ACLP How To Guide: Medication Syndromes

How to Approach Medication-Related Psychiatric Emergencies: *Serotonin Syndrome, Neuroleptic Malignant Syndrome (NMS), Anticholinergic Toxicity and Posterior Reversible Encephalopathy Syndrome (PRES)*

Learning Objectives

1) Describe the basic approach to evaluating the patient with possible medication toxicity
2) List the features of serotonin syndrome, neuroleptic malignant syndrome and anticholinergic toxicity and describe the approach to management
3) Differentiate the toxidromes based on clinical features and course
4) Explain the presumed mechanism of PRES and list which medications may contribute

Step 1: Obtain the history; this should include knowing the risk factors and medications associated with these toxicity syndromes

- Timeline of symptom onset
- Assessment of baseline risk factors, making sure to consider these toxicity syndromes in patients on multiple psychotropics with unexplained mental status changes, abnormal movements, catatonia and/or autonomic instability
- Precipitating events or factors (including any ingestions [intentional or otherwise])
    - All recent medications (prescribed, OTC/alternative, illicit), recent dose changes and adherence
    - Pay particular attention to serotonergic or anticholinergic agents, dopamine blockers, and immunosuppressants
- Any recent changes in medical condition (such as worsening renal or liver function) that might impact drug metabolism or elimination
- Any drug-drug interactions
    - Databases: Up-to-Date, Micromedex, PubMed
    - Indiana University School of Medicine: http://medicine.iupui.edu/clinpharm/ddis/

Step 2: Conduct a physical exam

- Consider specific signs and symptoms that differentiate the various toxidromes as described in greater detail below.
- Check vitals (HR, blood pressure [BP, temperature, RR, oxygen saturation])
- Check bowel sounds, skin/mucosa, tone, reflexes, muscles, pupils
- Conduct mental status/cognitive examination
- These syndromes can often present with a spectrum of findings, ranging from mild to severe

Step 3: Order Tests that will help you investigate potential causes and determine the most likely diagnosis

- Labs
    - Fingerstick glucose, to rule out hypoglycemia
    - Acetaminophen, salicylate and blood alcohol levels
    - Serum creatinine kinase (CK) level- to rule out rhabdomyolysis
    - BMP, CBC, LFTs
    - Urine drug screen, pregnancy test
- EKG- to rule out cardiac effects (such as QT prolongation); may need telemetry
- Head CT- to rule out acute bleed/infarct

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Step 4: Develop Your Differential Diagnosis, familiarizing yourself with the signs and symptoms of the major toxidromes involving psychotropic medications

- Table 1 summarizes the clinical presentations of the major toxidromes
- **Serotonin Syndrome**
  - Overview: Life threatening adverse drug reaction from therapeutic use, overdose, or drug interaction involving serotonergic medications
  - Symptoms/Exam Findings
    - Spectrum of clinical findings and intensity; mild to life threatening
    - Typical clinical triad:
      - Cognitive/behavioral (delirium, agitation, catatonia, lethargy, coma)
      - Autonomic instability (hyperthermia, tachycardia, diaphoresis, diarrhea/increased bowel sounds, mydriasis)
      - Neuromuscular (akathisia, tremor, hyperreflexia, spontaneous or inducible clonus, ocular clonus, myoclonus, rigidity, seizures)
  - Labs/Tests
    - Nonspecific laboratory findings may include ↑WBC, CK levels, and transaminases and ↓serum bicarbonate.
    - Severe cases can include disseminated intravascular coagulation (DIC), rhabdomyolysis, metabolic acidosis, renal failure.
  - Risk Factors
    - Administration of 2 or more serotonergic medications (partial list)
      - Antidepressants (SSRIs, SNRIs, trazodone, mirtazapine, TCAs, MAOIs)
      - Analgesics (meperidine, fentanyl, tramadol, pentazocine)
      - Antiemetics (ondansetron, granisetron, metoclopramide)
      - Antimigraines (triptans)
      - Antibiotics (linezolid)
      - Over the counter (dextromethorphan)
      - Drugs of abuse (MDMA/Ecstasy, LSD, amphetamines, cocaine)
      - Dietary supplements/Herbals (tryptophan, St. John's wort)
      - Other: Lithium, fenfluramine, reserpine, buspirone
    - Overdose on a serotonergic medication
    - Pharmacodynamic or pharmacokinetic interactions
    - Conditions with similar presentations
      - SSRI discontinuation syndrome
      - Catecholamine excess
      - Anticholinergic toxidrome
      - Alcohol and substance withdrawal
      - Infections
      - Toxic-metabolic delirium
      - Extrapyramidal side-effects
      - NMS
      - Pheochromocytoma
      - Carcinoid tumor
  - Diagnosis
    - Clinical, based on the history and exam findings

