↑ increased LOS (12 v 9 days)
 - ↑ increased mean cost of stay

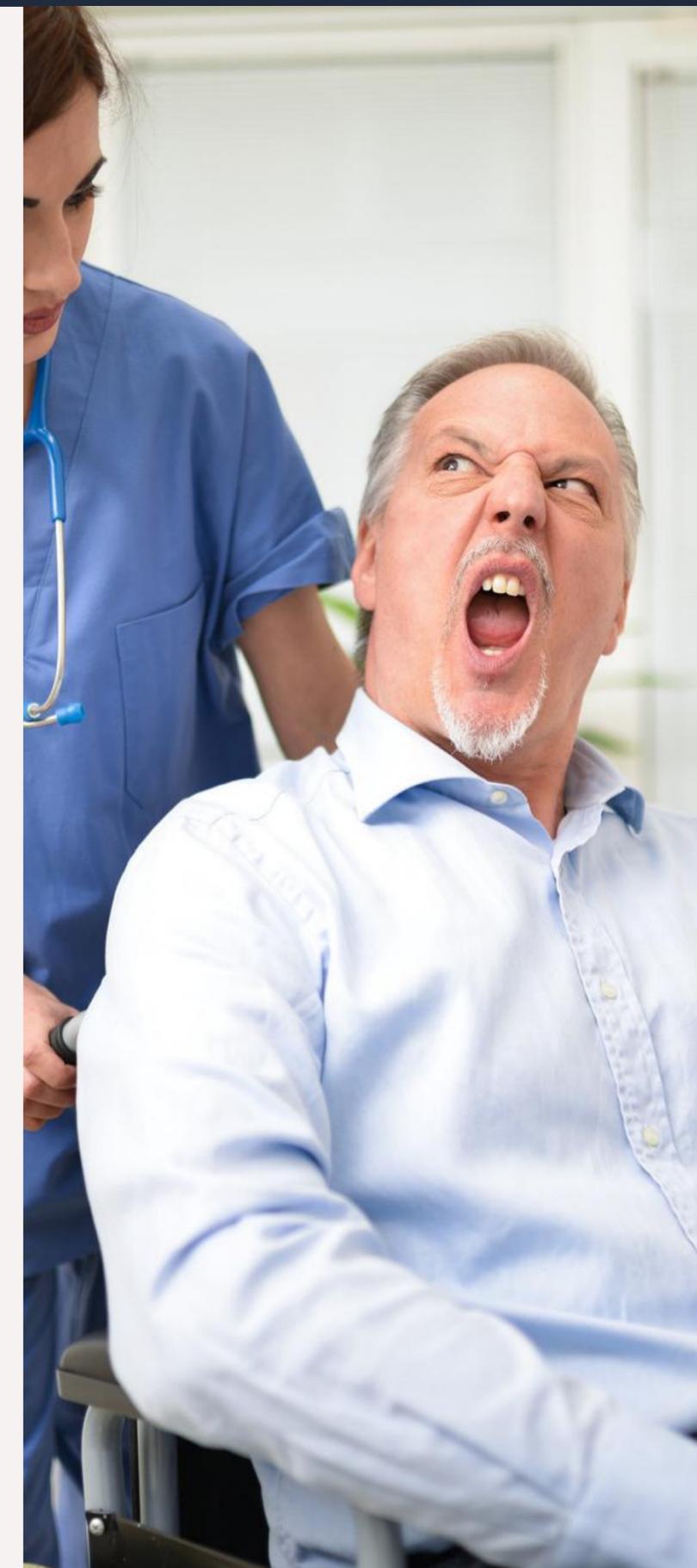
Role of CL Psychiatrist



- Aid in Assessment and Diagnosis
- Tailored treatment recommendations
 - nonpharmacological approaches
 - medication management
 - trauma-informed care
- Collaboration and enhanced communication
- Education and Training
 - early recognition of agitation
 - De-escalation guidance
 - support
- Ethical and Legal considerations
- Facilitating Debriefing
- Prevention

Approach to the Agitated Patient

- Recognizing Agitation
 - What is it?
 - Who?
 - Where?
- Priorities:
 - Maintaining Safety
 - Establishing Provisional Diagnosis
 - Identifying life-threatening conditions
- Collaborative Team Approach
- Verbal de-escalation and other non-pharmacological interventions
- Use of medication if needed
- Comprehensive evaluation and treatment plan



