Psychiatric Emergencies: Catatonia, Neuroleptic Malignant Syndrome, and Serotonin Syndrome

Nathan Praschan, MD, MPH
Medical Psychiatry: A Comprehensive Update
9/17/2024

Disclosures: None

FYI: Interesting AI generated images

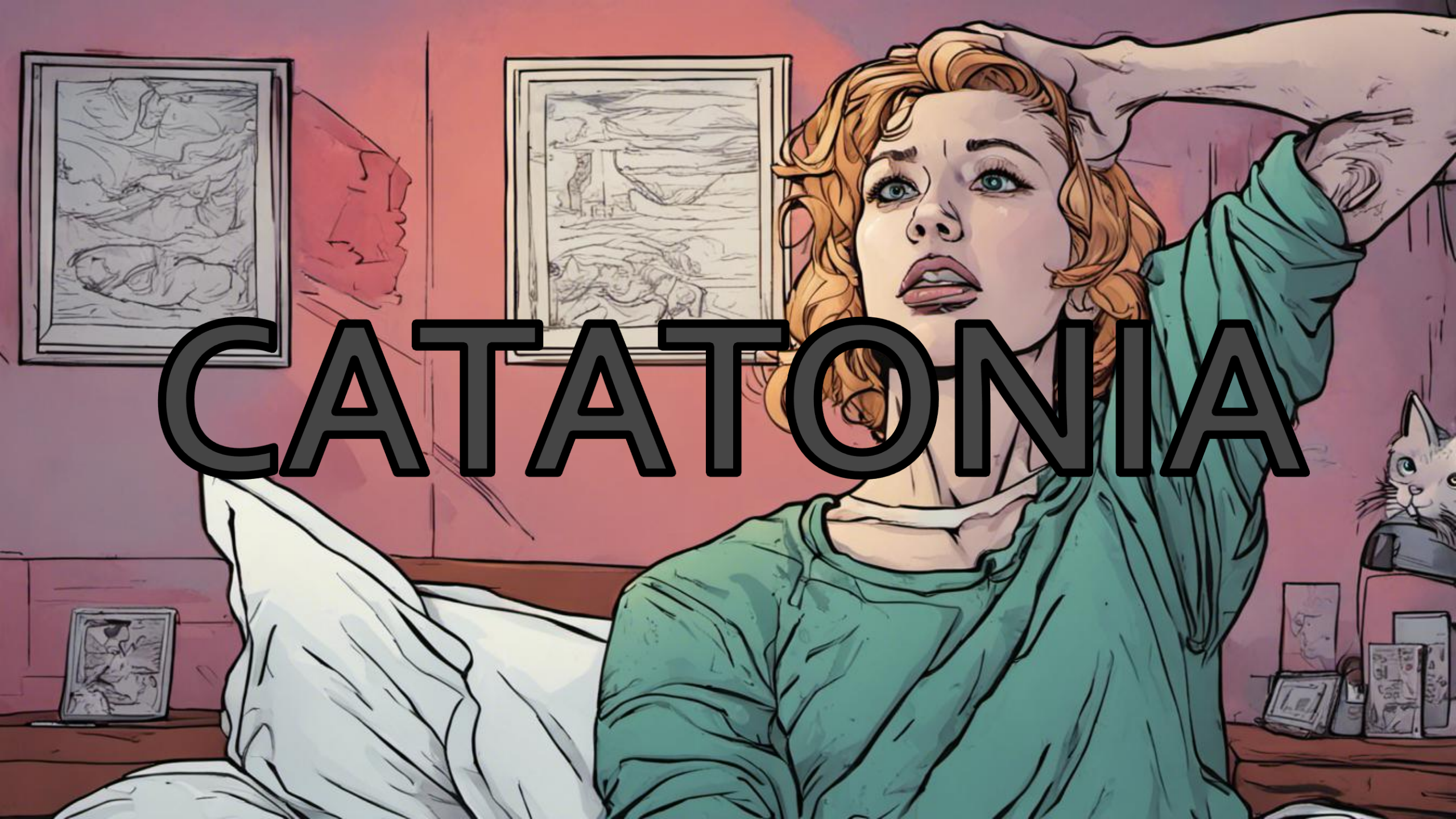
Objectives

UNDERSTAND EXAMINATION FOR CATATONIA

DESCRIBE TYPICAL DIFFERENTIAL DIAGNOSIS OF CATATONIA, NMS, AND SS

APPRECIATE KEY DISTINCTIONS BETWEEN NMS AND SS

DESCRIBE TREATMENT APPROACHES, INCLUDING WHEN FIRST-LINE TREATMENTS FAIL


CATATONIA

Case 1: Background

- **ES** was a **42-year-old left-handed man**, married with children, living locally and working as an investment banker…
- …with a history of *pineal glial cyst s/p resection in 1996* c/b posterior fossa edema necessitating **partial cerebellar resection**, as well as (possibly) *premorbid episodes of depression and mania*…
- …who was brought to the ED for concerns about **catatonia** in the context of *depression precipitated by allostatic overload*.

Case 1: HPI

Preceding *months*…

- Ongoing mood instability
- Depression → increased mirtazapine
- Mania → discontinued mirtazapine, increased quetiapine
- Depression again in context of work changes → lamotrigine added, lorazepam decreased
- Ongoing difficulty to executive function

Preceding *weeks*…

- Onset of odd behaviors, negativistic thinking
- Perseveration and severe indecision
- Latency of speech and thought, large amplitude movements of arms and body

ED

- **BFCRS 30**
- *Stuporous* and *mute*
- *Staring*, *grimacing*, *posturing*
- *Echophenomena* and *stereotypies*
- *Paratonia* and *grasp reflex*
- *Ambitendency* and *perseveration*
- *Tachycardia*

Case 1: Workup

- CMP WNL
- CBC WNL
- TSH 1.17
- UA negative
- Stox, Utox negative
- Ammonia 35
- CK 286
- B12 WNL
- EEG WNL
- MRI brain: stable cerebellar encephalomalacia
- Med Rec
  - ↑ QTP
  - + LTG

Case 1: Course

- Psychiatry consulted in ED → lorazepam 2 mg IV → improved symptoms
- Admitted to internal medicine, psychiatry following for catatonia, followed by transition to med-psych unit
- Medication changes → resolution of catatonia
  - Lorazepam 2 mg q4h → 1 mg BID by discharge
  - Discontinued lamotrigine
  - Discontinued quetiapine

History (Shorter and Fink 2018)

- Described by Kahlbaum in 1847
- Kraeppelin and Bleuler thought 2/2 *dementia praecox* → schizophrenia
- Fink and Gelenberg later reclassified as a **syndrome with many causes**

Definition (DSM-5 2013)

Disturbance of **motor activity** associated with changes in **thought** and **affect**

- Key features: **purposelessness**, **avolition**
- *"The patient is behaving bizarrely"* or *"Patient won't move or eat"*

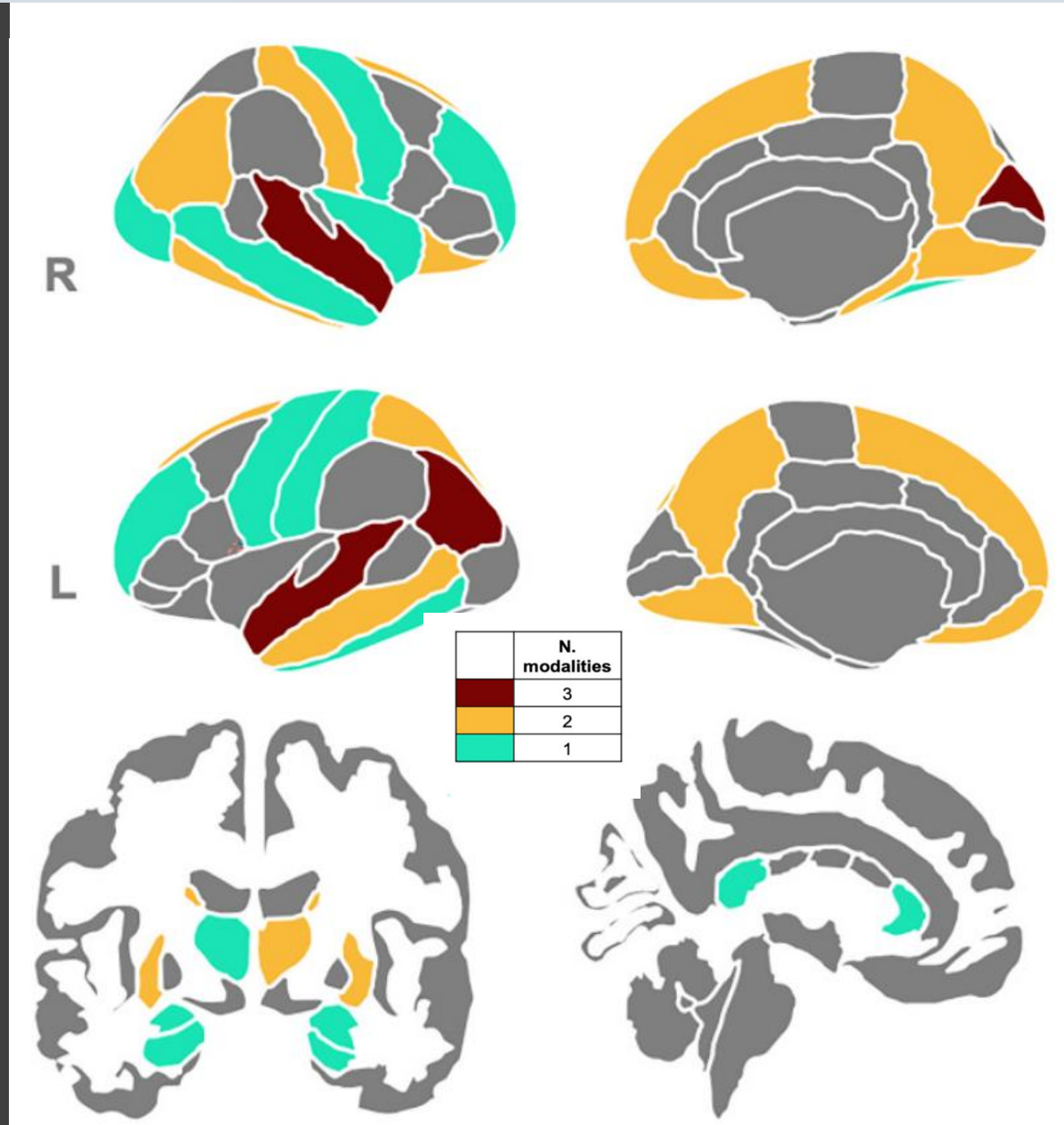
Symptom	Description
Stupor/immobility	No psychomotor activity; no relation to environment
Mutism	No, or very little, verbal response
Negativism	Opposition or no response to instruction or external stimuli
Catalepsy	Passive induction of posture held against gravity
Waxy flexibility	Slight, even resistance to positioning by examiner
Posturing	Spontaneous and active maintenance of posture against gravity
Mannerism	Odd, circumstantial caricature of normal actions
Stereotypy	Repetitive, abnormally frequent, non-GDA
Agitation	Without apparent cause
Grimacing	Facial expression of disgust, disapproval, or pain
Echolalia	Mimicking another's speech
Echopraxia	Mimicking another's movements