        - *Hunter Serotonin Toxicity Criteria (may miss mild cases)*: Serotonergic agent in past 5 weeks + ANY of the following symptoms: 1) tremor and hyperreflexia; 2) spontaneous clonus; 3) Muscle rigidity, temperature >38C, and either ocular or inducible clonus; 4) ocular clonus and agitation or diaphoresis; 5) inducible clonus and agitation or diaphoresis
        - *Sternbach Criteria (Non-specific and overlap with other toxidromes)*: 1) Recent addition or increase in known serotonergic agent; 2) Absence of other possible etiologies; 3) No recent addition or increase of a neuroleptic agent; 4) ≥3 of the following symptoms: mental status change, agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, incoordination, fever
    - Management Strategies
        - Early recognition of the syndrome
        - Removal of the precipitating drug
        - Supportive care: hydration, cooling, management of autonomic instability
        - Benzodiazepines: may blunt hyperadrenergic component of the syndrome, help with catatonic features, act as muscle relaxants and control agitation
        - Cyproheptadine: first-generation antihistamine with serotonin antagonist properties (5-HT1A and 5-HT2 receptors) and efficacy in case reports and series.
            - Initial dose: 12mg PO followed by 2mg q2 prn.
            - Maintenance dose; 8mg q6 and total daily dose is 12-32mg over 24 hours.
            - Chlorpromazine: effective in some cases (5-HT2 and 5-HT1A receptor antagonist properties). Can be administered IM but use with caution due to side effects
        - Clinical course
            - Rapid onset (minutes) and resolution usually within 24 hours of stopping the medication unless long half-life or impaired metabolism
            - Limited data on rechallenging, though successful cases reported.
- **Neuroleptic Malignant Syndrome**
    - Overview: Idiosyncratic, life-threatening complication of dopamine blocking medications. Many consider NMS to be a subtype of malignant catatonia but not all catatonia resulting from antipsychotic use has malignant features or represents NMS
    - Symptoms/Exam Findings
        - Classic symptoms include *fever, muscle rigidity, autonomic instability, and mental status changes*.
        - Rigidity is often described as “lead pipe rigidity.”
        - Autonomic dysfunction: tachycardia, diaphoresis, labile blood pressure.
        - NMS secondary to atypical antipsychotics (aripiprazole, clozapine) may be milder
        - Mental status can range from delirium to catatonia.
    - Labs/Tests
        - Rhabdomyolysis is indicated by ↑ CPK
        - Other findings include leukocytosis, low serum iron and metabolic acidosis
        - EEG findings are usually consistent with delirium
        - CSF and neuroimaging are typically normal
    - Risk factors
        - CNS dopamine abnormalities/basal ganglia disorders

        - Dehydration
        - High potency dopamine blockers
            - Antipsychotics
            - Dopamine antagonist anti-emetics (metoclopramide, prochlorperazine, promethazine)
            - Abrupt withdrawal of dopamine agonists or baclofen
            - Iron deficiency
            - IM/IV administration
            - Faster titration
            - Higher dose
            - Substance use disorders (especially GABA withdrawal)
        - Conditions with similar presentation
        - Infectious: meningitis/encephalitis; sepsis; abscess
        - Neuro/psych: idiopathic malignant catatonia; agitated delirium; delirious mania; non-convulsive status; midbrain lesion; "benign" EPS
        - Toxic: sedative-hypnotic, alcohol, baclofen withdrawal; cocaine, ecstasy, PCP; serotonin syndrome; malignant hyperthermia
        - Endocrine: thyrotoxicosis; pheochromocytoma
        - Environmental: heatstroke
    - Diagnosis
        - NMS is a clinical diagnosis.
        - DSM-5 offers a description of diagnostic features that includes:
            - Exposure to dopamine antagonist within 72 hours
            - Hyperthermia (>100.4F or >38.0C on at least 2 occasions + profuse diaphoresis)
            - Generalized rigidity ("lead pipe")
            - CK elevated at least 4 times normal
            - Change in mental status
            - Autonomic activation and instability
            - Tachypnea and respiratory distress
            - Work-up has excluded other etiologies
                - Possible lab abnormalities: ↑WBC, metabolic acidosis, hypoxia, ↓serum iron, ↑serum muscle enzymes and catecholamines
                - CSF and neuroimaging generally normal
                - EEG: generalized slowing
    - Management Strategies
        - Supportive: early recognition, cessation of neuroleptics, re-introduction of dopamine agonists if removed, hydration, temperature reduction
        - **Benzodiazepines** may be helpful with agitation, rigidity or catatonia. IV lorazepam is preferred; high doses (18-24mg daily) often required
        - **Dopamine agonists** may reverse parkinsonism, reduce time to recovery but can worsen psychosis. Bromocriptine 2.5mg BID-TID, titrated to 45mg total daily dose or Amantadine 200-400mg/day in divided doses.
        - **Dantrolene** may be useful in extreme temperature elevations and rigidity; can dose 1-2.5mg/kg IV, then 1mg/kg q6 hours if fever/rigidity resolve. Total daily dosing 1-10mg/kg/day in divided doses.

