MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Catatonia, NMS, and Serotonin Syndrome

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Disclosure: Christopher Celano, MD

My spouse/partner and I have the following relevant financial relationship with a commercial interest to disclose:

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Overview

- Catatonia
  - Prevalence
  - Pathophysiology
  - Manifestations
  - Diagnosis
  - Treatment
- Neuroleptic Malignant Syndrome
- Serotonin Syndrome

Catatonia

- Catatonia is a “motor dysregulation syndrome [in which] patients [are] unable to move normally despite full physical capacity.”

Fink 2009

Catatonia: Prevalence

- 7.8-9.0% prevalence rate
  - Highest rates in non-psychiatric (i.e., medical) settings and in patients undergoing ECT.
- 1.6-5.5% of all patients seen on psychiatry consultation service
  - Prevalence higher for older patients

Grover 2015, Carroll 1994, Jaimes-Albornoz 2013, Fricchione 2008

Pathophysiology of Catatonia

- Disruption in the tracts connecting the basal ganglia and the cortex, leading to relative hypodopaminergia.
  - Dorsolateral prefrontal and anterior cingulate / medial orbitofrontal → akinetic mutism, dysautonomia
  - Lateral orbitofrontal → imitative and repetitive behaviors
  - Supplementary motor / motor / posterior parietal → rigidity, initiation and termination of movement
- Hyperactivity of the supplementary motor area and presupplementary motor area → motor control, initiation and inhibition of movement
- Alterations in brainstem structures

Fricchione 2008, Walther 2019, Fritze 2020

Pathophysiology of Catatonia

- GABA and serotonin may be involved
  - The dopaminergic projections in the brain are modulated by GABA-ergic and serotonergic neurons.
  - Benzodiazepines (GABA-A agonists) are helpful
  - GABA-B agonists (baclofen) are harmful and can induce catatonia
  - Serotonergic medications also may induce catatonic symptoms.
- Glutamate may also play a role
  - Anti-NMDA receptor encephalitis can cause catatonia.
  - NMDA receptor antagonists have been used as treatments in some cases.

Mann 1986, Rogers 2019

Manifestations of Catatonia

Staff reports the patient is “Playing **POSSUM**”

- **P**erseveration (speech or behavior)
- **O**ppositionality to all requests
- **S**peech that trails off or is whispered
- **S**lowed response to questions or commands
- **U**ndernourished (reports of decreased PO intake)
- **M**otionless but awake

Diagnosing Catatonia: DSM-5

Clinical picture is dominated by 3 or more:

- Catalepsy
- Waxy flexibility
- Stupor
- Agitation
- Mutism
- Negativism
- Posturing
- Mannerisms
- Stereotypies
- Grimacing
- Echolalia
- Echopraxia

American Psychiatric Association 2013

Bush-Francis Rating Scale

- Excitement
- Immobility/stupor
- Combativeness
- Autonomic Abnormality
- Impulsivity
- Mutism
- Staring
- Posturing/catalepsy
- Grimacing
- Echopraxia/echolalia
- Stereotypy
- Mannerisms
- Verbigeration
- Rigidity
- Negativism
- Waxy flexibility
- Withdrawal
- Automatic Obedience
- Mitgehen
- Gegenhalten
- Ambitendency
- Grasp Reflex
- Perseveration

Bush 1996

Challenges with Diagnosis

- Clarifying specific symptoms can be difficult
  - Rigidity vs. gegenhalten vs. negativism
- Inconsistency between scales
- Symptoms occur on a spectrum
- Wide variety of manifestations

Prototypes of Catatonia

- The Distant Mute
  - Mutism, immobility, interpersonal withdrawal
  - Team may be concerned this is volitional
- The Waxy Stiff
  - Catalepsy, waxy flexibility, rigidity
  - Often identified by physicians; may misattribute to psychiatric illness
- The Broken Record
  - Echophenomena, verbigeration, hyperactivity
  - Often misdiagnosed as delirium
- The Stubborn Grouch
  - Negativism, repetitive movements, excitement
  - Medical workup often not completed due to lack of cooperation.

Evaluating Catatonic Patients

- Observe patient while trying to engage in conversation.
- Scratch your head in an exaggerated manner.
- Examine the patient's arms for cogwheeling. Move the arms with alternating lighter and heavier force.
- Move patient's arm into different positions and observe whether they remain in position.
- Ask the patient to extend his/her arms. Place one finger beneath each hand and try to raise it slowly after stating, "Do not let me raise your arms."

Evaluating Catatonic Patients

- Extend your hand and state, “Do not shake my hand.”
- Reach into your pocket and state, “Stick out your tongue. I want to stick a pin in it.”
- Check for grasp reflex.
- Check the chart for reports from prior 24 hours. Check for PO intake, VS, and incident.
- Observe the patient indirectly daily to observe for other catatonic symptoms.