DSM-5 requires **3/12** present

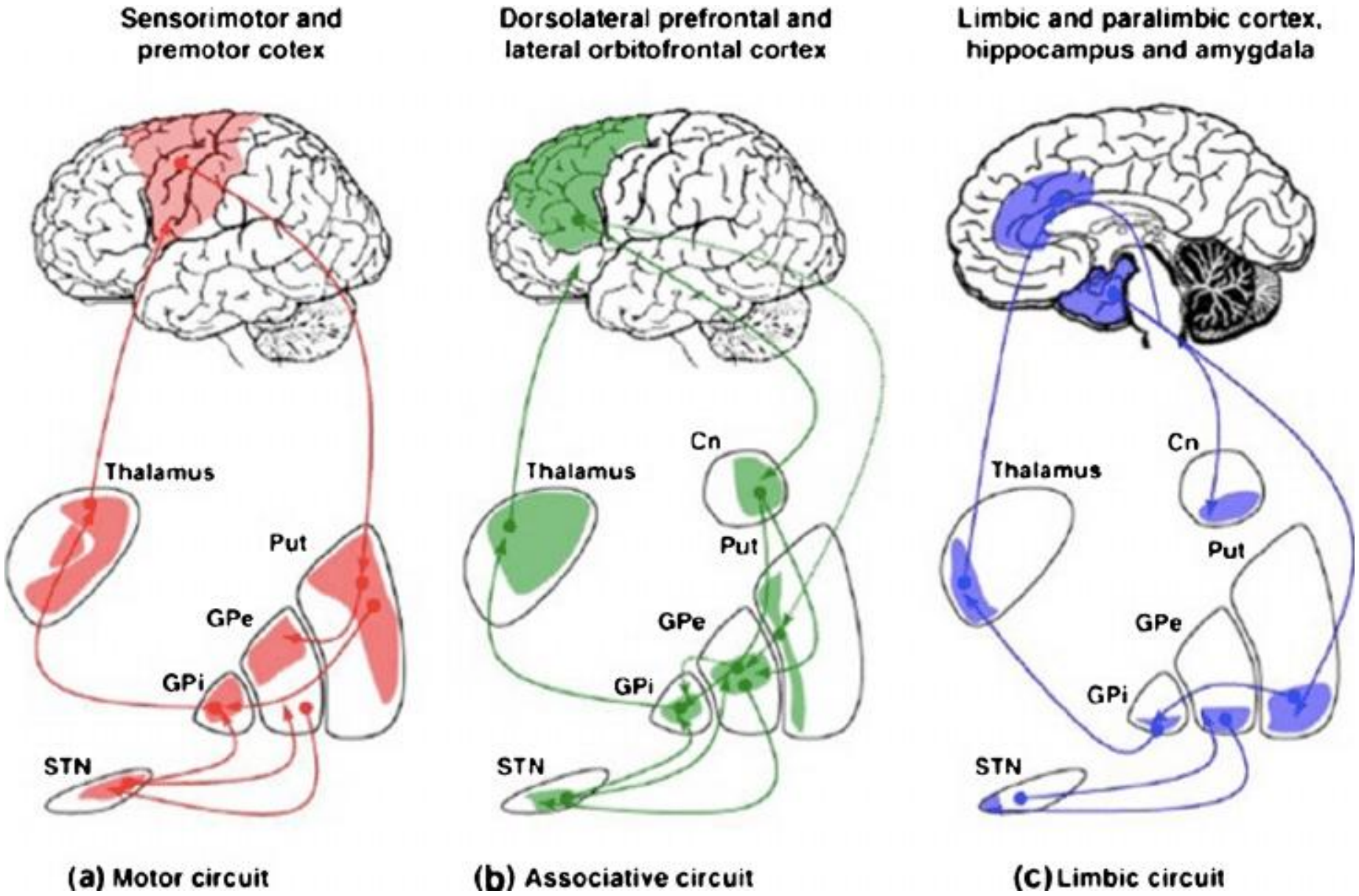
Pathophysiology

(Cattarinussi et all. 2022)

- Pathophysiology hypothesized but not proven to date
- Neurotransmitters: GABA, glutamate, dopamine, norepinephrine
- Neuroanatomy: widely distributed, involving **fronto-parietal networks**, **CSTC loops**, **salience network**, and **DMN dysfunction**
- Other studies have also implicated the **cerebellum** (particularly posterior hemispheres and vermis)

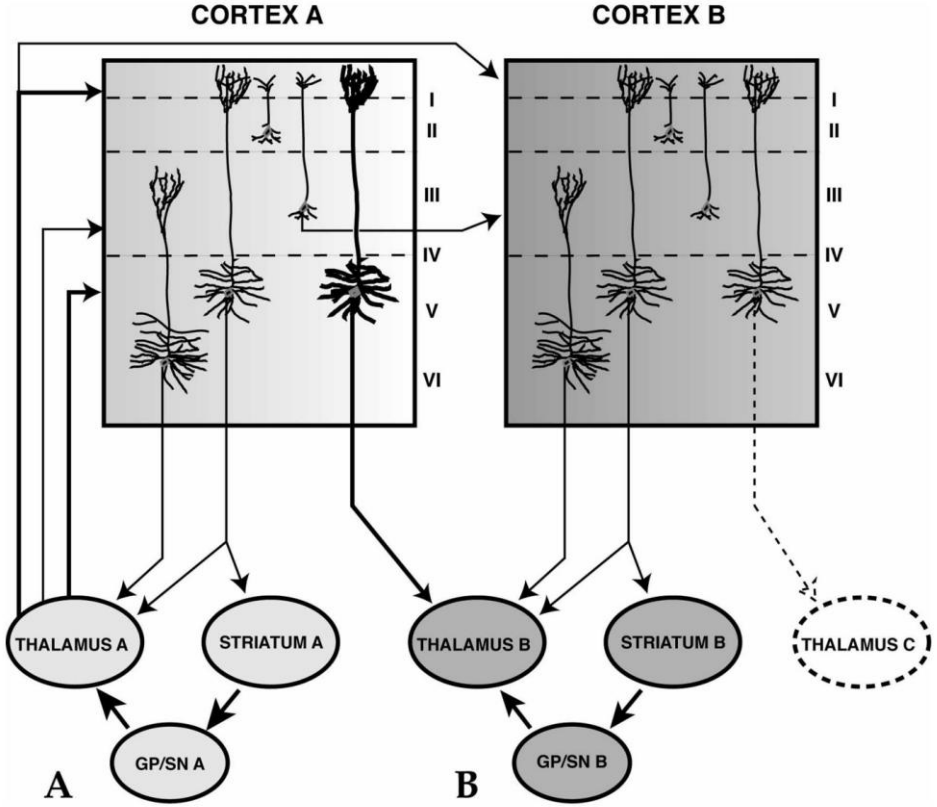


From Lapidus et al. (2014), based on Alexander's 5 parallel CSTC loops



Pathophysiology (Northoff et al. 2002)

- "**Top down**": altered modulation across the "motivation to action" pathway through cortico-cortical connections leads to aberrant motor programming vs CSTC
- "**Bottom up**": limbic overdrive or hypodopaminergic states
  - Mammalian fear response?
  - Neuroleptic malignant syndrome