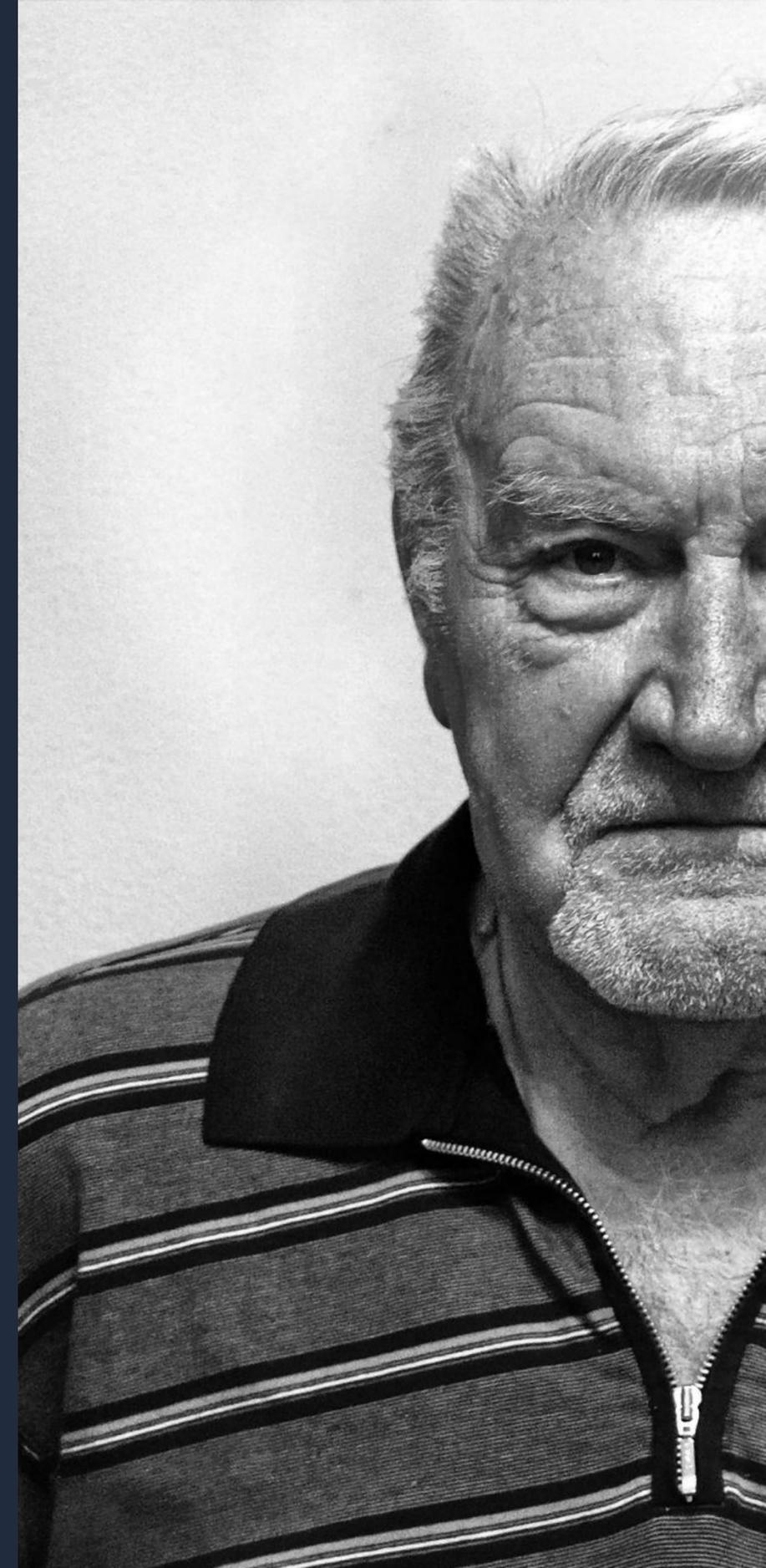


The Spectrum of Agitation

- irritability
- loud speech
- Repetitive and non-goal directed behaviors (foot tapping, hand wringing, fiddling with clothing or items nearby)
- repetitive thoughts, verbal outbursts
- tense posturing
- heightened responsiveness to stimuli
- pacing
- threatening or destructive behaviors
- aggressive acts (pounding walls, throwing objects, hitting self)

