

# Drug-Induced Movement Disorders

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## Goals

- Recognize the two main clinical presentations of drug-induced movement disorders
- Understand the how drugs can cause movement disorders
- Ask important questions when considering a drug-induced movement disorder
- Highlight differences between drug-induced and idiopathic/acquired movement disorders
- Appreciate when a drug-induced movement disorder may be an emergency!



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## Objectives

- Define specific types of movement disorders
- Identify specific drugs that are culprits for causing movement disorders
- Recognize signs and symptoms of each drug-induced movement disorder
- Note potential risk factors for drug-induced movement disorders
- Discuss interventions to treat drug-induced movement disorders



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## Acute vs Tardive

- *Acute*  
Rapid development of movement disorder following drug initiation (or dose alteration)
- *Tardive*  
Gradual or late-onset of movement disorder (typically months to years) after drug initiation and at times persisting despite drug withdrawal



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## Clinical Definitions of Movement Disorders

- *Myoclonus*  
Sudden, brief, shock-like movements
- *Dystonia*  
Involuntary muscle spasm that leads to sustained, abnormal postures of the affected body part
- *Tremor*  
Rhythmic, oscillatory movements produced by alternating or synchronous contractions of antagonist muscles

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## Clinical Definitions 2



- *Parkinsonism*  
Cardinal features include bradykinesia, rigidity, tremor and postural instability
- *Tic*  
Brief, paroxysmal movements or vocalizations sometimes accompanied by premonitory urge
- *Chorea*  
Brief, irregular, purposeless, involuntary that flow into one another in a random fashion

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## Drugs Associated with Movement Disorders

- Dopamine Receptor Blockers\*\*\*
  - Antipsychotics: e.g. Haloperidol, Thioridazine, Perphenazine
  - Anti-emetics: e.g. Metoclopramide; Prochlorperazine; and Promethazine.
- Lithium
- Stimulants: e.g. amphetamines
- Antidepressants: e.g. Selective-serotonin reuptake inhibitors (SSRIs), Tricyclic antidepressants (TCAs)
- Anti-epileptics: e.g. Valproic acid

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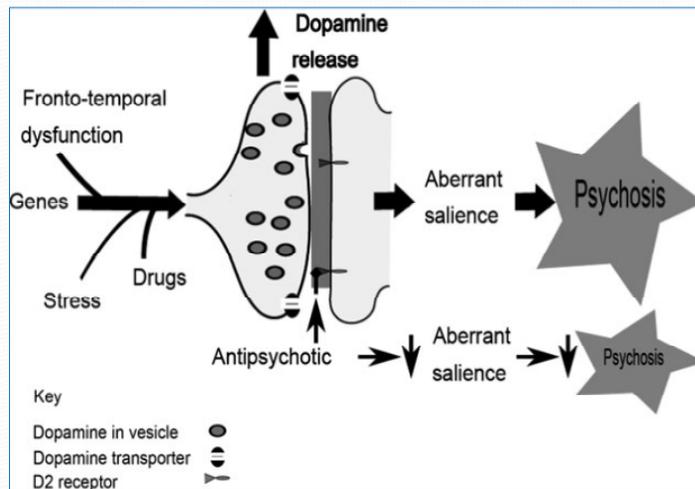
# High vs Low Potency Antipsychotics

	High Potency	Low Potency
D <sub>2</sub> Blockade***	High	Low
Anticholinergic	Low	High
Examples	Haloperidol (Haldol) Fluphenazine (Prolixin)	Chlorpromazine (Thorazine) Thioridazine (Mellaril)
Typical Doses	0.5-100mg	Up to 1000mg

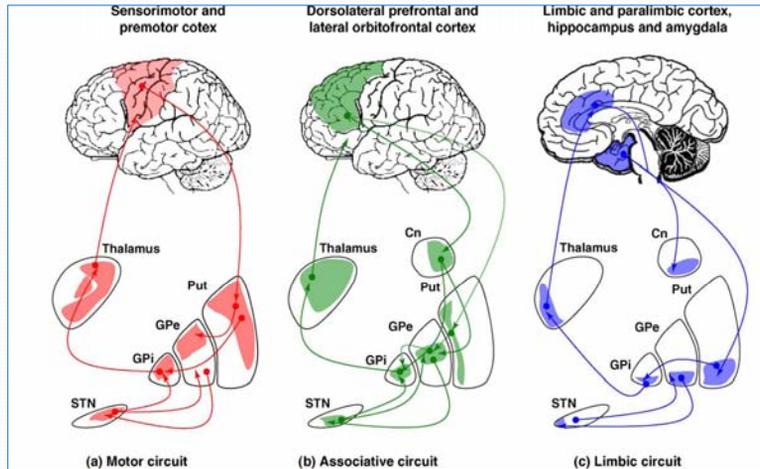
*Anticholinergic side effects:* dry mouth, urinary retention, constipation, mental confusion/delirium, blurred vision, decreased sweating