Epidemiology (Oldham 2018, Wilson et al. 2017)

Nearly always secondary

Overlap: NMS, SS, EPS

13-31% of *mood disorder* patients (esp BPAD)

17% of *ASD* patients

7-30% of *schizophrenia* patients

30% of *hospitalized delirious* patients

20% of catatonia presentations are *nonpsychiatric*—**majority CNS illnesses**

Epidemiology (Oldham 2018)

TABLE 3. Features Suggestive of Primary or Medical Catatonia

Features favoring medical catatonia	Features favoring primary catatonia
• Comorbid delirium (81% vs 0%)[18]	• History of psychiatric illness (90% vs 47%)[13]
• Autonomic change (38% vs 5%)[18]	• Female gender (65% vs 40%)[13]
• Catatonic excitement (50% vs 11%)[18]	• Presenting neuroleptic use (52% vs 16%)[13]
• Grasp reflex (26% vs 0%)[18]	
• Pneumonia (57% vs 0%)[18]	
• Known history of a neurological condition (68% *vs* 37%)[13]	
• History of seizures (42% vs 14%[13]; 48% vs 0%[18])	

TABLE 4. Medical Causes by Category

Miscellany	59 (19.5%)
Inflammation of the CNS	87 (28.8%)
Neural injury	58 (19.2%)
Developmental disorder	6 (2%)
Structural CNS pathology	29 (9.6%)
Epilepsy	28 (9.3%)
Toxin or medication	35 (11.6%)
Total	302

Endocrine disorders

Metabolic disturbances (including hypovitaminoses)

Electrocution

Epidemiology (Oldham 2018)

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Infectious meningoencephalitis: HSV, HIV, SSPE, COVID-19, malaria, prion, etc.

Limbic encephalitis: autoimmune encephalitis targeting limbic regions, associated with regulation of emotion and motion (**NMDAR**, LGI1, GAD65, CASPR2, GABA)

Lupus encephalitis and *MS*

Epidemiology (Oldham 2018)

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Traumatic brain injury

Hypoxemic-ischemic and *post-hypoxic leukoencephalopathy*

Neurodegenerative disease

PRES

Epidemiology (Oldham 2018, Rogers et al. 2024)

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Typically non-convulsive status epilepticus originating from the medial temporal lobe.

May present in an ictal, post-ictal, or interictal pattern.

Epidemiology (Oldham 2018)

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DA⊗	Sedatives	Others	Abuse
APs	GABA w/d	Disulfiram	Stimulants
Antiemetics	Z-drug w/d	Antibiotics	K2/MJ
Clozapine withdrawal	Baclofen	Immunomod (tacrolimus)	PCP
HXY, BSP	Gabapentin	CO	Inhalants

Prototypical Presentations (Rogers et al. 2023)

Type
Psycho-motor activity
Symptoms
DDx and subtypes
Notes

Related Syndromes and Subtypes

(Rogers et al. 2023, Karmacharya et al. 2008, Fusunyan et al. 2022)

Periodic catatonia

- Onset typically in adolescence, but described in older adults as well
- Historically considered an "idiopathic" catatonia, strong genetic basis
- Longitudinal course of acute, weeks-long episodes followed by prolonged remission
- Episodes characterized by rapid switches between hypo- and hyperactive
- Lithium may be treatment of choice for maintenance

Delirious mania

- Acute mania with delirious features, typically accompanied by purposeless motor activity typical of hyperactive catatonia
- Other canonical features include *denuditiveness*, *inappropriate toileting*, and *water obsession*
- Tempo is often more rapid than typical mania
- High-dose lorazepam and ECT treatment of choice, followed by low-potency neuroleptics (clozapine, quetiapine preferred)

Akinetic mutism

- Characterized by immobility, mutism, paratonia (indicative of frontal release)
- Thought to represent profound motivational deficit (on spectrum from apathy to abulia to AM)
- Lacks affective and hyperkinetic features of catatonia
- Typically follows neurological injury (particularly to ACC) but also inflammatory states
- Does not respond to lorazepam, may improve with amantadine or stimulants

Complications (Clinebell et al. 2014, Park et al. 2017)

Venous thromboembolism

Pressure ulcers

Rhabdomyolysis

Muscle contractures

Nutritional deficiencies

50% mortality → **10%** with ECT/BZDs for MC/NMS

Evaluation: History

PRODROMAL FEATURES

TEMPO OF ONSET

AFFECTIVE SYMPTOMS

NEUROLOGIC SYMPTOMS

Evaluation: Data

(Hosseini et al. 2023, Blackman et al. 2023, Ross et al. 2021)

Labs

- Definitely:
  - CMP and CBC
  - TSH
  - CPK
  - Tox
  - B12/folate
  - Serum iron
- Consider:
  - AM cortisol
  - Heavy metals
  - Vitamin C, zinc

EEG

- Useful to distinguish psychiatric from GMC/N catatonia and to rule out NCSE
- *Any abnormality: SN 0.76, SP 0.67 for GMC/N*

MRI

- If first lifetime episode OR concerning history
- *5.9% findings relevant in FEP, and motor findings such as catatonia enhance cost-effectiveness*

LP

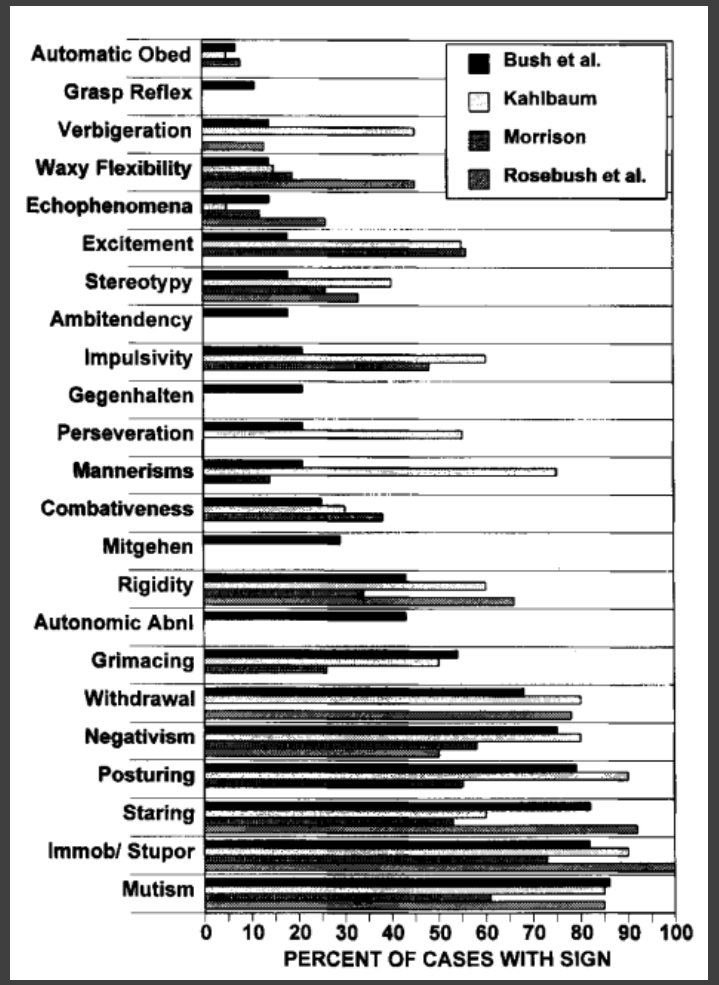
- If concerns for meningitis or encephalitis
- *May be cost effective to screen for autoimmune encephalitis in any FEP, particularly with motor features*

Evaluation: Exam

(Bush et al. 1996)

