Objectives

- Identify the principles of the “cycle of violence.”
- Describe the broad differential diagnosis behind the symptoms of agitation and aggression.
- Apply nonpharmacologic and pharmacologic approaches to management of the agitated patient in the general medical setting.

The Case

- A 47 year-old male with a history of substance abuse and bipolar disorder along with morbid obesity, DM and COPD presents to the ED at 0200 after calling 911 and reporting chest pain.
- Initially cooperative in the ED, but the staff indicate that he has been mumbling to himself and staring at them suspiciously. They gave him some lorazepam to “calm” him.
- Since arrival to the floor to r/o MI he has been becoming increasingly irritable, confrontational and restless. Eventually he starts to become uncooperative with care and then verbally and physically threatening to the staff.
- They call a psychiatry consult for “HELP!!!!”
Definitions

- Agitation
  - Excessive motor or verbal activity

- Aggression
  - Actual noxious behavior that can be verbal, physical against objects, or physical against people

- Violence
  - Denotes physical aggression by people against other people

(Chirone and Volavka, 2002)

Component Behaviors of Agitation

- Aggressive behaviors
  - Physical
    - Fighting
    - Throwing things
    - Grabbing objects
    - Destroying items
  - Verbal
    - Cursing
    - Screaming

- Nonaggressive behaviors
  - Restlessness (akathisia, restlessness)
  - Wandering
  - Inappropriate behavior (disrobing, intrusive, repetitive questioning)

Epidemiology

- There is little direct data on the prevalence, clinical impact, or financial consequences of agitation
- Behavioral emergencies responsible for 6% of all ED visits (Larkin et al 2005)
- Marco and Vaughn (2005)
  - 4.3 million psychiatric emergency visits/year
    - 21% (900,000) agitated patients with schizophrenia
    - 13% (560,000) agitated patients with bipolar
    - 5% (210,000) agitated patients with dementia
Epidemiology

- Studies for health care workers
  - California:
    - 465 assaults per 100,000 hospital workers vs. 82.5 assaults per 100,000 for all workers (Peek-Asa et al. 1997)
  - Minnesota Nurses Study (Gerberich et al. 2004):
    - 13.2 per 100 persons per year for physical assaults
    - 38.8 per 100 persons per year for non-physical assaults
  - Greatest risk for persons working in:
    - Long term care facility
    - Intensive care
    - Psychiatric unit
    - Emergency department
    - Geriatric patients

Etiology of Agitation

- A. Disease-related: three major categories
  - Psychiatric manifestations of general medical conditions
  - Substance intoxication/withdrawal
  - Primary psychiatric illness
- B. No “disorder”; unlikely to benefit from medical intervention (e.g., criminal behavior)
  - Consider calling security or the police, depending on the severity
- Not mutually exclusive

Etiology of Agitation: A Sample of the Varied Conditions that may Present with Pathologic Agitation

- Dementia
- Huntington’s disease
- Brain injury
- Organic brain syndrome (delirium)
- Korsakoff’s psychosis
- Brain tumors
- Mental retardation
- Autism
- Seizure disorder
- Major depression
- Dysthymia
- Bipolar disorder
- Substance intoxication or withdrawal
- Psychosis
- Premenstrual dysphoric disorder
- PTSD
- Panic disorder and GAD
- Antisocial personality disorder
- Borderline personality disorder
- ADD

Etiology of Agitation: Medical Causes

- Head trauma
- Encephalitis, meningitis, other infection
- Encephalopathy, liver or renal failure
- Environmental toxins
- Metabolic abnormalities (sodium, calcium, glucose)
- Hypoxia
- Thyroid disease
- Seizures
- Toxic levels of medications

Etiology of Agitation: Medical condition

- Delirium
  - Disturbance of consciousness
  - A change in cognition or development of perceptual disturbance
    - Not accounted for by a dementia
    - Disturbance develops over a short period of time and tends to fluctuate
    - Caused by a general medical condition

Etiology of Agitation: Substances

- Substance intoxication (ETOH, cocaine, amphetamines, ketamine, bath salts, inhalants)
- Substance withdrawal (ETOH withdrawal delirium/DTs)
- CNS effects of non-psychiatric medications (steroids)