Contributors to Agitation in Hospitalized Patients

- Delirium/acute medical conditions
- Neurocognitive disorder
- Medication/substances
- Primary Psychiatric Disorder
- Change in Environment
 - hospitalization
- Pain
 - chronic and acute
- Communication Barriers
- coping/stress reactions
- Sleep disruption/insomnia
 - consider parasomnias, OSA
- Chronic medical conditions
- CHF, diabetes with fluctuating BG
- Falls/orthostatis
- Fluid status
- normative aging



Evaluation of Agitation

Pertinent HPI

onset, quality, duration, severity, precipitants, concomitant symptoms

Past history

- Medical and surgical history
- Psychiatric history
- Neuropsychiatric history, and onset, course and symptoms of dementia
- substances
- home functioning/ADL/IADLs

Physical exam

Cognitive and behavioral Rating Scales - standardized assessment and documentation of behavioral disturbance symptoms and severity

- Neuropsychiatric Inventory (NPI)
- Cohen-Mansfield Agitation Inventory (CMAI)
- Behavioral Pathology in Alzheimer's Disease (Behave-AD)
- Folstein Mini-Mental Status Examination (MMSE)
- Montreal Cognitive Examination (MoCA)
- Brief Agitation Rating Scale (BARS)



Identification and management of contributing medical conditions can delineate, stabilize, and improve a patient's behavioral, psychiatric, and neurocognitive symptoms

Diagnostic Workup

Investigative Workup may include:

- Labs: CBC, Electrolytes, Glucose, Renal function, LFT, Vitamine B12, thiamine, levels of therapeutic drugs (lithium, VPA, carbamazepine, clozapine, TCA, tacrolimus), HIV, RPR, CK
- Microbiology: UA/culture, blood cultures (T>38.5), sputum (productive cough), LP (r/o encephalitis)
- Drug screen: urine or blood tests
- Imaging: CXR, CT head, MRI Brain
- Cardiac: ECG, echo
- Neuro: EEG



Agitation in Hospital Patients

Therapeutic Interventions

Practices and Protocols

Behavioral Response Code /BERT

- Rapidly bring primary team, nursing, social worker or other psychiatric resources, security, and other interdisciplinary team members
- help address agitation and psychiatric needs of hospitalized patients
- provide targeted interventions with clinical focus
- use interdepartmental expertise

Code De-escalation: use of a standardized team protocol to rapidly respond to and assess agitation in the ED with prioritization of de-escalation techniques and reduction in restraint use.

- Parker CB. Psychiatric emergencies in nonpsychiatric settings: perception precludes preparedness. *Psychosomatics*. 2019 Jul 1;60(4):352-60.
- Bukhman A, Im D, Powell R, Grant J, Schmelzer N, Baymon D, Callahan C, Kim I, Waters B, Sanchez L, Chen P. 270 Code De-Escalation: Effectiveness and Feasibility Pilot Study of Intervention to Decrease Restraint Use and Health Inequities in Agitation Management in a Community Hospital Emergency Department. *Annals of Emergency Medicine*. 2022 Oct 1;80(4):S118.

Non-Pharmacological Interventions

- Verbal De-escalation
- Environmental modifications for a therapeutic milieu
- Physical comforts
- Sensory interventions
- skillful nonverbal behaviors

Why De-Escalate?

- Help the patient gain control of their emotions and behaviors
- Empowers patient to manage their own distress
- Increase staff and patient safety
- Model nonviolent problem-solving and self-control
- Engages patient in treatment
- Increase disposition options (if from ED)
- Increase patient satisfaction
- Lowers use of restraints, seclusion and other coercive interventions
- Reduces overall staff involvement

Be Prepared to De-escalate

- Atmosphere charged with intense, often negative, emotions.
- The patient is experiencing this more intensely than you
- Consider: diagnosis, safety, therapeutic alliance
- Be resolved to search out common ground and be respectful
- Engage early and safely

