DSM-5: Medication-Induced Movement Disorders and Other Adverse Effects of Medication

DSM-5 Notes

- **Neuroleptic medications** include:
  - Typical antipsychotics, atypical antipsychotics
  - Dopamine receptor-blocking drugs (used in the treatment of symptoms such as nausea and gastroparesis)
  - Amoxapine (marketed as an antidepressant)

Neuroleptic Malignant Syndrome "FEVER LAD"

- Heterogenous in onset, presentation, progression, and outcome
- **Diagnostic Features**
  - Exposed to a dopamine antagonist within 72 hours prior to symptoms development
  - Hyperthermia (>38 degrees Celsius on at least 2 occasions, measured orally)
  - Profuse diaphoresis
  - Generalized rigidity ("lead pipe")
  - Creatine kinase elevation of at least 4 x upper limit of normal
  - Changes in mental status (delirium or altered consciousness)
  - Autonomic activation and instability (tachycardia, diaphoresis, elevated or fluctuation in BP, urinary incontinence, and pallor)
  - Tachypnea and respiratory distress (from metabolic acidosis, hypermetabolism, chest wall restriction, aspiration pneumonia, or PE)
  - Lab abnormalities include leukocytosis, metabolic acidosis, hypoxia, decreased serum iron concentrations, and elevation in serum muscle enzymes and catecholamines
  - **NORMAL** CSF analysis and neuroimaging
  - EEG shows **generalized slowing**
  - Fever, encephalopathy, vitals unstable, elevated CL, rigidity, leukocytosis, acidosis, diaphoresis

- **Development and Course**
  - Incidence rates = 0.01% to 0.02% of individuals treated with antipsychotics
  - Alteration in mental status and neurological signs **precede** systemic signs
  - Onset varies from hours to days after drug initiation (most are within 1st week, virtually all within 30 days)
  - Mean recovery time = 7-10 days after drug discontinuation
  - Fatality rates of **10-20%** reported when the disorder is not recognized
  - Can recur if antipsychotics are reinstituted soon after an episode

- **Risk and Prognostic Factors**
  - Potential risk in **anyone** after antipsychotic administration
  - Patient factors associated with increased risk
    - *Agitation, exhaustion, dehydration, and iron deficiency*
  - Drug factors associated with increased risk
    - High-potency antipsychotics pose a greater risk
    - Parenteral administration routes, rapid titration rates, and higher total drug dosages

- **Differential Diagnosis**
  - Other serious neurological or medical conditions
    - CNS infections, inflammatory or autoimmune conditions, status epilepticus, subcortical structural lesions, and systemic conditions (pheochromocytoma, thyrotoxicosis, tetanus, heat stroke)
  - Syndrome from use of other substances or medications
    - Serotonin syndrome
    - Parkinsonian hyperthermia syndrome
    - Alcohol or sedative withdrawal

        - Malignant hyperthermia
        - Hyperthermia with abuse of stimulants and hallucinogens
        - Atropine poisoning
    - Malignant catatonia

Antidepressant Discontinuation Syndrome "FINISH"

- Set of symptoms that can occur after an abrupt cessation (or significant dose reduction) of antidepressant that was taking continuously for at least 1 month
- Begin within 2-4 days
- Include specific sensory symptoms, somatic, and cognitive-emotional manifestations
- Frequently reported symptoms:
    - Flashes of lights, "electric shock" sensation, nausea, hyper-responsivity to noises or lights, and nonspecific anxiety and feelings of dread
    - Flu-like sx, insomnia, nausea, imbalance, sensory disturbance, hyperarousal
- Relieve by restart the medication or a different medication of similar mechanism of action

- **Diagnostic Features**
    - Following treatment with TCAs, SRIs, and MAOis
    - Incidence depends on the dosage and half-life of the medication, as well as rate of tapering
    - Short half-life and abrupt discontinuation have higher risks
    - **Paroxetine** (short-acting SSRI) is most associated with discontinuation symptoms
    - No pathognomonic symptoms: symptoms are vague and variable