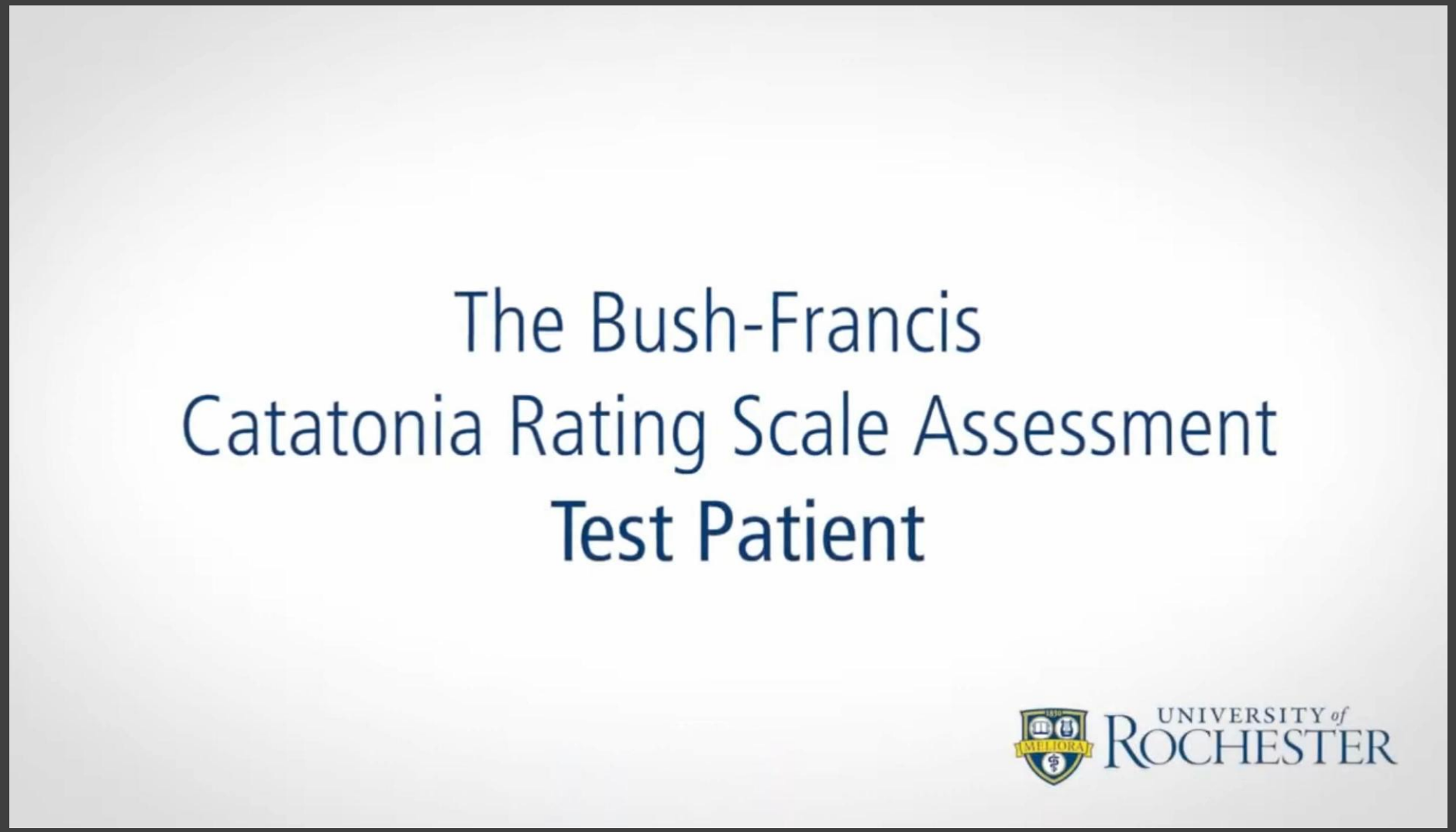
Screen Symptoms	Scoring Symptoms
Excitement	Impulsivity
Immobility	Automatic obedience
Mutism	*Mitgehen*
Staring	*Gegenhalten*
Posturing/catalepsy	Ambitendency
Grimacing	Grasp reflex
Echophenomena	Perseveration
Stereotypy	Combativeness
Mannerisms	Autonomic disturbance
Verbigeration	
Rigidity	
Negativism	
Waxy flexibility	
Withdrawal	

- Each item scored 0-3 (some 0 or 3)
- **Catatonia present** if *2+* of first 14 present (typically between *3-10+* **signs**)
- High interrater reliability (R=0.93-0.95)



Evaluation: Exam

1. Observe the patient from the door. Maintain safety at all times.
2. Tone exam, rotating arm (fulcrum wrist, fulcrum elbow)—fast and slow
3. Ask to hold arms up but maintain them in the same position, and then push upward
4. Position arms in an odd position, and ask them to let them fall
5. Give conflicting instructions (put hand out but tell them "do not shake my hand")
6. Rub hand along palm to fingers distally
7. Provide a movement to copy (e.g. scratching head)
8. Odd command: "I have a pen in my pocket. Stick your tongue out so I can write my name on it."
9. As much a cognitive and elemental neurological exam as patient will tolerate


The Bush-Francis
Catatonia Rating Scale Assessment
Test Patient
UNIVERSITY of ROCHESTER

Evaluation: Diagnostic Challenge

Complete BFCRS or other standardized diagnostic exam (e.g. Northoff)

Administer 1-**2** mg IV lorazepam (consider SE risk: elderly, resp compromise)

Repeat BFCRS in 30-120 minutes (response may range widely)

Continue **lorazepam 1-2 mg q6-8h** if the patient improves, or if there continues to be a very high suspicion of catatonia

Treatment: Lorazepam (Rogers et al. 2023, Ungvari et al. 1999)

- Response rate: **66-100**%, typically within 10 days
- Preferred due to rapid onset of action (especially IV), longer effective duration, ease of administration (IV, IM, SL, PO), preferential binding to $GABA_A$ receptor
- Starting dose: 6-8 mg/day, increase as necessary to 24-30 mg TDD
- Standing for 24-48 hours after adequate response (hold for respiratory depression), then transition to PO and taper slowly
- If **minimal response** or **malignant symptoms** emerge, *move to ECT*
- *Limited benefit in chronic catatonia (typically associated with schizophrenia)*

Treatment: ECT (Rogers et al. 2023, Mann et al. 1990, Beach et al. 2017)

- Response rate: **59-100%**
  - Potentially higher in malignant catatonia
  - May response within 2-3 treatments, although 20+ occasionally required
- Bilateral, three times weekly is most effective
- Drawbacks
  - Limited availability
  - Complicated consent process (substituted decision-making in emergencies)
- Indications
  - Malignant catatonia
  - Limited response to lorazepam after 2-5 days
  - Very poor self-care
  - Underlying MDD or BPAD

Treatment: NMDA-receptor antagonists

- Small case series level of evidence, reviewed by Beach et al. (2017)
- Thought to inhibit NMDA receptors (inhibitory for DA signalling), which may be involved in catatonia
- Amantadine 100 mg daily to BID, increased to 600 mg TDD over 3-4 days
- Memantine 5-10 mg BID, increased to 10 mg BID over 3-4 days
- A small systematic review of case reports documenting success without significant adverse events with ketamine treatment (Caliman-Fontes et al. 2024)
- Very limited evidence for others, including ketamine and dextromethorphan

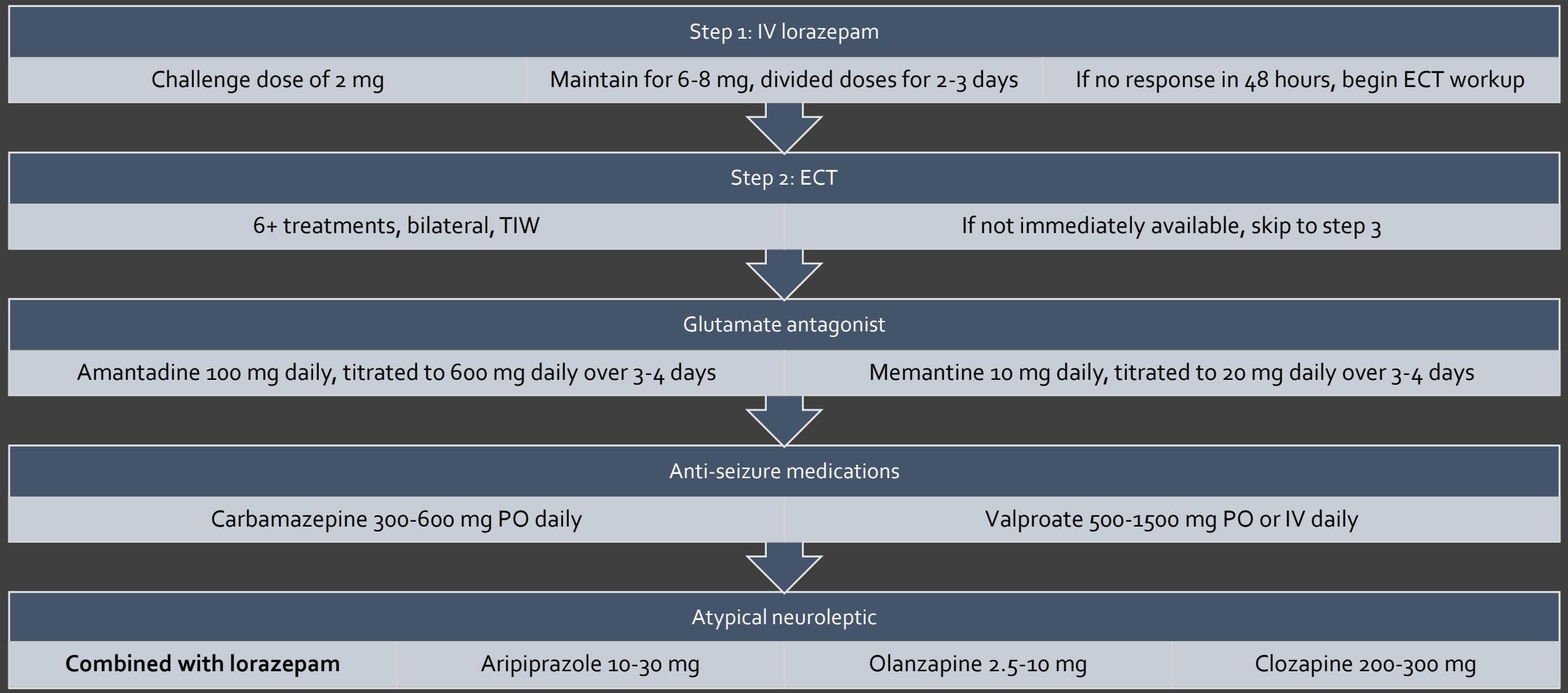
Treatment: Others (Beach et al. 2017, Almeida 2021, Sienaert et al. 2014)