Engage Early

- Agitation is painful.
- Waiting is irritating and provokes acting up or shutting down
- Treatment begins the moment the interaction starts (i.e. the sum total of how the patient is treated)
- Focus on engaging the patient in their own de-escalation

Elements of De-Escalation

Respect personal space

Do not be provocative

Establish verbal contact

Be concise

Identify wants and feelings

Listen closely to what the patient is saying

Agree or agree to disagree

Set clear limits

Offer choices and optimism

Debrief the patient and staff

Engaging around Medication

- Patients with agitation may need medication
- Voluntary medication: timing is key
 - Requested by patient: often best to stabilize first
 - Offering too early may leave the patient feeling dismissed
- foster autonomy and choice



Pharmacological Considerations

- Goal: to CALM the patient
- Make a Provisional Diagnosis
- Patient characteristics: Age, comorbid conditions, environment, medication/substance exposures
- Selection of Medication:
 - easy to administer and non-traumatic
 - rapid effects without oversedation
 - fast onset of action and sufficient duration of action
 - low risks of adverse effects and drug interactions
 - patient preference
 - Availability



Selecting **Route of Administration**

Oral (PO) :

- Preferable if the patient is accepting
- Tabs, liquid, or orally dissolving tablets
- slowest onset of action - enters through the lower GI tract

Intramuscular (IM):

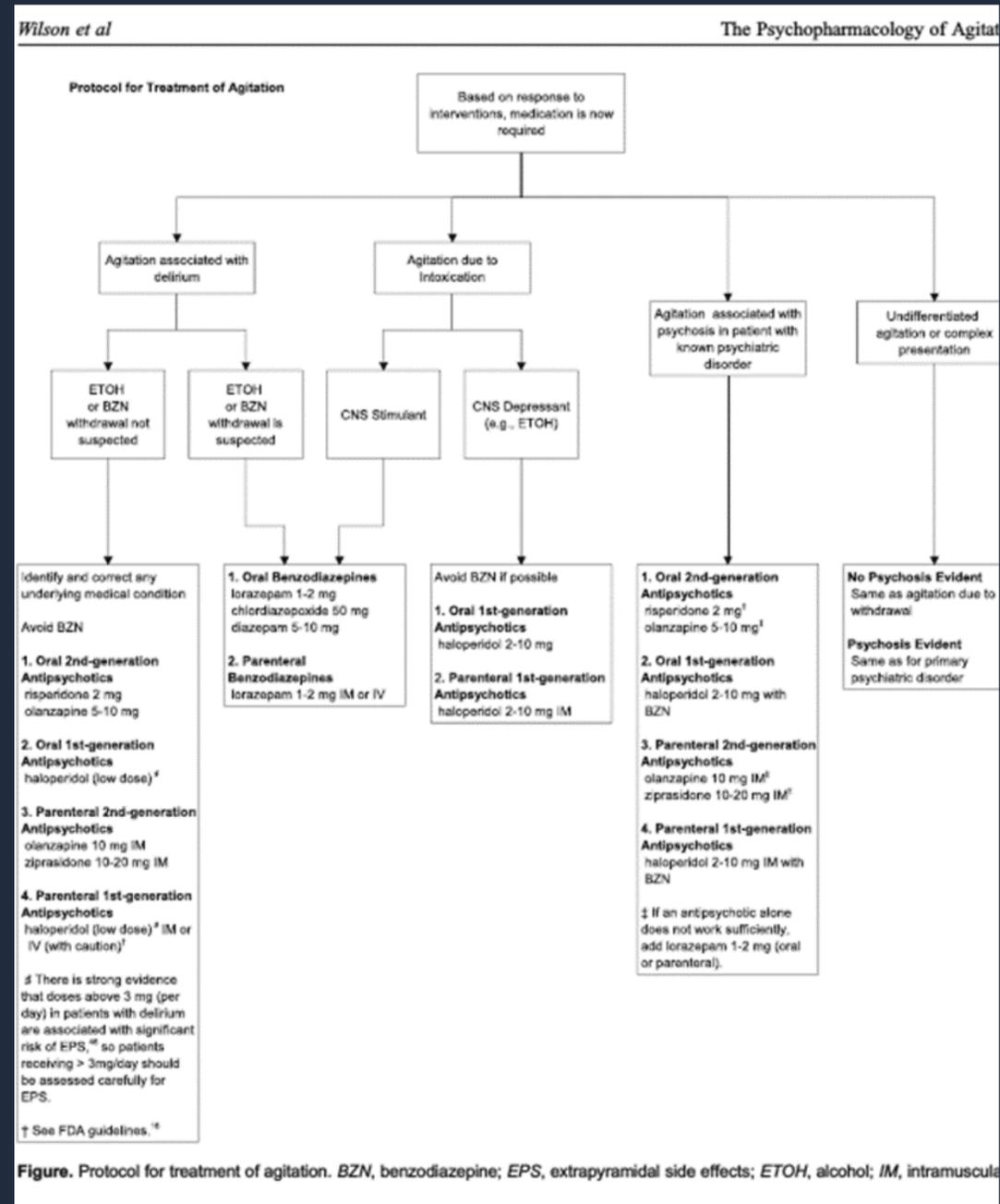
- Rapid elevation of plasma level
- Higher transient concentration