        - **ECT** if unresponsive to pharmacologic treatment in the first 24-48 hours, prominent features of catatonia or severe rigidity, and/or develops psychosis; 6-10 treatments are typically needed
    - Clinical Course
        - Develops quickly over hours to days; often insidious to start
        - Mental status changes/neurological signs precede systemic signs in >80%
        - Most cases occur within 30 days of medication exposure, although later onset can be seen after a dose increase or a drug interaction.
        - Self-limited in most cases once the medication is discontinued, with a mean recovery time of 7-10 days; can be prolonged with depot antipsychotics.
            - Mortality rates are decreasing and appear to be about 6%.
            - Complications: renal failure, respiratory failure, cardiac morbidity, cognitive
            - Recurrence rate with antipsychotic rechallenge may be as high as 30-50%. Favor lower potency or atypical agents and close monitoring if you decide to rechallenge.
- **Anticholinergic Toxicity**
    - Overview: Toxicity syndrome secondary to medications with anticholinergic effects.
    - Symptoms/Exam Findings
        - Flushed skin
        - Anhidrosis/dry skin
        - Hyperthermia
        - Mydriasis
        - Delirium (often with visual hallucinations, picking, agitation)
        - Urinary retention
        - Tachycardia, elevated blood pressure
        - Decreased or absent bowel sounds
        - More severe cases can be associated with seizures, cardiac conduction abnormalities, circulatory collapse and coma
    - Labs/Tests
        - Tests are not a key part of the workup for anticholinergic toxicity
        - EEG findings are usually consistent with delirium
        - Occasionally, blood levels of specific anticholinergic medications may be useful.
    - Risk Factors (partial medication list)
        - Antihistamines: H1 receptor antagonists (diphenhydramine, doxylamine, hydroxyzine, meclizine)
        - Antiparkinsonian: Benztropine, trihexyphenidyl
        - Antimuscarinic: oxybutynin, atropine, hyoscyamine, glycopyrrolate, scopolamine, ipratropium, tiotropium, ophthalmic drops
        - Gastrointestinal: Antiemetics (e.g., promethazine, scopolamine)
        - Muscle relaxant: Cyclobenzaprine, tizanidine
        - Psychotropic: antipsychotics (low potency 1st gen, olanzapine, clozapine), TCAs
    - Conditions with Similar Presentation
        - Broad differential that should include other toxicity syndromes (serotonin toxicity, NMS, sympathomimetic overdose), malignant hyperthermia, infectious, metabolic, and neurological etiologies.
    - Management Strategies

        - Start with stabilization of airway, breathing and circulation
        - Sodium bicarbonate for the treatment of prolonged QRS or for arrhythmias
        - Benzodiazepines should be used to treat agitation and seizures
        - Cooling mechanisms, and anti-pyretics should be used for hyperthermia
        - GI decontamination with activated charcoal may be used if appropriate
        - Supportive care alone is adequate for most patients with anticholinergic toxicity
        - Some may benefit from physostigmine (acetylcholinesterase inhibitor), particularly when evidence of peripheral and central anticholinergic toxicity, but involve a medical toxicologist because it should not be used in certain situations. Observe symptomatic patients with pulse oximetry and cardiac monitoring
    - o Clinical Course
        - Onset of symptoms usually occurs within 1-2 hours of ingestion, but can vary
        - Most patients recover fully; recovery time may last up to 2-3 weeks
- **Posterior Reversible Encephalopathy Syndrome (PRES)**
    - Overview: Clinicoradiological disorder of reversible subcortical vasogenic brain edema (usually parieto-occipital) in patients who present with acute neurological symptoms in the setting of one of a number of known precipitating etiologies.
    - Symptoms/Exam findings
        - Seizures
        - Encephalopathy (ranges from confusion to stupor)
        - Headache
        - Visual disturbances (visual loss, hallucinations, hemianopia, neglect, auras, cortical blindness)
        - Altered consciousness
        - Focal neurological deficits
        - Hypertension (not all patients have hypertension)
    - Labs/Tests
        - Typical brain MRI findings are T2 hyperintensities primarily within posterior white matter; cortical-subcortical vasogenic edema, usually in the posterior cerebral hemispheres, particularly the parieto-occipital regions
        - Variations do occur and edema can be seen in the posterior frontal, temporal, cerebellar, basal ganglia and brainstem locations
    - Risk Factors/Etiologies
        - Pre-eclampsia/Eclampsia
        - Hypertension: frequent, regardless of the etiology, but not invariable.
        - Medications
            - Immunosuppressants (cyclosporine, tacrolimus, sirolimus)
            - Chemotherapy (cisplatin, methotrexate, gemcitabine, vincristine, cytarabine)
            - Interferon alpha
            - IV immunoglobulin
            - Monoclonal antibodies (rituximab, bevacizumab, ipilimumab)
            - Tyrosine kinase inhibitors (pazopanib, sorafenib, sunitinib)
        - Sepsis
        - Autoimmune: Nearly half of patients have a history of an autoimmune disorder
        - Thrombocytopenia
        - Alcohol withdrawal