\*\*\* The focus of much of the talk

# Dopamine Receptor Blocking Agents



# Cortico-striatal-pallido-thalamo-cortical Loops



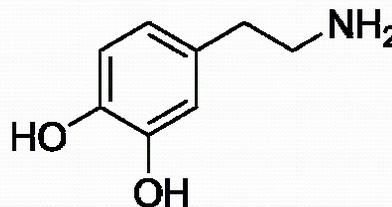
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# Typical (1<sup>st</sup> gen) versus Atypical (2<sup>nd</sup> gen) Antipsychotics

All antipsychotic medications have some activity at Dopamine D<sub>2</sub> receptors, but...

- *Receptors:* Atypicals have less activity at D<sub>2</sub> receptors and more at 5-HT<sub>2A</sub> (serotonin) receptors
- *Side effects:* Less movement disorder, but host of other side effects
- *Examples:*
  - Clozapine
  - Olanzapine
  - Quetiapine
  - Risperidone
  - Ziprasidone
  - Aripiprazole



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## Important ?s When Considering Drug-Induced Movement Disorder

- When did movement disorder start in relation to the start of new medications?
- Was there a change in dose of an established medication?
- Are there any factors that may have increased the plasma levels of medications prior to onset?
- Specifically ask about exposure to DRBs, including for anti-nausea, etc?
- Exposure to: OCPs, illicit drugs, alcohol, nicotine, caffeine, OTC medications, herbal/nutritional preps?

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## Acute Drug-Induced Movement Disorders

- Acute dystonic reactions
- Drug-induced parkinsonism
- Akathisia
- Drug-induced tremor\*

### *Potential Emergencies!*

- Neuroleptic Malignant Syndrome
- Serotonin Syndrome\*

(\* Not related to DRBs, necessarily)

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## Acute Dystonic Reaction: Signs and Symptoms

CAN BE:

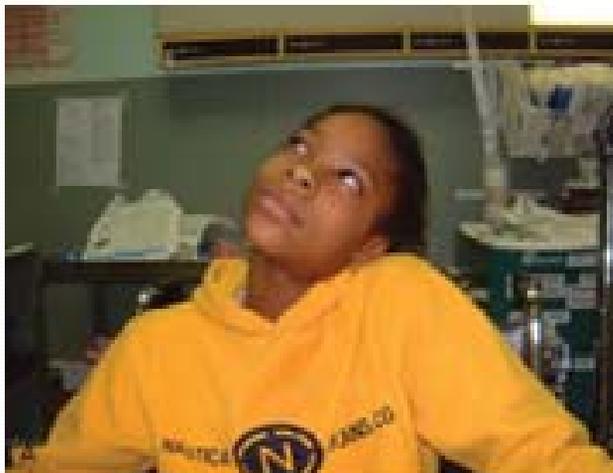
- Oculogyric crisis
- Trismus
- Laryngeal-pharyngeal dystonia
- Torticollis
- Opisthonos
- Limb dystonias



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## Acute Dystonic Reaction



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## Acute Dystonia: Epidemiology

- Occur early in the course of treatment
  - 2% of those starting treatment with a DRB
  - 90% will have onset in first 5 days of treatment
- Usually related to high potency antipsychotics, often after given intramuscularly
- Most common in men under the age of 30 yo
- Can be painful and frightening for the patient, even if typically benign
- But, may be an emergency if causing respiratory compromise!

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## Acute Dystonia: Treatment

- Treat with intramuscular anticholinergics (Diphenhydramine 50 mg)
- Benzodiazepines also effective (Diazepam, Lorazepam)
- Short-course of oral anticholinergic to stop recurrence and typically switch from offending agent
- Prophylaxis with anticholinergic can prevent occurrence
- May need life support: Airway, Breathing, Circulation, O<sub>2</sub>

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## Parkinsonism

- Resting tremor- *less common in drug-induced*
- Bradykinesia (slowed movement)
- Muscle Rigidity
- Shuffling gait
- Autonomic instability
- Drooling



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## Drug-Induced Parkinsonism

- 15% of those treated with antipsychotics
- First 90 days of treatment
- Elderly females most at risk, but occurs at any age
- Tends to be symmetric when drug-induced
- Can be difficult to differentiate from idiopathic Parkinson's Disease in older patients on DRBs
- Also, can be difficult to distinguish from severe depressive symptoms (psychomotor slowing, flat affect)

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## Drug-Induced Parkinsonism: Treatment

- If possible, stop the offending agent... But not always possible with psychosis
- Anticholinergic agents
  - Benztropine (Cogentin), Diphenhydramine (Benadryl)
- Some patients will develop tolerance to parkinsonian effects and anticholinergics may be withdrawn
- Parkinsonian symptoms may last as long as 3 months after DRB is discontinued