- **Overall, based on case report level of evidence**
- **Zolpidem**: Success reported on up to 10 mg QID for patients in whom lorazepam and ECT has failed
- **Dopamine agonists**
  - May be useful if likely to be neuroleptic induced, but *may worsen underlying psychosis*
  - Options include *bromocriptine*, *dantrolene*, *Sinemet*, *stimulants*

Treatment: Others (Beach et al. 2017, Almeida 2021, Sienaert et al. 2014)

- **Overall, based on case report level of evidence**
- **Antiseizure medications**: May potentiate GABA signaling and/or treat underlying illness
- **Atypical neuroleptics** may be useful for refractory cases, particularly if underlying diagnosis is schizophrenia
- **rTMS** targeting DLPFC and **TDCS** have been tried with anecdotal success (particularly if BZDs intolerable, ECT unavailable)

Treatment algorithm (Beach et al. 2017)



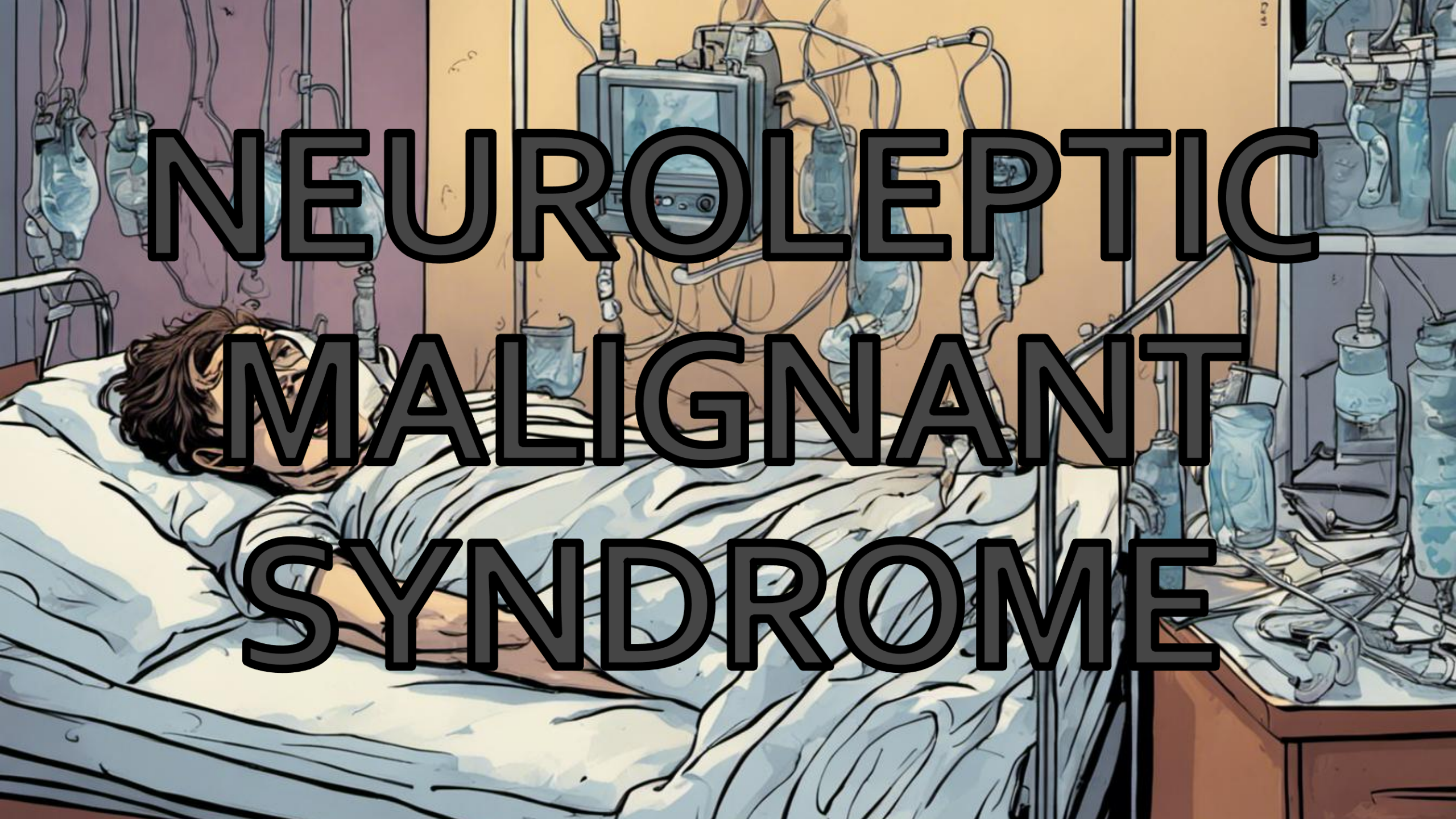
Treatment: General Management

IV fluids and nutrition if necessary; monitor UOP and labs if possible

Prophylactic anticoagulation for most, if not all (Padua score can be useful)

Frequent turning, barrier protection, skin exams

Discontinue high-risk agents (particularly neuroleptics), treat underlying cause


NEUROLEPTIC
MALIGNANT
SYNDROME

Case 2

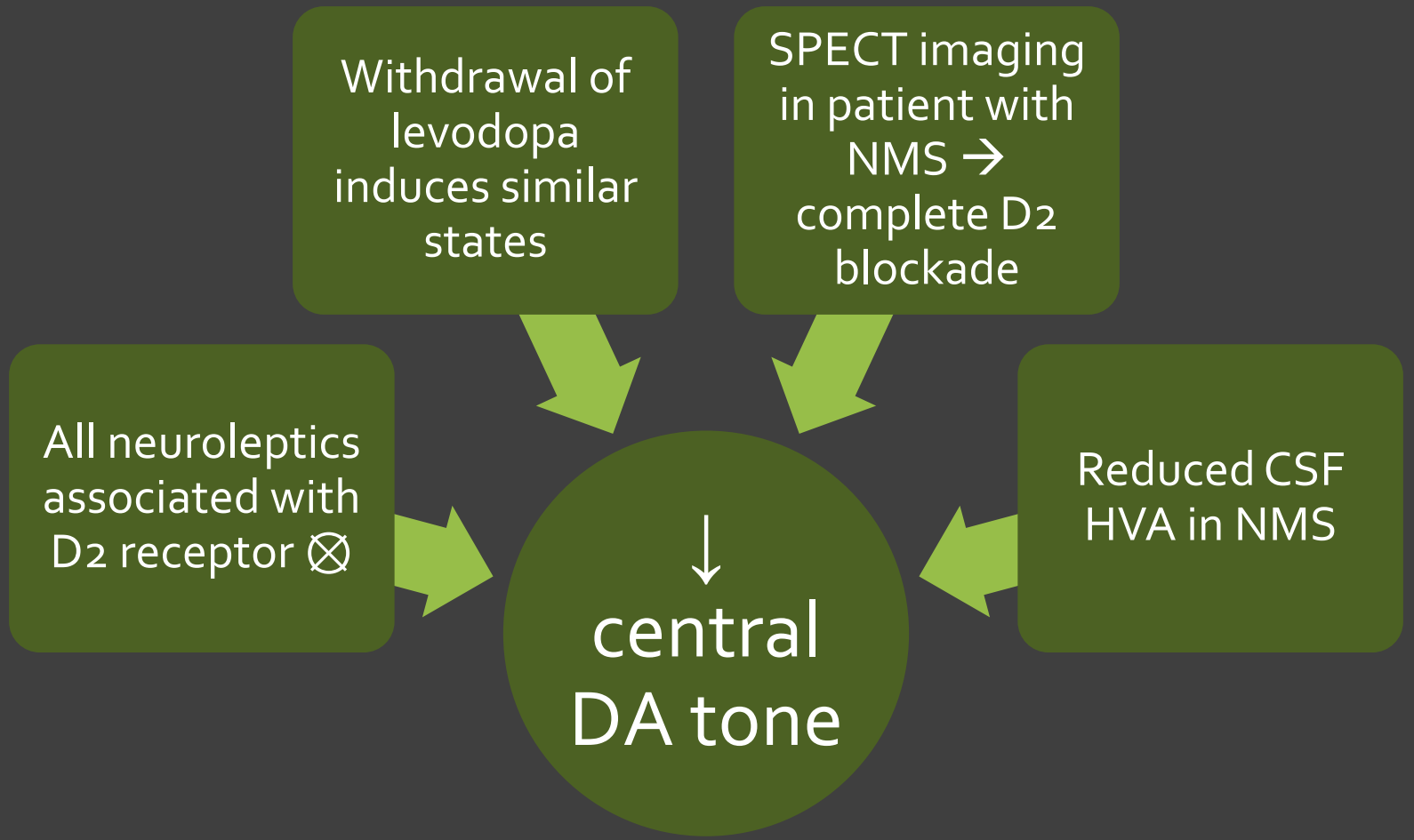
- AB was a 56-year-old woman with bipolar disorder who was admitted to the hospital after arguing with her husband.
- She was agitated in the ED, required restraint, and received haloperidol 5 mg IM atop home medications perphenazine, lithium, sertraline.
- Soon after the administration, she was noted to be **withdrawn**, **hypokinetic**, **mute** and **rigid**.
- VS were notable for tachycardia, hypothermia, and work-up demonstrated elevated CPK, generalized slowing on EEG.
- Home neuroleptics were held and she was treated with lorazepam, ultimately achieving a good response.