Intravascular (IV):

- rapid plasma levels
- access may be difficult



Project BETA: The psychopharmacology of Agitation



First Generation Antipsychotics

- Dopamine antagonism with antipsychotic and anti agitation properties
- Side Effects:
 - EPS including dystonias, akathisias, Parkinson-like symptoms
 - QTc-prolongation
 - lower seizure threshold (Low potency > high-potency)
- High Potency: ex. **Haloperidol, Fluphenazine**
 - Fast Acting with onset within 30 minutes
 - Duration up to 12-24 hours
 - Low/no risk for: anticholinergic effects, suppressing respiration, hypotension
 - Can be administered IV (Not FDA approved)
 - Little cardiotoxicity - concern for QTc prolongation

Droperidol

- In a RCT by Taylor et al (2016) of agitated ED patients using Droperidol alone, droperidol + midazolam, or olanzapine, they found that droperidol + midazolam was more efficacious at achieving sedation in 10 min and adverse profiles did not differ
- Martel et al. (2021) RCT of undifferentiated agitated patients in ED comparing treatment of droperidol, ziprasidone, and lorazepam demonstrated increased efficacy of droperidol at sedation
- Limitations: these studies are ED-based, do not target patient populations based on age or underlying diagnoses, and end points are sedation.

- Taylor DM, Yap CY, Knott JC, Taylor SE, Phillips GA, Karro J, Chan EW, Kong DC, Castle DJ. Midazolam-droperidol, droperidol, or olanzapine for acute agitation: a randomized clinical trial. *Annals of Emergency Medicine*. 2017 Mar 1;69(3):318-26.
- Martel ML, Driver BE, Miner JR, Biros MH, Cole JB. Randomized double-blind trial of intramuscular droperidol, ziprasidone, and lorazepam for acute undifferentiated agitation in the emergency department. *Academic Emergency Medicine*. 2021 Apr;28(4):421-34.

Atypical Antipsychotics:

Risperidone

- In patients willing to take PO form
- combination of Risperidone + Lorazepam shown to be equally effective to Haldol + Lorazepam (Currier and Simpson, 2001)

Olanzapine

- available PO, IM, IV (non FDA)
- IM dose is 15-45 min until peak plasma concentration
- Longstanding concern about co-administration of IM formulation with Benzodiazepines or CNS depressants
- off label use of IV olanzapine:
 - Tsai et al (2021) found IV olanzapine appears to be efficacious in reducing the need for sedatives and antipsychotics with low risk for QTc prolongation and respiratory depression in acutely agitated patients with neurological injuries.

- Currier GW, Simpson GM. Risperidone liquid concentrate and oral lorazepam versus intramuscular haloperidol and intramuscular lorazepam for treatment of psychotic agitation. *Journal of Clinical Psychiatry*. 2001 Mar 1;62(3):153-7.
- Tsai YV, Fawzy JH, Durkin JB, Then JE, McGinnis CB. Off-label use of intravenous olanzapine for agitation after neurologic injury. *Hospital Pharmacy*. 2021 Dec;56(6):697-701.