Etiology of Agitation: Primary Psychiatric disorders

- Schizophrenia
- Bipolar
- Dementia
- Personality Disorders

Etiology of Agitation: Schizophrenia

- Acutely, patients may present to the ED with acute psychosis
  - Hallucinations
  - Delusions
  - Disorganized speech and/or behavior
  - Lack of insight
  - Bizarre behavior
- Fertile conditions for the development of agitation
  - Psychosis and agitation have a reciprocal relationship
Etiology of Agitation: Schizophrenia

- Patients at highest risk for violence
  - More suspicious and hostile
  - More severe hallucinations
  - Less insight into delusions
  - Greater thought disorder
  - Poor impulse control

- Risk factors for becoming a target
  - Parent or immediate family member
  - Cohabitation
  - Patient financially dependent on you

Etiology of Agitation: Personality Disorders

- Some personality disorders are more prone to agitation
  - Decreased stress tolerance
  - Poor impulse control

- Borderline personality disorder

- Antisocial personality disorder

Etiology of Agitation: Dementia

- Overall, the incidence of agitation is estimated to be between 60-80% (median 44%) (Bartels et al. 2003)
  - 50% become frankly physically aggressive
  - 24% become verbally aggressive

- Burden of institutionalization
  - Residents with dementia complicated by agitation have the highest 3-month rate of ED visits and greatest use of restraints (Sachs, 2006)
  - Despite use of restraints, over 40% receive no psychiatric medications

Etiology of Agitation: Dementia

- Agitation may be a final common pathway for the expression of...
  - Depression
  - Anxiety
  - Psychosis
  - Pain
  - Delirium

- While agitation may be of multifactorial etiology in patients with dementia, it is also true that many patients have only agitation as a target symptom for treatment (Madhusoodanan, 2001)
Etiology of Agitation

- Psychodynamic perspectives of agitation and violence
  - "...motive or cause of violent behavior is the wish to ward off or eliminate feelings of shame and humiliation [ego integrity]..." (Hodas, 2004)
  - Crisis can be defined as an assault on the person's sense of self (Bernstein, 2007)
  - Violence is often in response to blocking of demands or loss of control (Bernstein, 2007)

- A psychological understanding of aggressive behavior can help temper counter-transference

The Case (continued)

- Potential etiologies for our gentleman's growing agitation
  - Substance intoxication
  - Bipolar disorder
  - Personality disorder
  - Delirium

Assessment of Agitation

- Decisions regarding diagnostic tests must be made in the context of available history and physical examination
- Goal is to evaluate patients at risk for medical comorbidities
- Many questions involve forced decisions based on...
  - Assumptions
  - Information available
  - Diagnostic confidence
  - Patient's individual risk factors

Assessment of Agitation

- For a known schizophrenic with typical behavioral features
  - Expectant management is appropriate
- For patients with atypical features additional diagnostic tests may be required
  - Atypical presentations
    - Delirium
    - History of trauma
    - Overdose
    - Headache
    - Fever
  - Diagnostic tests to consider
    - Toxicology screens
    - CT of brain
    - BMP, CBC, and LFTs
    - Urinalysis
    - Endocrine tests
    - Lumbar puncture
The Case (continued)

- Examination of the patient
  - The patient is febrile with normal vitals
  - Malnourished, disheveled, and stinky
  - Heart, lungs and abdomen are benign
  - No tremor or asterixis
  - Mental status/state examination reveals...

- Laboratory evaluation of the patient
  - CBC, BMP are normal except for a glucose of 211
  - LFTs are normal except for a low albumin
  - TSH, B12, Folate, and RPR are also normal
  - U/A is positive for glucose and trace
  - CT of head is read as “negative”
  - EKG shows QTc < 400msec
  - UDS and serum toxicology are negative
  - VPA, carbamazepine, and lithium are all negative

Before the Acute Intervention

- The staff on Med/Surg units are often less informed about what feelings and behaviors their actions may elicit in patients
- Studies indicate that staff training and education can change this lack of appreciation
- Psychiatric consultants can provide education about
  - Establishing goals from the patients perspective
  - Interventions that support a structured setting
    - Private or semi-private room
    - Establish clear set of expectations with a written schedule
    - Identify staff that are responsible for the patients care
  - Attempting to enlist the patient in the treatment, i.e. which route of medication has worked the best in the past as a “choice” which retains some patient control