Definition and Epidemiology

(Schneider et al. 2020, Caroff and Mann 1988)

- Severe, life-threatening motor disturbance with altered mentation associated with start of antipsychotic or removal of dopamine agonist (but not always—**96% within 30 days**)
- **0.16%** of patients treated with neuroleptics
- Generally considered to be a severe form of catatonia with a specific etiology
- Risk factors
  - High-potency neuroleptic use > low-potency/atypical
  - Multiple neuroleptics
  - Long-acting injectable formulations
  - History of catatonia/NMS
  - Basal ganglia disorders
  - State specific: withdrawal, dehydration, low-serum iron

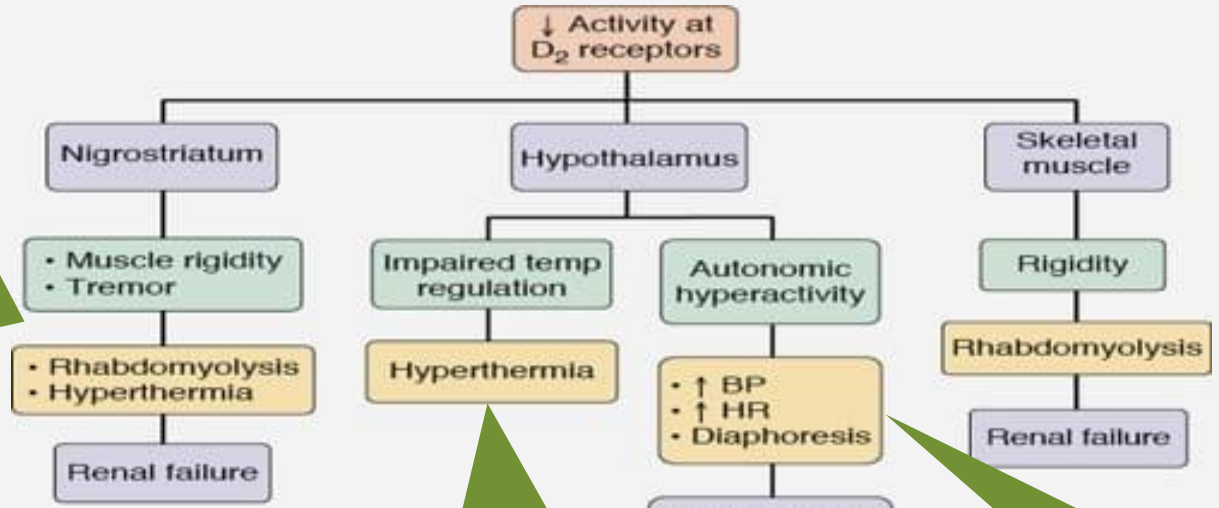
Dopamine Hypothesis



Clinical Characteristics (Mann et al. 2003)

7.6% mortality even with treatment

97% Generalized, severe (often unable to be moved)



98%

60-90%

97% encephalopathic

Very likely to meet criteria for catatonia

Atypical NMS (Troller et al. 2009, Murri et al. 2015)

- Majority of cases of NMS produced by atypical antipsychotics present with "typical" NMS signs and symptoms
- However…
  - Clozapine: may be less likely to cause rigidity—but CK may still be elevated!
  - Aripiprazole: may be less likely to cause delirium and hyperthermia
- Many cases of so-called "atypical NMS" may represent non-malignant catatonia induced by antipsychotics
- Mortality of atypical NMS is 5.5%, close to typical findings

ICD Diagnostic Criteria (Gurrera et al. 2011)

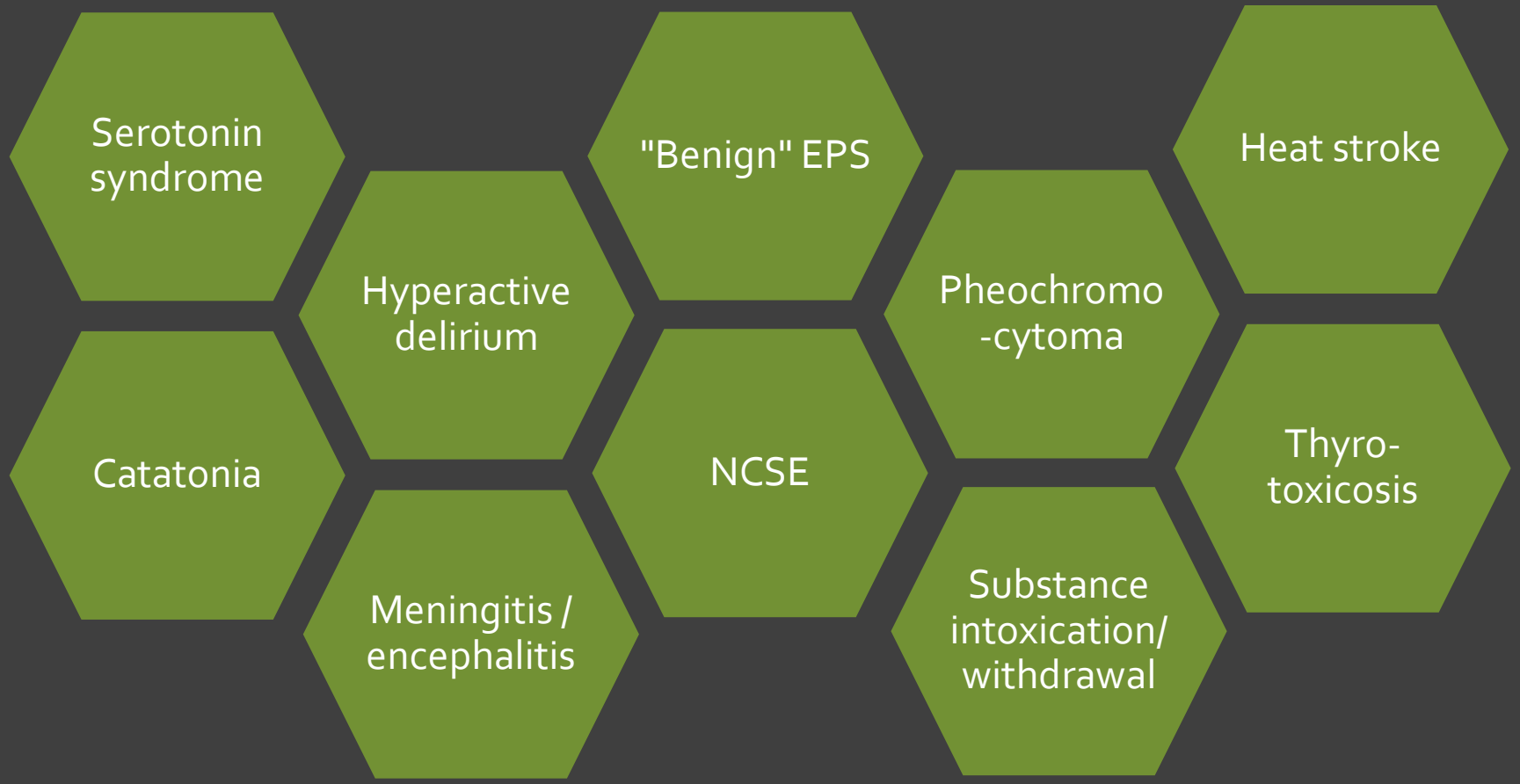
Criterion	Points
Exposure to dopamine antagonist or agonist withdrawal in last 72 hours	20
Hyperthermia (>100.4˚F on 2 occasions, oral)	18
Rigidity	17
Altered mental status	13
Elevated creatine phosphokinase (>4x ULN)	10
Sympathetic nervous system lability, defined by 2+ • ↑BP (>25% above baseline) • ↓↑ BP (change of 20 mmHg DBP or 25 mmHg SBP in 24 hours) • Diaphoresis • Urinary incontinence	10
Tachycardia (>25% of baseline) and tachypnea (>50% above baseline)	5
Negative workup for infectious, toxic, metabolic, and neurologic causes	7

Cut-off of 74:
- 70% sensitive
- 91% specific

(against expert opinion)

Moderate to severe:
- Level of rigidity +
- HR>100-120
- T>38-40˚C

Differential Diagnosis



Management (Caroff 1988)

- Discontinue all dopamine antagonists/reinstitute dopamine agonists—syndrome typically self-limited (9.6±9.1 days)
- Remove anticholinergic medications (to limit hyperthermia)
- Supportive management and benzodiazepines for mild cases
- High-dose benzodiazepines and ECT for severe (response typically within days)—most definitive treatment
- Could consider dopamine agonists for moderate cases

Management (Sakkas et al. 1991)

- Old review of dopamine agonist found dramatic benefits in survival and time response—however, based on case reports only
- Included amantadine, bromocriptine, levodopa
- **All dopaminergic medications carry risk of worsening underlying psychosis**

Management (Rogers 2023)

- Rechallenge? Recurrence is 30-50%!
- Wait **2 weeks** for resolution, then **gradually** titrate an **atypical** antipsychotic (ideally *clozapine*) in a **hospital**.