        - Renal failure
    - Conditions with Similar Presentation
        - Infectious encephalitis
        - Autoimmune or paraneoplastic encephalitis
        - Malignancy or tumor
        - Subcortical leucoaraiosis
        - CNS vasculitis
        - Progressive multifocal leukoencephalopathy
        - Osmotic demyelination syndrome
        - Acute demyelinating encephalomyelitis
        - Toxic leukoencephalopathy
        - Primary or secondary headaches
        - Toxic-metabolic encephalopathy
        - Vascular pathology
    - Diagnosis
        - This is a clinical and radiological diagnosis without established diagnostic criteria
        - Symptoms are usually non-specific and an MRI is needed to make the diagnosis.
        - Diffusion weighted imaging (DWI) can distinguish PRES from infarction.
        - Most research criteria include the following:
            - Typical MRI findings
            - Known risk factor
            - Acute neurotoxic syndrome
            - Other causes ruled out
        - Clinical symptoms and imaging findings resolve with treatment
    - Management Strategies
        - Immediate removal or treatment of the underlying pathology.
        - Blood pressure management may improve the symptoms and prevent progression. Anti-epileptic medication should be used for seizures.
        - If onset is peri-partum, treat for pre-eclampsia/eclampsia.
        - Offending medications should be reduced or discontinued.
    - Clinical Course
        - The neurological symptoms manifest acutely or subacutely, over hours-days
        - Hypertensive crisis may precede neurological symptoms by 24 hours or longer.
        - Prognosis generally favorable with discontinuation of offending medication or treatment of underlying etiology and most recover within days to 2 weeks, although can have fatalities, epilepsy and persisting motor deficits.
        - Less favorable outcomes with neurotoxicity secondary to chemotherapy or sepsis.
        - Resolution of imaging findings tends to lag behind clinical resolution.

Step 5: Implement Management Strategies

- Early recognition is key
- Remove offending agent
- Start with stabilization of airway, breathing, circulation
- Provide supportive care, including management of autonomic instability and hyperthermia
- Consider consultation with medical toxicologist and/or regional poison control centers
- Consider specific antidotes/medications used to counter toxicity syndromes as described above

- Most patients will need close monitoring, possibly telemetry

Step 6: Anticipate Clinical Course

- Resolution usually occurs after stopping the medication
- May be prolonged if offending agent has long half-life or metabolism is impaired
- Limited data on rechallenging after symptom resolution, but successful cases reported
- Consider risk-benefit analysis of rechallenge after symptom resolution
- Before a rechallenge is initiated, document clear indication and informed consent, reduce potential risk factors and wait at least 2 weeks from symptom resolution. The rechallenge would ideally occur in a hospital with gradual titration of low starting dose and close monitoring for signs of recurrent toxicity syndrome

Table 1: Clinical Presentation of Major Toxidromes

	Neuroleptic Malignant Syndrome	**Serotonin Syndrome**	**Anticholinergic Toxicity**
Precipitated by	Dopamine antagonists	Serotonergic agents	Anticholinergic agents
Onset	Variable (1-3 days)	Variable (<1d)	< 12 hours
Vital signs	Hypertension, tachycardia, tachypnea	Hypertension, tachycardia, and tachypnea	Hypertension, tachycardia, tachypnea
Temperature	Hyperthermia	Hyperthermia	Hyperthermia (<38.8)
Mucosa	Sialorrhea	Sialorrhea	Dry
Skin	Diaphoresis	Diaphoresis	Hot/red
Mental Status	Delirium	Delirium	Delirium
Muscles	“Lead pipe” rigidity	Increased tone	Normal
Reflexes	Hyporeflexia	Hyperreflexia, clonus	Normal
Pupils	Normal	Dilated	Dilated
Bowel sounds/ movements	Normal or decreased	Hyperactive, diarrhea	Decreased or absent, constipation

Selected References and Further Reading

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