Benzodiazepines:

- Facilitate the activity of GABA, a major inhibitory neurotransmitter
- Therapeutic effects appear linked to decreased arousal
- In terms of psychiatric symptoms - can target anxiety, catatonia
- Long history in use of management for agitation either alone or in combination with antipsychotics
- Best for patients in whom agitation is secondary to alcohol or sedative withdrawal, stimulant intoxication, or agitated/hyperactive catatonia
- side effects: excessive sedation, can be additive with other CNS depressants, avoid in patients at risk for CO₂ retention, paradoxical disinhibition

- Lorazepam
 - only benzodiazepine with complete and rapid IM absorption
 - Can be given PO, IM, IV

- Midazolam
 - rapid onset of action
 - short duration of effect, may require repeat dosing

Valproate:

- VPA blocks voltage-dependent sodium and calcium channels, increases GABA synthesis, potentiates GABA activity at postsynaptic receptors, blocks GABA degradation, and attenuates the activity of glutamate receptors
- few studies to support its use in agitation in general medical setting
- several limited studies for ICU patients as second or third line
 - often used as alternative in patients with prolonged Qtc
 - TBI
- Gagnon et al (2017): shown to reduce agitation, delirium, and concomitant psychoactive medication use in ICU setting
- Less effective for agitation in dementia patients with increased side effects (Lonergan 2009)

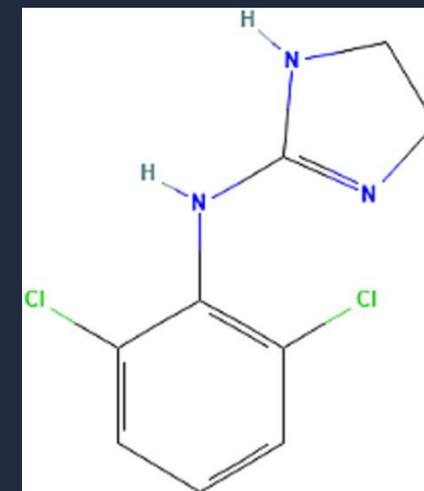
Gagnon DJ, Fontaine GV, Smith KE, Riker RR, Miller III RR, Lerwick PA, Lucas FL, Dziodzio JT, Sihler KC, Fraser GL. Valproate for agitation in critically ill patients: a retrospective study. *Journal of critical care*. 2017 Feb 1;37:119-25.

Lonergan E, Luxenberg J. Valproate preparations for agitation in dementia. *Cochrane Database of Systematic Reviews*. 2009(3).

Sublingual Dexmedetomidine

- acute treatment of agitation associated with schizophrenia or bipolar I or II disorder
- Dosing:
 - •Mild or moderate agitation: Sublingual film: sublingual/buccal: Initial: **120mcg**. If agitation persists, up to 2 additional doses of 60mcg may be administered at least 2 hours apart. Max 240mcg/day
 - •Severe agitation: Sublingual film: sublingual/buccal: Initial: **180mcg**; if agitation persists, up to two additional doses of 90 mcg may be administered at least 2 hours apart. Max: 360 mcg/day
 - •Dose reductions in geriatrics, hepatic impairment: Initial 60-90 mcg can be given.
 - •Administer Sublingual (6-8min to dissolve) or buccal (18 min to dissolve). Keep in foil pouch until ready to administer. Should be self-administered by patient under supervision.
- Warnings/precautions:
 - •Avoid use in patients with Hypotension, orthostatic hypotension, bradycardia, syncope, history of arrhythmias, hypokalemia, and/or hypomagnesemia
 - •Avoid use in patients with known QTc prolongation
 - •Avoid use in patients with alcohol intoxication
- Adverse events: Somnolence, dizziness, headache, paresthesia/oral hypoesthesia, orthostatic hypotension, QTc prolongation

Clonidine



- antihypertensive with sedative and analgesic effects
- clinical use: HTN, anxiety, ADHD, chronic pain, withdrawal symptoms, post-op shivering
- off-label use for agitation (pediatrics, ICU/critical care, palliative care, behavioral disturbances in autism)
- used as adjunct to opioids in nonmalignant chronic pain
- administered oral, sublingual, intravenous, subcutaneous, epidural, transdermal and topical routes
- Precautions: transient BP increase for initial dosing