SEROTONIN
SYNDROME

Case 3

- A 69-year-old woman with recurrent episodic MDD presented for follow-up reporting partial response to paroxetine 40 mg/day.
- The dose was increased to 60 mg, and buspirone 5 mg TID and trazodone 100 mg nightly were added two weeks later.
- Within 24 hours, she presented to the ED confused, diaphoretic, febrile, hyperreflexic, and mildly rigid.
- All medications discontinued and her condition gradually improved over 2 days.

Definition and Epidemiology

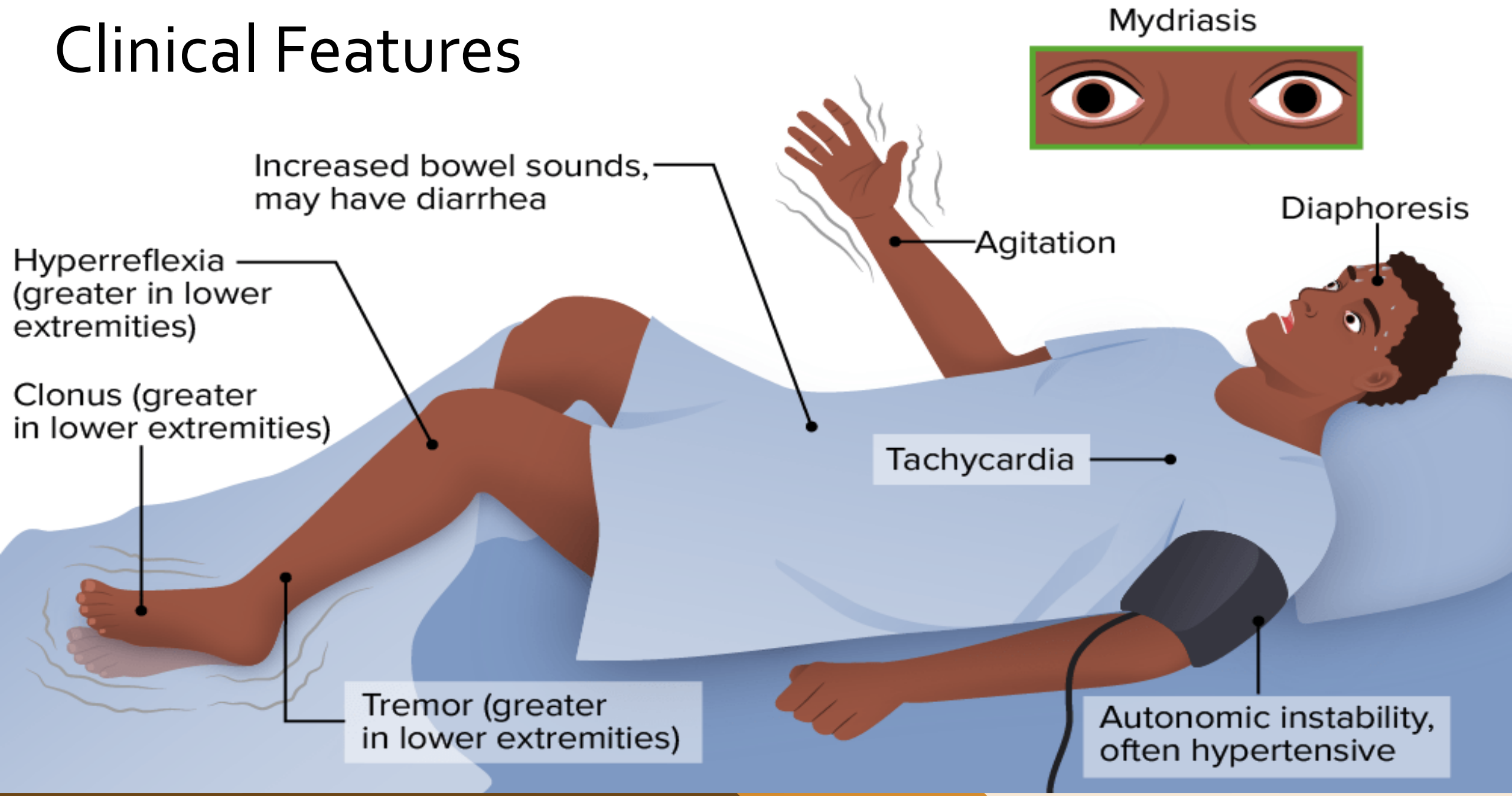
(Boyer and Shannon 2005, Nguyen et al. 2017)

- Enhanced central serotonergic tone (particularly 5-HT_{1A}), likely associated with increases in dopaminergic and noradrenergic tone as well.
- Classically associated with MAOI + another serotonergic agent; now much more common in overdose of use of 3+ agents.
- 14-16% of SSRI overdoses, annual incidence (among psychiatric VA patients) of 0.07-0.09%
- Typically associated with psychotropics, but many medications are potentially serotonergic

Serotonergic Agents

Agonism	Decreased metabolism	Increased release	Decreased reuptake
• Buspirone • Lithium • LSD • L-tryptophan • Trazodone	• Irreversible MAOIs (phenelzine, selegiline, tranylcypromine) • Reversible MAOIs (linezolid)	• Amphetamines and MDMA • Cocaine • Fenfluramine • Ergot alkaloids and triptans • Mirtazapine	• SRIs and TCAs • Meperidine • Tramadol • SJW

Clinical Features



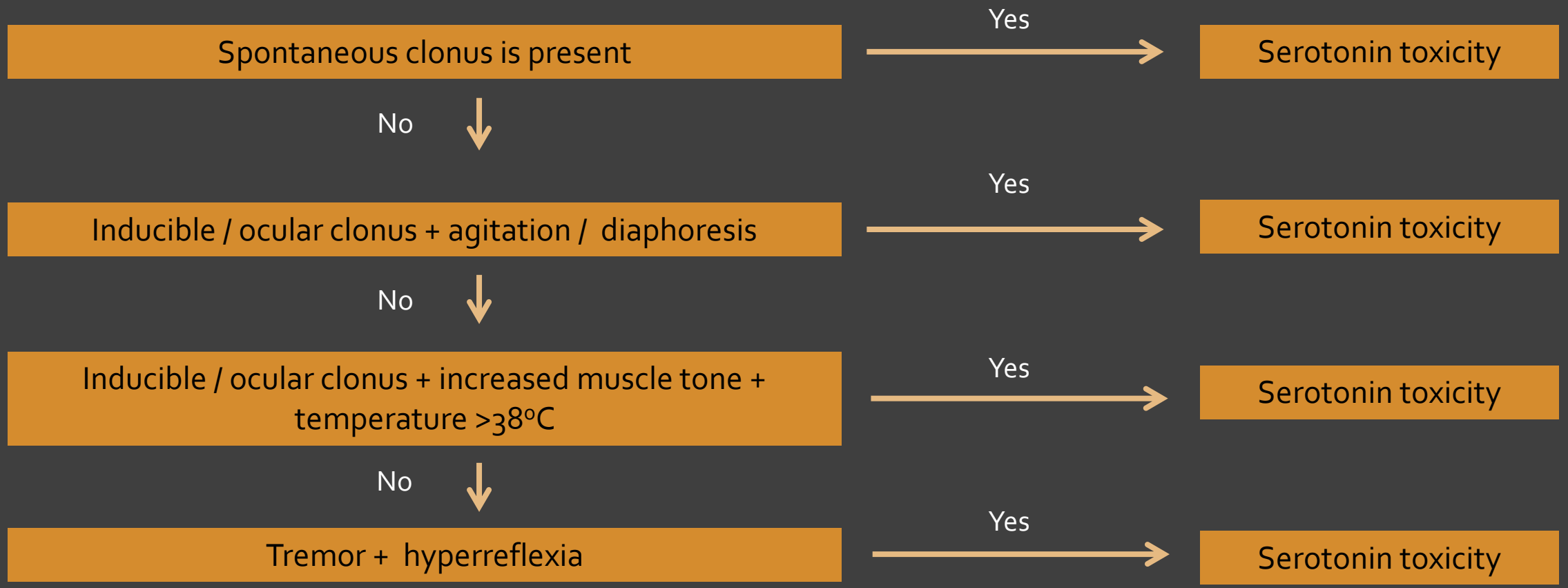
Clinical Features (Boyer et al. 2005, Scotton et al. 2019)

- No specific test: blood levels irrelevant
- WBCs ↑, CPK ↑, LFTs ↑, HCO_3^- ↓
- Severe cases can evolve to include:
  - **Disseminated intravascular coagulation (5%, but high risk of death: 67%)**
  - **Seizures (1%, but high risk of death at 39%)**
  - **Rhabdomyolysis (25%)**
  - **Myoglobinuric renal failure (5%)**
  - **Aspiration** and **adult respiratory distress syndrome**