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## Akathisia

- *A feeling of inner restlessness and desire to move followed by the physical expression of this feeling*
- Describe: Sense of anxiety, “jittery,” inability to relax, “crawling out of skin”
- Display: Pacing, fidgeting, shifting weight, alternation from sitting to standing, or even running
- Middle-aged women at ↑ risk
- Time course similar to drug-induced parkinsonism
- Associated with poor treatment outcome

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## Akathisia Treatment

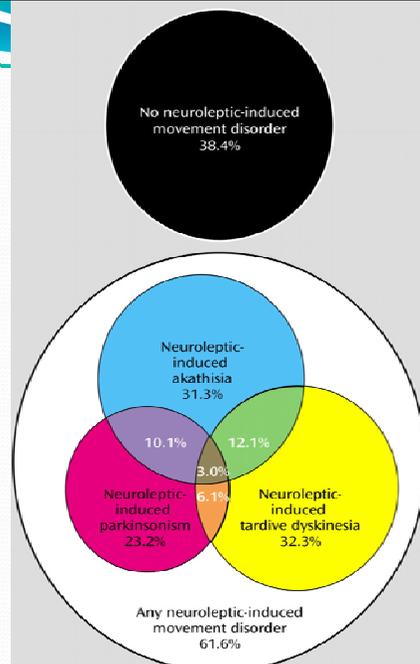
- 1) Reduce dose of offending agent
  - 2) Attempt treating with appropriate drugs
    - $\beta$ -adrenergic antagonists (propranolol)
    - Anticholinergics
    - Benzodiazepines
  - 3) Discontinue/change antipsychotic
- In some cases, no treatment seems to be effective
  - Severe cases have led to patient suicide

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## Neuroleptic-Induced Movement Disorders in 99 Inpatients With Chronic Schizophrenia Treated With Conventional Antipsychotics or Clozapine

Janno et al, Am J Psychiatry. 2004;161(1):160-163



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All Patients (N=99)

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## Drug-Induced Tics and Myoclonus

- Tics
  - Can be caused by: methylphenidate, amantadine, fenfluramine, levodopa, carbamazepine, and drugs of abuse such as cocaine, ecstasy, and amphetamines
- Myoclonus
  - Can be caused by: opioid analgesics, benzodiazepines, TCAs, anticonvulsants (gabapentin, pregabalin, carbamazepine, lamotrigine, VPA), SSRIs, anesthetic agents

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## Drug-induced Tremor

- Typically a postural or “enhanced physiologic” tremor
- Different than parkinsonian rest tremor associated with DRBs
- Potential drug causes:
  - Beta agonists e.g. albuterol
  - Anticonvulsants e.g. valproic acid
  - Thyroid hormone replacement
  - Lithium
  - Caffeine and Nicotine
  - Drugs of abuse (cocaine, amphetamine)

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## Neuroleptic Malignant Syndrome (NMS): Signs and Symptoms

- A life-threatening complication of antipsychotic treatment; first described in 1960
- Can occur anytime during the course of treatment
- Symptoms:
  - Motor/Behavioral: muscular rigidity, akinesia, mutism, obtundation, agitation
  - Autonomic: diaphoresis, fever, elevated pulse and BP
  - Labs: increased CPK, WBC, liver enzymes, myoglobin; myoglobinuria; renal failure from rhabdomyolysis

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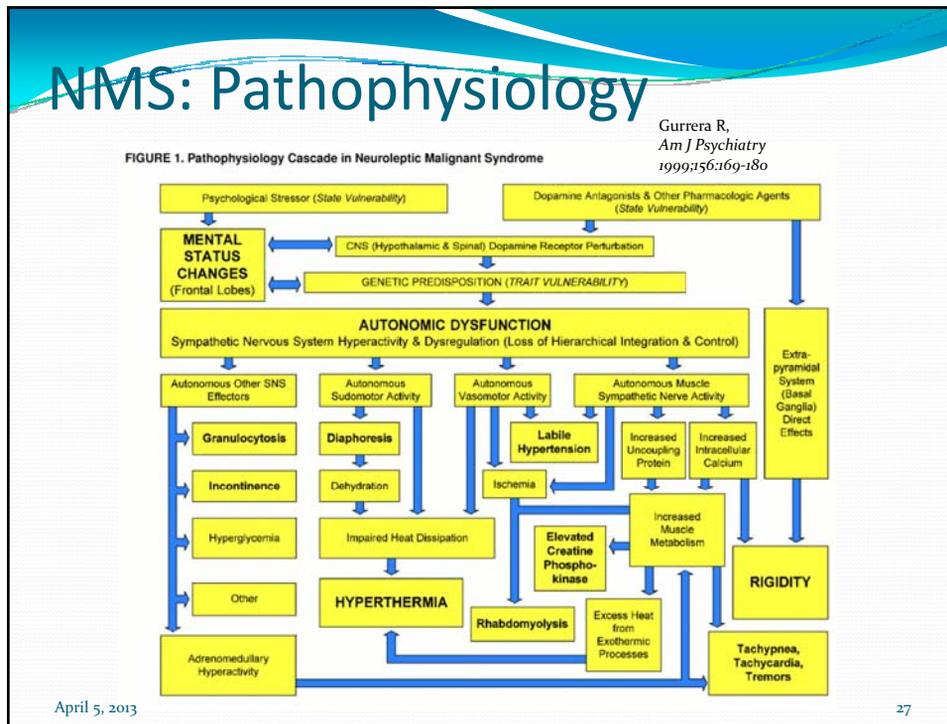
## NMS: Epidemiology