Goals of Intervention

- Acute agitation or a violent patient modifies the normal caregiver-patient relationship
- The first goal of treatment is to do only what is necessary to assure the safety of the patient and others while facilitating the resumption of more normal interpersonal relations
  - Calming without over-sedation
Agitation Management

- Medical evaluation and triage
- Psychiatric evaluation
- Verbal de-escalation
- Psychopharmacologic interventions
- Use of seclusion/restraint


Environmental Interventions

- Examples of effective non-pharmacological treatments
  - Clearing the room
  - Removing dangerous objects
  - Having staff available as a “show of force”
  - Close observation
  - Calm conversation
  - Decrease sensorial stimulation

Communication/Behavioral Interventions

- Nonverbal
  - Maintain a safe distance
  - Maintain a neutral posture
  - Do not stare; eye contact should convey sincerity
  - Do not touch the patient
  - Stay at the same height as the patient
  - Avoid sudden movements

- Verbal
  - Speak in calm, clear tone
  - Personalize yourself
  - Avoid confrontation; offer to solve the problem

(APA Textbook of Psychosomatic Medicine, 2nd ed. Edited by James L. Levenson. 2011)
The Case (continued)

- You and the nursing staff
  - Clear the room
  - Keep dangerous objects out of reach
  - Call security
- You attempt to approach the patient using everything you learned in this amazing talk
- Despite these great interventions the patient makes further threats, rips-off telemetry lines, and starts to pace with clenched fists while mumbling incoherently

Serotonin-Dopamine Model of Regulation of Agitation

- Dynamic interaction between the amygdala, nucleus accumbens, and the prefrontal cortex

![Diagram illustrating serotonin-dopamine model of regulation of agitation]

Goals of Intervention

- Definition of psychopharmacologic treatment endpoint (rapid tranquilization)
  - Sleep
    - Conflicts with goal of patient participation
    - Has not been found to be essential to improvement in agitation or decrease in psychotic symptoms
  - Tranquillization
    - Calming process separate from total sleep induction
    - Allows patient to participate in care
    - Enables clinician to gather history, initiate a work-up, and begin treatment of unidentified conditions
    - Better therapeutic endpoint

Pharmacologic Considerations

- Ease of preparation/administration
- Rapid onset of action: IV > IM > PO
- Sufficient duration of effect
- Low risk of adverse reactions or drug interactions
- What is known about the patient’s underlying condition(s)?
  - Age
  - Comorbid conditions
  - Medication/other substance exposure

![Diagram illustrating serotonin-dopamine model of regulation of agitation]
Pharmacologic Treatment

- Most important factors in medication selection (Marder, 2006; Allen et al, 2005)
  - Etiology of agitation
  - Acute effect on behavioral symptoms
  - Multiple means of administration
  - Limited side effects
  - Ease of administration
  - Patient preference
  - History of response
- Goal is a balance between effectiveness and tolerability

Pharmacologic Treatment

- Route of administration
  - Oral administration
    - Preferred if patient accepts
    - Liquid or orally dissolving tablets
  - Intramuscular administration
    - Rapid elevation of plasma level
    - Higher transient concentration
    - Faster reduction in agitated behavior

Association for Emergency Psychiatry Recommendations

- No Data/Suspect Intoxication
  - benzodiazepines or benzodiazepines + haloperidol

- Schizophrenia or Mania
  - olanzapine alone orally
  - risperidone alone or + benzodiazepine orally
  - haloperidol + benzodiazepine orally
  - olanzapine alone if IM required

Benzodiazepines

- BZDs act by facilitating the activity of GABA
  - GABA is a major inhibitory neurotransmitter
- Therapeutic effects appears linked to decreased arousal
  - Little benefit for psychiatric symptoms other than anxiety
- Long history of use in the management of acute agitation
  - Individually
  - Combination with antipsychotics
  - Preferred in a patient in whom agitation is secondary to alcohol or sedative withdrawal