- **Prevalence -** Unknown
    - Depends on dosage, half-life, receptor binding affinity of the medication and possibly individual's rate of metabolism

- **Course and Development -** Little is known about clinical course - symptoms appear to abate over time

- **Differential Diagnosis**
    - Anxiety and depressive disorders
    - Substance use disorders
    - Tolerance to medication

- **Comorbidity -** Original symptoms of MDD may return

Neuroleptic-Induced Parkinsonism/ Other Medication-Induced Parkinsonism

- Parkinsonian tremor, muscular rigidity, akinesia, or bradykinesia
- Developing within a few weeks of starting or raising the dosage of a medication (neuroleptic) or after reduction in the dosage of a medication used to treat EPS

Medication-Induced Acute Dystonia

- Abnormal and prolonged contraction of the muscles of eyes (oculogyric crisis), head, neck (torticollis or retrocollis), limbs, or trunk
- Develop within a **few days** of starting or raising the dosage of a medication (e.g., neuroleptic) or after reduction in the dosage of a medication used to treat EPS

Medication-Induced Acute Akathisia

- Subjective complaints of restlessness, often accompanied by observed excessive movements (fidgety movements of the legs, rocking from foot to foot, pacing, inability to sit or stand still)
- Developing within a **few weeks** of starting or raising the dosage of a medication (e.g., neuroleptic) or after reduction in the dosage of a medication used to treat EPS

Tardive Dyskinesia - assess with AIMS

- Involuntary athetoid or choreiform movement (lasting at least a few weeks)
- Tongue, lower face and jaw, and extremities (sometimes involving pharyngeal, diaphragmatic, or trunk muscles)
- Developing in association of a neuroleptic for at least of **few months** (shorter period in older persons)
- May appear after discontinuation or change/reduction in dose = neuroleptic withdrawal-emergent dyskinesia (lasting less than 4-8 weeks)

Tardive Dystonia/Akathisia

- Late emergence during treatment
- Potentially persist for months to years, even with discontinuation or dose reduction of neuroleptic

Medication-Induced Postural Tremor

- Fine tremor (usually in the rage of 8-12 Hz)
- Occurring during attempts to maintain a posture
- Associated with use of medication (e.g., lithium, antidepressants, valproate)

Other Medication-Induced Movement Disorder

- Medication-induced movement disorders not captured by above specific disorders
- Presentation resembling NMS associated with medications other than neuroleptics
- Other medication-induced tardive conditions

Other Adverse Effect of Medication

- Adverse effects of medication are the main focus of clinical attention
- Examples include severe hypotension, cardiac arrhythmias, and priapism

Canadian Schizophrenia Guidelines

Examination for Extrapyramidal Symptoms - observe, assess, perform

- Observation of spontaneous movement
  - **Hyper**kinetic movements (akathisia, dyskinesia, tremor) while patient is at rest
  - Poverty of movement suggest drug-induced parkinsonism
  - Postural and kinetic tremor (hold posture and actively move through the range of motion)
- Assessment of tone
  - Cogwheel rigidity
- Performance of repetitive tasks
  - Bradykinesia
  - Pronation-supination of arms
  - Opening closing of hands
  - Foot tapping

Validated rating scales to screen for Extrapyramidal symptoms

- Standardized scales may be used to quantify symptoms and to compare symptoms between visits.
- *Extrapyramidal Symptom Rating Scale*
  - Assess for all 4 subscales and 4 clinical global impression severity scales
  - Parkinsonism, akathisia, dystonia, and tardive dyskinesia (assess for all types of EPS)
  - High interrater reliability
- Abnormal Involuntary Movement Scale (AIMS) - for TD
- Simpson Angus Scale - for antipsychotic-induced parkinsonism
- Barnes Akathisia scale - for akathisia