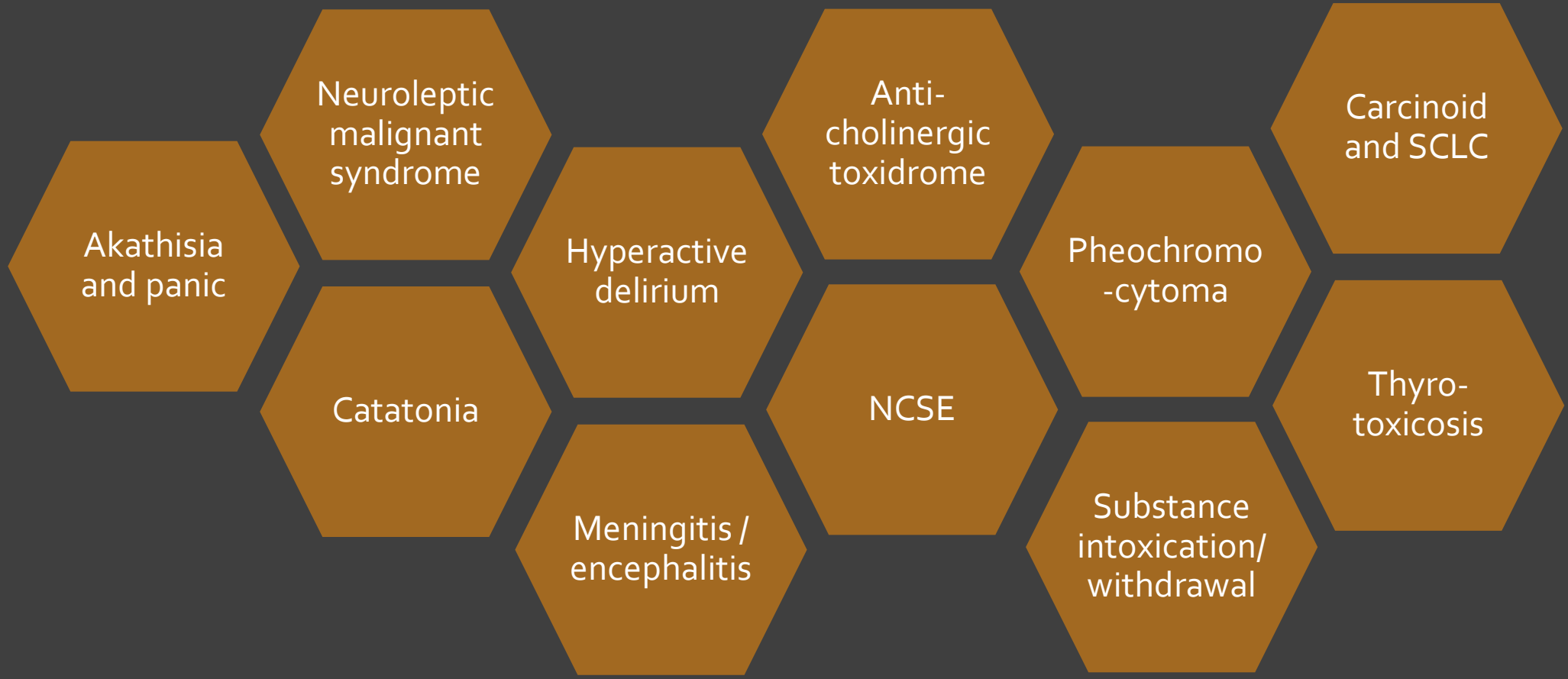
Consider serotonin syndrome in…
All overdoses
All patients on >4 psychotropics
Patients with critical illness, renal dysfunction, liver dysfunction + psychotropics
Catatonic patients, particularly hyperactive
Delirious patients, particularly the twitchy ones

Hunter Criteria (Dunkley et al. 2003)

In the presence of a serotonergic agent, serotonin toxicity is diagnosed:



Differential Diagnosis



Management (Boyer 2005, Scotton et al. 2019)

- Discontinue the offending agent
- Often self-limited, requiring support only (including hydration and cooling, management of VS as appropriate)
- ASMs if seizures arise
- Avoid physical restraint if possible. Avoid neuroleptics and anticholinergics.

Benzodiazepines	Serotonin antagonists
Useful for agitation and catatonic features Useful for hyperadrenergic state	Helpful in some case reports **Cyproheptadine** 12 mg initial → 2 mg q2h until improvement → 8 mg q6h maintained then tapered

Suggested Reading

BAP Guidelines

Evidence-based consensus guidelines for the management of catatonia: Recommendations from the British Association for Psychopharmacology

Jonathan P Rogers[1,2], Mark A Oldham[3], Gregory Fricchione[4,5], Georg Northoff[6], Jo Ellen Wilson[7,8], Stephan C Mann[9], Andrew Francis[10], Angelika Wieck[11,12], Lee Elizabeth Wachtel[13,14], Glyn Lewis[1], Sandeep Grover[15], Dusan Hirjak[16], Niraj Ahuja[17], Michael S Zandi[18,19], Allan H Young[20,2], Kevin Fone[21], Simon Andrews[22], David Kessler[23], Tabish Saifee[19], Siobhan Gee[24,25], David S Baldwin[26] and Anthony S David[27]

Psychopharm

Journal of Psychopharmacology
2023, Vol. 37(4) 327–369

DOI: 10.1177/02698811231158232
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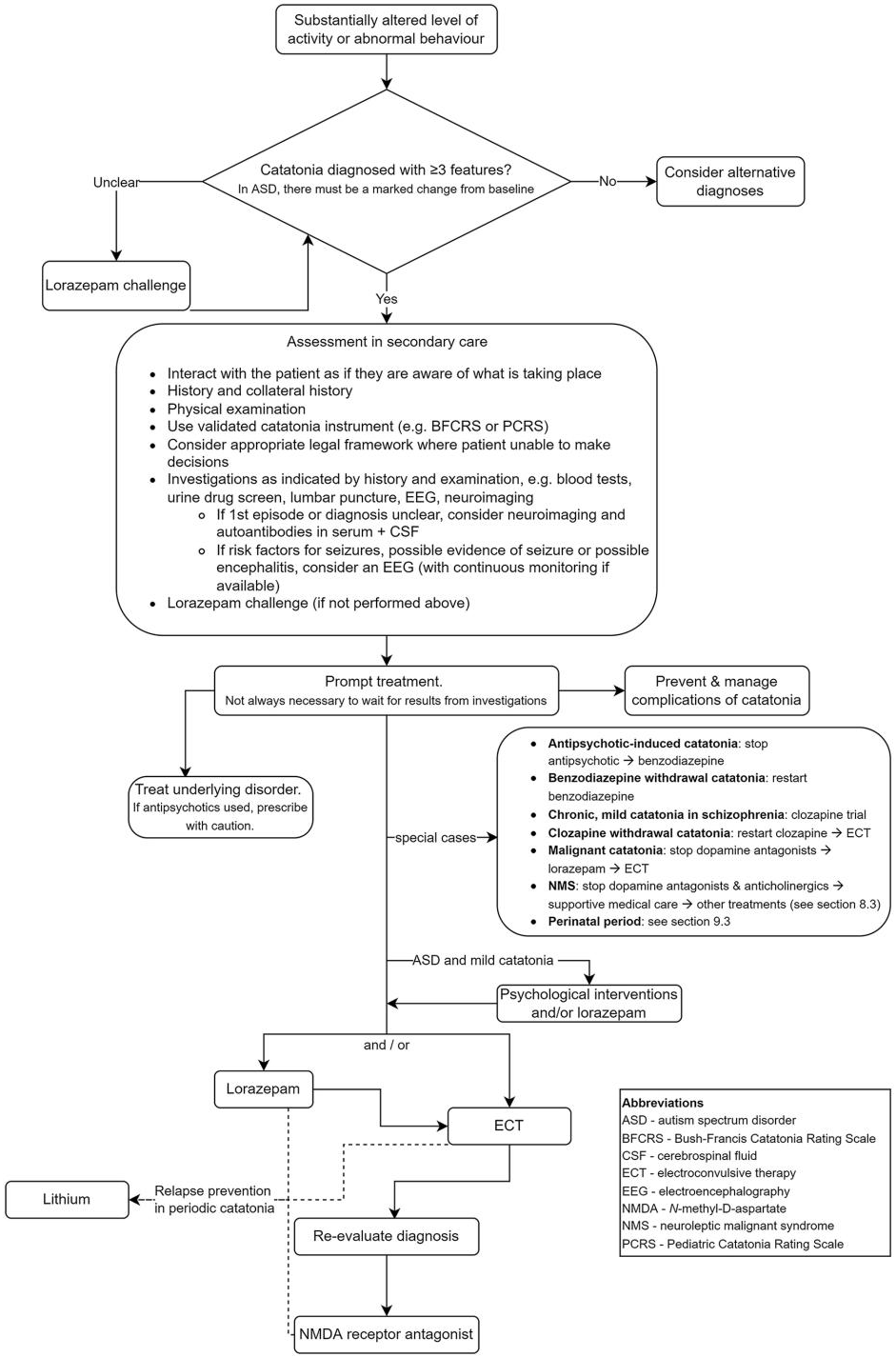

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From *Neuroscience, 3rd Ed. Ch 17: Modulation of Movement by the Basal Ganglia*