Potential Causes of Catatonia

- DSM-5
  - Catatonia associated with another mental disorder (specifier)
  - Catatonic disorder due to another medical condition
- ICD-11
  - Catatonia associated with another mental disorder
  - Catatonia induced by psychoactive substances, including medications
  - Secondary catatonia (due to a medical condition)

APA 2013, Reed 2019

Potential Causes of Catatonia

- Medical Illness
  - Seizures
  - CNS structural damage
  - Encephalitis (e.g., anti-NMDA) or other CNS infection
  - SLE with or without cerebritis
  - Disulfiram
  - Phencyclidine
  - Neuroleptic exposure
  - Corticosteroid exposure
  - Porphyria
  - Post-partum state
  - Iron deficiency
- Psychiatric Illness
  - MDD
  - Bipolar Disorder
  - Psychotic disorders

Carroll 1994, Denysenko 2015, Mulder 2021, Vazquez-Guevara 2021, Amouri 2021

Workup for Catatonia

- Complete Blood Count, Comprehensive Metabolic Panel
- Creatine Kinase (to look for rhabdomyolysis)
- Iron studies
- Toxicology screens
- Other bloodwork as indicated
  - Cultures
  - HIV
  - Paraneoplastic panel
  - Autoimmune studies
- Consider head CT, brain MRI, and EEG

Catatonia vs. Delirium

- DSM-5 states that catatonia cannot be diagnosed when symptoms are present exclusively in the setting of delirium
- Clinical practice suggests that most patients with neuromedical etiology for catatonia also have delirium
- 12-37% of patients with delirium may have features of catatonia
  - More commonly associated with hypoactive delirium and more common in women
  - Common features of catatonia include excitement, immobility, mutism, negativism, staring, withdrawal

Oldham 2015, Grover 2014

Subtypes of Catatonia

- DSM-5 specifiers:
  - Hyperactive
  - Hypoactive
  - Mixed level of activity
- Malignant Catatonia (aka Lethal Catatonia)
  - Characterized by severe muscle rigidity, hyperthermia, and autonomic instability
    - Delirious Mania
    - Neuroleptic Malignant Syndrome
    - Serotonin Syndrome

APA 2013, Mann 1986

Management of Catatonia

- Identify the underlying cause.
  - Perform full psychiatric evaluation to identify mood or psychotic disorders.
  - Obtain collateral information about patient's mood and behavior prior to admission.
  - Perform medical workup, especially for those with other symptoms of medical illness.
- Frequent vital signs
- Supportive care
- Remove possible culprit medications
- Initiate treatment with medications or ECT

Treatment of Catatonia: Benzodiazepines

- Intravenous lorazepam is greatly preferred
  - Quick onset of action
  - Despite a shorter half-life than other benzos, effective clinical activity may be longer because tissue distribution is less rapid and extensive
  - Also demonstrates a higher binding affinity for $GABA_A$ receptor
- Initial dose of 2mg
  - Follow-up dose based on response and sliding scale of suspicion
- If established efficacy or diagnosis certain, continue with standing regimen
  - 8-24mg/day is typical
  - Taper very slowly after improvement

Denysenko 2015

Treatment of Catatonia: ECT

- Effective in 85-90% of cases; 60% of cases that fail medication
- Should be considered for failure to respond to lorazepam in 48-72 hours, malignant symptoms, excited subtype
- Maintenance ECT often required