- Incidence is low, 0.2%
- Men > Women
- Young > Old
- Possible genetic susceptibility (case reports of identical twins with NMS)
- Mortality can reach 20%, especially if long-acting (depot) medications involved
- Can last 10-14 days untreated
- Death by renal failure, respiratory failure, aspiration, DVT → PE



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- # NMS: Treatment
- Supportive medical treatment (BP and temp control, etc)
  - Discontinuation of the offending agent
  - Dopamine agonists (1<sup>st</sup> line)
    - Bromocriptine used most often
    - Levodopa, ropinirole, pramipexole have also been used
  - Dantrolene, a muscle relaxant
  - 7-10 days of treatment
  - Electroconvulsive therapy (ECT) has also been used
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## Serotonin Syndrome 1

- In order of appearance with worsening severity:  
Diarrhea → restlessness → extreme agitation, hyperreflexia, autonomic instability → myoclonus, seizures, hyperthermia, rigidity, shivering → delirium, coma, status epilepticus, cardiovascular collapse and death
- Treatment involves:
  - Discontinuation of offending agents
  - Supportive medical treatments
  - Cyproheptadine (antiserotonergic) for severe cases

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## Serotonin Syndrome 2

- Any combination of drugs that excessively enhances serotonergic transmission:
  - SSRI/SNRIs
  - MAOIs
  - TCAs
  - L-tryptophan
  - Buspirone
  - Opioids (especially fentanyl, meperidine)
  - Lithium
  - triptans
  - LSD, ecstasy, amphetamines, cocaine

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## Tardive Drug-Induced Movement Disorders

- Tardive dyskinesia and
- Tardive dystonia

(Tardive akathisia, myoclonus, and tremor have also been reported...)



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## Tardive Dyskinesia (TD)

- First described in the 1950, within 5 years after the first DRB, chlorpromazine (thorazine) became widely available
- “Classic” TD involved oral-buccal-lingual dyskinesias, still the most common presentation
  - Tongue twisting and protruding, lip-smacking, and chewing movements in a repetitive and stereotypic fashion
  - May also involve limbs and trunk
- Differs from dyskinesias in HD, which are random and unpredictable
- Assess using Abnormal Involuntary Movement Scale (AIMS)

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## Tardive Dyskinesia: Epidemiology

- More likely to emerge for first time when DRB is reduced or discontinued
- 20% of those treated with typical antipsychotics are affected
- Age is most consistent risk factor- higher incidence rates and lower remission in older patients
- Other risk factors: women, affective disorders, poor tx response, previous brain damage, pre-existing parkinsonism, greater total drug exposure, and alcoholism

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## Tardive Dystonia

- Can be focal, segmental, or generalized
  - Typically retrocollis when affecting neck, and opisthonos when affecting back
  - In contrast to lateralcollis and lateral twisting more common in idiopathic dystonia
- May coincide with tardive dyskinesia, where idiopathic dystonia would not
- Prevalence rates from 2-20%
- May be more common in men

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## Tardive Dyskinesia/Dystonia- Treatment

- *Prevention* is best option
  - Presynaptic dopamine depleters- tetrabenazine and reserpine
  - Trihexyphenidyl
  - Reintroduction of antipsychotics
  - Clozapine\*
  - Clonazepam
  - Botulinum toxin\*
  - Deep Brain Stimulation\* (if medication refractory)
- (\*More effective for tardive dystonia)

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## Drugs of Abuse and MD

- Cocaine and Amphetamines
  - Stereotypic motor behaviors, punding, tremor, tics, dystonia, chorea, myoclonus
- 3,4-Methylenedioxymethamphetamine (MDMA, Ecstasy)
  - Tremor, ataxia, rigidity, myoclonus, nystagmus, NMS/SS type syndrome from massive serotonin release
- Opioids
  - Myoclonus; Meperidine and fentanyl more likely to contribute to SS

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Thank you...



Any Questions???