Lorazepam

- Only BZD with complete and rapid IM absorption
- No involvement of P450 system
- IM or sublingual administration
  - 60-90 minutes until peak plasma concentration
  - 8-10 hour duration of effect
  - 12-15 hour elimination half-life
- Studies suggest that lorazepam 2mg is at least as effective as haloperidol in controlling acute agitation

Side effects

- Excessive sedation
  - Additive with other CNS depressants
- Respiratory depression
  - BZDs avoided in patients at risk for CO2 retention
  - Paradoxical disinhibition
    - More likely with high doses in patients with structure brain damage, mental retardation or dementia
- Ataxia

Typical Antipsychotics

- Dopamine antagonist
  - Positive
  - Antipsychotic
  - Antiagitation
  - Negative
    - Extrapyramidal symptoms (EPS)
    - Neuroleptic Malignant Syndrome (NMS)
- Many authors consider typical antipsychotics the treatment of choice in acute agitation
Typical Antipsychotics

- Low potency
  - Not recommended

- High potency - haloperidol
  - Virtually no anticholinergic properties
  - Little risk of hypotension
  - Does not suppress respiration
  - Can be given IV
  - Not FDA approved
  - Little cardiotoxicity
  - Concern of QTc prolongation
  - Fast acting
    - Onset of action: 30 minutes
    - Duration of action up to 12-24 hours


Typical Antipsychotics: Loxapine

- Inhaled Loxapine has been recently endorsed by FDA for treatment for agitation in Bipolar I disorder
- Need to monitor for bronchospasm, especially in patients with asthma

- (Owen RT. Inhaled loxapine: a new treatment for agitation in schizophrenia or bipolar disorder. Drugs of Today. 49(3):195-201, 2013 Mar)

Atypical Antipsychotics

- Major advance in psychiatry
  - Broader spectrum of response
  - Different side effect profile
  - Less EPS and akathisia
  - QTc concern remains
  - Metabolic syndrome

- No randomized, controlled studies have examined the use of medications in populations with...
  - Severe agitation
  - Drug-induced agitation
  - Significant medical comorbidity
Atypical Antipsychotics

- Risperidone
  - Oral solution
  - Oral tablet
  - Oral tablet, disintegrating
- Olanzapine
  - Intramuscular
  - Oral tablet
  - Oral tablet, disintegrating
- Quetiapine
  - Oral tablet
- Ziprasidone
  - Intramuscular
  - Oral tablet
  - Oral tablet, disintegrating

- Aripiprazole
  - Intramuscular
  - Oral solution
  - Oral tablet
  - Oral tablet, disintegrating

Risperidone (Currier and Simpson 2001, Currier et al 2004)
- 2 studies have compared
  - Oral risperidone concentrate 2mg + oral lorazepam 2mg
  - IM haloperidol 5mg + IM lorazepam 2mg

The two interventions were equally effective at reducing agitation at 30, 60, and 120 minutes
- So... In agitated patients willing to take oral medication and comply with treatment, the combination of oral risperidone and lorazepam appears to be acceptable

Olanzapine
- IM dose range of 5-10mg
  - Maximum of 30mg/day
  - 15-45 minutes until peak plasma concentration
  - 21-54 hour elimination half-life
- PO dose range 5-10mg
  - 24-54 hour elimination half-life
  - 1-3 hours until peak plasma concentration, but benefits often occur in less time

Olanzapine
- Adverse events
  - Concern of orthostasis
  - Long-term use has been associated with the development of metabolic syndrome
  - IM olanzapine should NOT be administered with BZDs or CNS depressants given reports of adverse events and 8 deaths in Europe
  - Patients were also suffering from medical comorbidities
  - Cardiopulmonary depression, hypotension, and bradycardia reported
Atypical Antipsychotics

- Ziprasidone
  - First atypical with an IM formulation
  - IM dose range of 10-20mg
    - 10mg q2 hour
    - 20mg q4 hour
    - Maximum of 40mg IM/day
  - 30-40 minutes to peak plasma concentrations
    - 9x faster than oral administration
  - 2-4 hour elimination half-life
  - 4-6 hour duration of effect