Guanfacine

- alpha-2 receptor agonist
- anxiety, agitation, sedation, hypertension
- dose: 0.5mg -1mg BID-TID
- Fetters et al: dexmedetomidine was discontinued within 48 hours of guanfacine initiation in 58% of patients (N105)

Pharmacotherapy in ICU Agitation:

 Increasing literature over past decade

- Antipsychotics:
 - ACCM **Clinical Practice Guidelines** for Management of Pain, Agitation, and Delirium in the ICU found **no evidence** that haloperidol reduces duration of delirium, and **low quality evidence** for the use of atypical antipsychotics
 - Haldol does not significantly reduce mortality or modify the duration of delirium (Anderson-Ranberg et al, 2023, Page et al ,2013)
 - Case reports of successful use of **Quetiapine** in patients with previously failed weaning attempts (Seemuller et al., Rosenthal et al)
- Off label use of IV olanzapine:
 - IV olanzapine is as efficacious as IV haldol in ICU agitation, can increase risk of bradycardia and somnolence (Wang et al, 2022)
- Dexmedatomidine (Precedex) -
 - associated with reduction in sedative and analgesic use
 - recommended over benzodiazepines

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- Andersen-Ranberg NC, Barbateskovic M, Perner A, Oxenbøll Collet M, Musaeus Poulsen L, van der Jagt M, Smit L, Wetterslev J, Mathiesen O, Maagaard M. Critical Care. 2023 Aug 26;27(1):329.
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Restraints in the Medical Setting: A Last Resort

- Physical Restraints should only be used when all less restrictive measures have failed and there is imminent risk to the patient or others
- The goal is safety – immediate prevention of harm, followed up with additional stabilization and discontinuation as soon as possible
- Medical Context
 - Hospital medical restraint policies
 - Physical restraints restrict the direct physical movement of a patient:
 - Physical restraints: mittens, vests, soft restraints (wrist/ankles), brief hold
 - Non-mechanical: bed/chair sensor alarm, enclosure “net” bed, side rails*
- Restraint risks:
 - Physical injuries: skin breakdown, nerve injuries, asphyxiation
 - Psychological harm (trauma, loss of dignity, worsening agitation)



Special populations

Agitation in Geriatric patients

What does this look like?

Dementia with Behavioral Disturbance

Verbal Aggression

- screaming
- cursing

Non- Aggressive verbal

- repetitive questioning
- complaining

Physical Aggression

- Hitting
- Biting
- grabbing
- pushing

Non-Aggressive Physical

- wandering
- pacing
- intrusiveness
- hoarding
- Hiding
- Socially inappropriate behaviors

Mood-Affect

- Anxiety
- Depression
- Irritability

Thoughts and Behaviors

- hallucinations
- delusions
- paranoia

Sundowning



also known as Behavioral and Psychological symptoms of dementia (BPSD)



90% of patients with dementia eventually develop behavioral complications

Age-Related Medication considerations

- Multiple medical co-morbidities
- Polypharmacy/ concomitant use of multiple medications
- cognitive deficits impacting medication usage and compliance
- age-related pharmacodynamic/ pharmacokinetic changes --> vulnerability to adverse drug events and toxicity
- potential for multiple prescribers
- problematic prescription cascade
 - reduce medications or doses if possible
- “start low, go slow”

Antidepressants:

- citalopram has most compelling data though class effect of SSRIs
 - RCT of citalopram v perphenazine - both improved agitation, lability, psychosis (Pollock et al, Am J Psychiatry, 2002)
 - RCT citalopram v risperidone - both improved on agitation, psychosis, SE higher in risp group (Pollock et al, Am J Geri Psych 2007)
 - CitAD trial (Citalopram for Agitation in Alzheimer's Disease) - 9 week placebo RCT. Advantage of citalopram in treating agitation and reducing caregiver distress
 - ~9 weeks needed for response
 - 10-30mg citalopram used
 - residents in long term care had less robust response
 - CATIE-AD trial - (Siddique et al) apathy and irritability scores reduced (dosages 10-80mg/day)
 - Trials in sertraline, citalopram, fluvoxamine, escitalopram all demonstrate efficacy and tolerability

• Aga VM. When and how to treat agitation in alzheimer's disease dementia with citalopram and escitalopram. The American Journal of Geriatric Psychiatry. 2019 Oct 1; 27(10):1099-107.