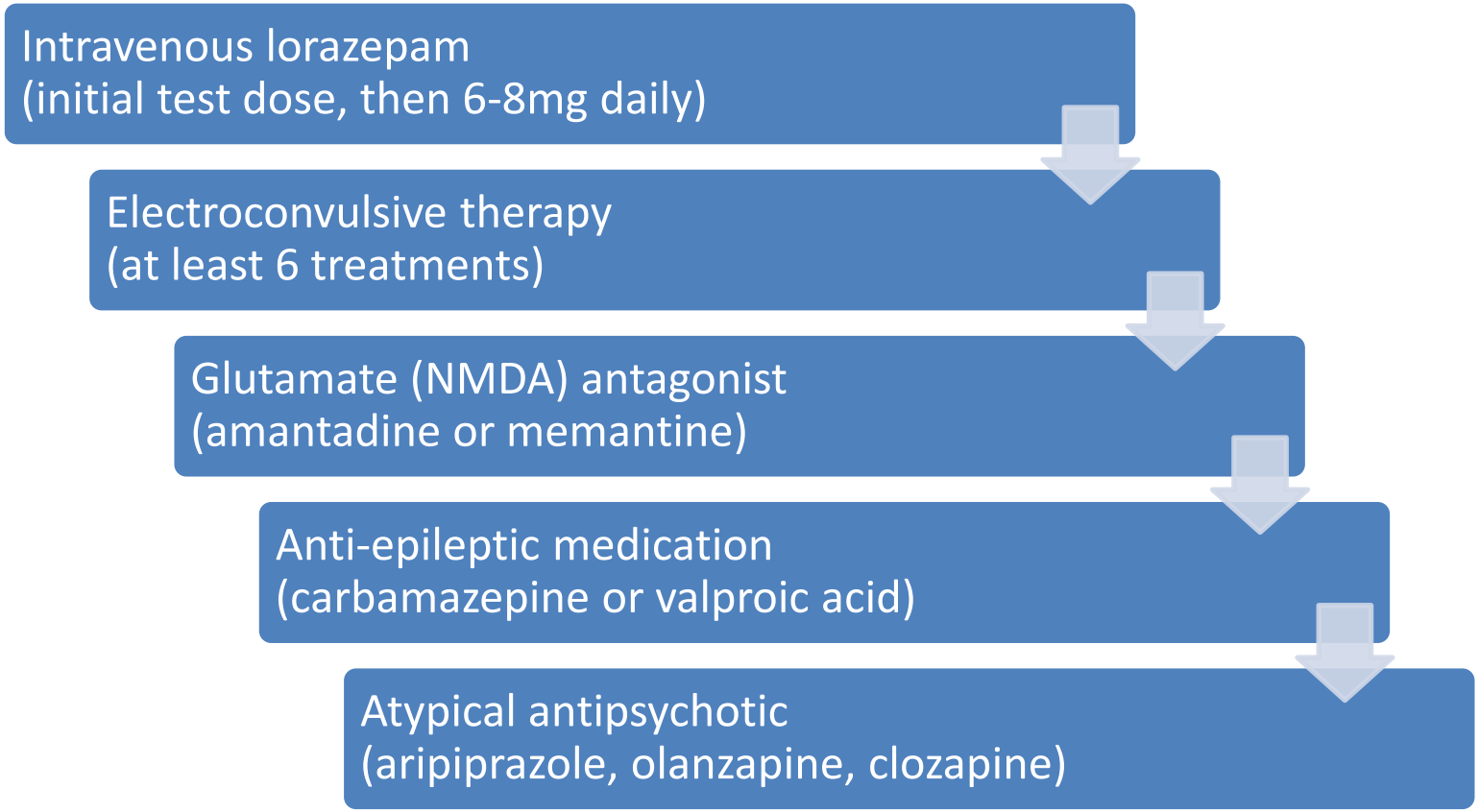
Treatment of Catatonia: Alternatives

- NMDA receptor antagonists
  - Amantadine (18 cases)
    - May also have dopamine agonist activity
    - Start at 100mg daily
    - Titrate by 100mg every 3-4 days to maximum of 400mg in 2-3 divided doses
  - Memantine (9 cases)
    - Start at 5mg bid
    - Increase to 10mg bid if ineffective
- Antiepileptic medications
  - Carbamazepine (7 cases)
    - 100-1000mg daily
  - Valproic acid (5 cases)
    - 600-4000mg daily
  - Topiramate (4 cases)
    - 200mg daily

Treatment of Catatonia: Alternatives

- Antipsychotic medications
  - Hypothesized to work through 5-HT1A agonism and 5-HT2A antagonism, which may lead to increased dopamine in the prefrontal cortex.
  - Aripiprazole (9 cases)
    - 3-30mg daily
  - Clozapine (9 cases)
    - 150-300mg daily
  - Olanzapine (7 cases)
    - 2.5-20mg daily
  - Risperidone (2 cases)
    - 0.5-8mg daily
  - Ziprasidone (2 cases)
    - 40-160mg daily

Treatment Algorithm



Neuroleptic Malignant Syndrome (NMS)

- No DSM diagnostic criteria
- Expert panel criteria:
  - Exposure to dopamine antagonist (or removal of dopamine agonist) within past 72 hours
  - Hyperthermia
  - Rigidity
  - Mental status alteration
  - CK elevation (>4 times upper limit of normal)
  - Autonomic instability
  - Hypermetabolism
  - Exclusion of other medical or substance-induced causes

Guerra 2011

NMS: Complications and Treatment

- Complications
  - Rhabdomyolysis
  - Seizures
  - Respiratory failure
  - Acute kidney injury
  - Sepsis
  - Acute MI
  - Acute liver failure
  - Pulmonary embolism
- Mortality rate 5.6%
- Treatment
  - Remove offending agent
  - Similar treatment to catatonia
  - Can potentially add dantrolene, bromocriptine, or amantadine.

Serotonin Syndrome (SS)

- Sometimes considered a subtype of malignant catatonia
- Symptoms:
  - Spontaneous clonus
  - Inducible clonus AND agitation or diaphoresis
  - Ocular clonus AND agitation or diaphoresis
  - Tremor AND hyperreflexia
  - Hypertonia AND hyperthermia AND ocular clonus or inducible clonus
- Classically induced by combination of MAOI with serotonergic medication
- Now more commonly seen with polypharmacy or overdose
- Clues to Serotonin Syndrome
  - Look for it in patients with antidepressant overdose
  - Look for it in any patient on >4 psychiatric medications
  - Consider it in all catatonic patients

Dunkley 2003

Treatment of Serotonin Syndrome

- Supportive treatment and wash-out is usually all that is needed
  - May use benzodiazepines to manage agitation or if catatonic symptoms are present
  - Short-acting antihypertensives
- If this is not working, can consider cyproheptadine (5-HT1A and 5-HT2A antagonist)

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