- Adverse events
  - QTc interval prolongation
    - Appears to prolong the QTc to a greater degree than haloperidol, risperidone, or olanzapine
    - No clinically relevant ECG changes observed in agitation studies
    - Somnolence, nausea, and dizziness were the most common reported in the agitation studies

- Aripiprazole
  - Newest atypical antipsychotic
  - It is unique in that it is a partial dopamine agonist
    - Decreases dopamine in hyper-dopaminergic areas of the brain
    - Increases dopamine in hypo-dopaminergic areas of the brain
  - IM Aripiprazole has been found effective in the management of agitation in psychiatric illness
  - Recommended IM dose is 9.75mg

- Quetiapine
  - 1-3 hours to peak plasma concentrations
  - Very low risk of EPS
  - Sedation and orthostasis are side effects
  - 1 open-labeled pilot study (N=20) (Currier et al, 2006)
    - 100mg (N=7), 150mg (N=6), or 200mg (N=7) administered
    - Fair efficacy in reducing agitation over 120 minutes
      - No clear dose-response pattern
      - 40% exhibited orthostasis by 120 minutes
      - 6 subjects were asleep at 120 minutes

(Gonzalez D., Binroth M., Curtis V., Debenham M., Jones S., Pitsi D.
George M. Consensus statement on the use of intramuscular aripiprazole for the rapid control of agitation in bipolar mania and schizophrenia. Current Medical Research & Opinion. 29(3):241-50, 2013 Mar)
Combination Therapy

– Individual medications can be targeted to the different components of agitation
  ▪ Anxiety and arousal → benzodiazepine
  ▪ Psychosis → antipsychotic
– Combining medications at low doses may reduce individual side effects (decrease Cmax), while obtaining desired effect
– Specific prevention of side effects while combining anti-agitation effect
  ▪ e.g., Haloperidol + Dipheniramine

Combination Therapy

▪ Most common combination
  – Haloperidol 5mg IM
  – Lorazepam 2mg IM
  – Benefits
    ▪ Faster reduction in agitation
    ▪ Less injections required
    ▪ Simple to administer
    ▪ Lower incidence of EPS

Combination Therapy

▪ Side effects
  – Overall, very well tolerated
  – Side effect profiles of both the BZDs and antipsychotics apply
  – Excess sedation most common adverse reaction
    ▪ However, recent studies suggest sedation rates appear similar to lorazepam treatment alone

Cost

<table>
<thead>
<tr>
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<th>Lorazepam 2 mg IM</th>
<th>Haloperidol 5 mg IM</th>
<th>Ziprasidone 20 mg IM</th>
<th>Olanzapine 10 mg IM</th>
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</thead>
<tbody>
<tr>
<td>Number of injections required (clinical trial data)</td>
<td>1 (42%) or 2 (37%)</td>
<td>1 (76%)</td>
<td>1 (76%)</td>
<td>1 (76%)</td>
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<td>Cost</td>
<td>$1.28</td>
<td>$7.49</td>
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Academy of Psychosomatic Medicine

### Summary for Acute Term

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>Medication</th>
<th>Dosing</th>
<th>Side Effects/Considerations</th>
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<tbody>
<tr>
<td>Typical antipsychotics</td>
<td>Haloperidol</td>
<td>PO, IM, IV; start at 5-10 mg IM, IV</td>
<td>*</td>
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<tr>
<td>Benzodiazepine</td>
<td>Alprazolam</td>
<td>Only available PO; initial dose is 0.5-4</td>
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**Disposition**

- Disposition depends on etiology of agitation and current condition
  - Delirium ➔ General medical hospital
  - Psychosis ➔ Psychiatric admission
  - Don’t have a clue ➔ General medical hospital to determine cause of agitation

### Special Population: ICU patients

- Mechanically ventilated ICU patients analgesia and sedation are recommended
- Dexmedetomidine, rather than benzodiazepines
- No evidence haloperidol decreases the duration of delirium
- Atypical antipsychotics may decrease the duration of delirium in ICU patients

Special Population: Weaning of Ventilation

- Dexmedetomidine (alpha 2 adrenergic sedative)
  - Better than midazolam (VS, time intubated)
    - (Ricker et al, 2009)
  - Better than haloperidol (time intubated, LOS)
    - (Heude et al, 2009)

Recommended Readings