Recommendations

- Patient should be informed of the risk of EPS
- Risk of EPS varies depending on the antipsychotic medication use and its receptor binding profile
  - Highest with the **first-generation** antipsychotics (Haloperidol and chlorpromazine)
  - Higher risk with lurasidone, risperidone, paliperidone, and ziprasidone
    - Olanzapine, quetiapine, aripiprazole, and asenapine not significantly different from placebo
  - Risk of EPS is significantly lower with clozapine
  - Aripiprazole has higher risk of akathisia compared to placebo
- Encourage patients to report any symptoms suggestive of EPS
- Be vigilant for presence of EPS, even if patients do not mention it
- Use a validated side effect scale **at least annually**
- If EPS are of particular concerns, second generation antipsychotics or lower potency first-generation antipsychotics should be considered
- If tardive dyskinesia is a specific concern, second generation antipsychotics should be considered

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The Assessment and Treatment of Antipsychotic-Induced Akathisia

- Subjective experience of mental unease and dysphoria
- Sense of restlessness that may sometimes drive impulsive behavior
- **Acute akathisia** - occurs during the early days of treatment with antipsychotic medication
- **Withdrawal akathisia** - following reduction of dosage or cessation of antipsychotic medication
- **Tardive akathisia** - occurs **late** during treatment, is exacerbated, or provoked by antipsychotic dose reduction or withdrawal, and improves at least temporarily when the dose is increased
- Can be associated with suicidality in individuals with first-episode psychosis, and violent or aggressive behavior

Assessment

- Before starting antipsychotic medication and during antipsychotic dosage titration, clinicians should systematically assess the symptoms and signs of akathisia using a **validated scal**e
- **Barnes Akathisia Rating Scale**
  - Measures objective signs and subjective (awareness and distress) symptoms
  - Includes a global assessment item (a score of 2 or more indicates the presence of akathisia)
- **Extrapyramidal Symptom Rating Scale**
  - Includes one item on the symptoms of akathisia, one item assessing objective signs of akathisia, and a clinical global impression of severity of akathisia
  - Extensively deployed and has established inter-rater reliability

Antipsychotic Polypharmacy and Dose Reduction

- Risk of akathisia is greater in patients prescribed antipsychotic medication for the **first time** or for whom antipsychotic drug dosage is **rapidly escalated**
- Akathisia tends to improve following dose reduction
- Prescribing more than one antipsychotic drug for patients is also a risk factor
- Recommended **against** the use of antipsychotic combination therapy and high-dose strategies
  - Clinicians should avoid rapid escalation of antipsychotic dosage
  - Clinician should consider dose reduction in patients with persistent akathisia on a stable dose of antipsychotic medication (also consider risk of clinical deterioration)

Antipsychotic Switching

- If continuing antipsychotic treatment and significant akathisia symptoms → consider switching to an agent with a perceived lower liability for extrapyramidal side effect - *clozapine, olanzapine or quetiapine*

Beta Blockers - Propranolol has the most evidence

- If propranolol is prescribed, clinicians should review its contraindications before starting treatment and monitor blood pressure and heart rate in the supine and standing position
  - Can cause hypotension and bradycardia, which can be exacerbated by antipsychotic medications.
- Start at a low dose (e.g., 10 mg twice daily), and gradually titrate based on clinical response

Anticholinergic Medications (Benztropine) - should **NOT** be routinely used for the treatment of akathisia

5-HT2A Antagonists (Mirtazapine)

- When propranolol is contraindicated, ineffective, or not tolerated and long-term pharmacological management of akathisia is anticipated, a trial of a *mirtazapine* may be considered

Benzodiazepine (Clonazepam) - consider as a *short-term therapy* option

Vitamin B6

- In patients failing to respond to alternative treatments for persistent antipsychotic-induced akathisia, *short-term treatment with vitamin B6* may be considered.