• Porsteinsson AP, Drye LT, Pollock BG, et al: Effect of citalopram on agitation in Alzheimer disease: the CitAD randomized clinical trial. JAMA 2014; 311:682-691

Antidepressants, cont.

- Trazodone: multiple trials demonstrate efficacy
 - Trazodone v haldol (RCT): both had modest efficacy in treating agitation, trazodone better tolerated. trend: the higher the MMSE score, the less improvement in agitation (Sultzer et al, 1997)
 - follow up study (2001): improvement in agitation that occurs with mod/severe dementia related to trazodone is associated with extent of concurrent mood symptoms
 - haloperidol, trazodone, behavioral management techniques, or placebo: with the highest proportion of improvement in agitated behaviors seen in the trazodone arm (Teri et al, 2000)
 - Trazodone/Placebo RCT in patients with FTD: an improvement on eating disorders, agitation, irritability, and depression/dysphoria.
 - sleep optimization - recommended doses 12.5mg-50mg at bedtime

 clinical tip: For acute agitation, **trazodone 12.5mg PO TID** (~AM, ~lunch, ~sunset), titrate as needed

Antipsychotics in BPSD

- Neither FGA or SGA have an indication for BPSD
- All antipsychotics have a black box warning for increased mortality for use in patients with dementia
- the etiology of the dementia may guide treatment
- antipsychotics should only be used when "agitation and/or psychosis is "severe, dangerous, and /or causing significant distress to the patient"
- LAI should not be used unless indicated for a co-occurring chronic psychotic disorder

Haldol

- benefit for aggressive behavior and some improvement in psychosis, but little improvement in agitation
- found to have highest mortality risk in two large retrospective cohort studies (compared to SGA)
- not recommended as first line, routine medication for agitation related to MNCD

Second generation:

- Aripiprazole, olanzapine, risperidone had small but stat sign benefit for treatment of BPSD (at doses ~50% less) in meta-analysis
- Olanzapine: first line for emergent agitation, 1.25mg-2.5mg IM
- Quetiapine: has not been found more efficacious than placebo. Best for LBD/PD
- Risperidone: 0.25mg-0.5mg to start
- Aripiprazole: 2-2.25mg to start, modest effect and milder side effects

APA guidelines for use of antipsychotics to treat agitation and psychosis in MNCD, 2016

Some BPSD symptoms may not respond to medications

Document discussion of benefits/risks and alternatives

Brexpiprazole

- Serotonin-dopamine activity modulator, partial agonist at 5-HT_{1A} and D₂ receptors, and antagonist at 5-HT_{2A} and noradrenaline α_{1B}/α_{2C} receptors.
- Indications: schizophrenia, adjunctive treatment for MDD, agitation associated with dementia due to Alzheimer's disease
- Agitation in cognitive disorders: patients exhibiting behavior consistent with emotional distress: excessive motor activity, verbal aggression, and/or physical aggression causing excess disability with regard to interpersonal relationships, social functioning, or activities of daily living.
- Initial: 0.5mg once daily for 7 days, increase to 1mg daily x 7 days for week 2, then can increase to 2mg daily. Max dose 3mg daily.
- Recommended for short-term adjunctive use while addressing underlying causes of symptoms. Only continue in patients with demonstrated benefit, and attempt to taper and withdraw and regular intervals (eg within 4 months of initiation)
- Grossberg et al (2020): in 2 multicenter, RCT, placebo-controlled studies in patients with AAD, in 12 week treatment period and 30 day post-treatment follow-up period, with agitation as a therapeutic end point, brexpiprazole 2mg daily demonstrated superior efficacy versus placebo in patients with AAD (study 1). Of note, those who were dosed 1mg or lower did not separate from placebo, and studies were in community or care facilities.

Prescribing pitfalls:

- Excess dosages
- Drug-drug interactions
- adverse effects
- inappropriate drug for target symptoms
- cumulative anticholinergic burden
- little evidence of efficacy
- multiple providers
- multiple drugs in same class
- monitor for relapse after discontinuing medication

Conclusion

- Preparation and Collaboration is key for agitation management
- Balance of nonpharmacological and medication strategies
- treatment plan should be individualized for the patient
- Prevention and Education