Tardive dyskinesia, Drug-induced parkinsonism, and other Drug-induced movement disorders: A review of pathophysiology, assessment and management

Amelia M. Kelley, MSN, APRN, FPMHNP-BC
The aforementioned presenter has no conflict of interest or financial disclosures associated with the content presented herein.
Objectives

- Review etiology, pathophysiology management and treatment of sub-acute/chronic and acute drug-induced movement disorders
- Identify causative medications/agents
- Discuss assessment and screening recommendations
- Discuss outcomes and prognosis
Drug-induced movement disorders: an overview

• Encompass various specific disease types, subtypes, clinical symptom presentation and/or complaints of patients
• Range from mild to severe
• Can range from acute onset and self-remitting to insidious and life-long
• Can overlap in symptom presentation making differentiation and diagnosis difficult at times
• Varying of interventions from discontinuation of the offending medication to symptomatic management with adjunctive medications
• Significantly impact patients adherence to treatment regimens and reduce quality of life
DSM 5 Medication-Induced Movement Disorders and Other Adverse Effects of Medication

• Acknowledged as pertinent to treatment of psychiatric illness due to frequency and severity of some disorders

• Importance of differentiation of “true” medication induced symptoms and disease presentation from other disorders with movement abnormalities (Huntington’s chorea, Tourette syndrome, autism spectrum disorder, Parkinson’s disease etc.)
DSM 5 Medication-Induced Movement Disorders and Other Adverse Effects of Medication

- Neuroleptic-induced and other medication-induced parkinsonism (Drug-induced parkinsonism)
- Neuroleptic Malignant Syndrome
- Medication-induced dystonia
- Medication-induced Acute akathisia
- Tardive dyskinesia, dystonia and akathisia
- Medication-induced postural Tremor
Tardive dyskinesia
Tardive dyskinesia

• A hyperkinetic disorder of movement caused by dopamine receptor blocking agents (DRBAs), most often at D2
• Commonly associated are antipsychotics and antiemetic agents
• Can be irreversible and permanent causing severe impairment in quality of life and level of functioning; however remission and improved outcomes are possible with appropriate preventative measures, screening, intervention and management
Tardive dyskinesia

• “tardive” meaning late onset
  • Presenting weeks to months after exposure to offending agent/medication
  • Different from other movement disorders d/t later onset of clinical manifestations (compared to EPS and other abnormal movements which can occur within hours of exposure)

• “dyskinesia” involving multiple types of aberrant movements and postures (chorea, athetosis, stereotypies, dystonia, akathisia, tics)
Tardive dyskinesia: Pathophysiology

- Multiple hypotheses, specific cause not yet clear
- Known implication of D2 blockade
  - Possible imbalance between D1 and D2 receptor mediation
  - Upregulation of D1 in striatal receptors to compensate following DBRA exposure
- Changes in basal ganglia neuronal systems
- GABA theory- increased glutamate presentation in striatum causing damage to neurons

(Deik & Tarsy, 2021)
Tardive dyskinesia: Clinical presentation

Most commonly identified when orofacial movements present
- Other possible movements can be seen in arms, trunk, legs and respiratory muscles
- Orofacial movements- puckering or twisting of mouth, lateral jaw movements or chewing appearance, smacking and licking lips, involuntary protrusion of tongue, blepharospasm.
  - usually starts off minimal, but in the cognizant and high functioning client, they may be hyperaware of the movements and indicate issues with mouth/jaw discomfort, tooth sensitivity or broken dentures, orofacial pain, trouble eating and swallowing, and/or general aggravation with the feeling of movement prior to clinician awareness
Tardive dyskinesia: Clinical presentation

• Truncal, peripheral and respiratory involvement
  • Twisting and gyration of arms, legs and trunk
  • Splaying of hands “piano fingers”
  • Tapping and twisting movements of legs and feet
  • Shoulder shrugging, neck movements including torticollis
  • Circular or lateral rocking movements, hip thrusting
  • Tachypnea, grunting, irregular respirations
Tardive dyskinesia: Clinical presentation

- Tardive dystonia, akathisia, tics and tremors
  - Indicative of a more specific and predominant symptom presentation of TD
    - Dystonia- marked rigidity, sustained or repetitive muscle movements
      - More common under age 40
    - Akathisia- restlessness and urge to move incessantly, subjective feeling
    - Tics, myoclonus, stereotypies, tremors and oral pain syndromes
Tardive dyskinesia: Clinical presentation

- Children manifest sx predominantly after abrupt discontinuation of DBRA and is termed “withdrawal-emergent” TD
- Often self-limiting
- Choreiform presentation: involuntary, brief, non-rhythmic type movements occurring usually below the neck
Tardive dyskinesia: offending agents

• ALL DBRAs and any medications/agents affecting dopamine reuptake through signaling cascade have the potential to cause TD
• Antipsychotics- particularly first-generation (FGA) but second generation (SGA) are implicated as well
• Antiemetic agents
• Other offending medications- antidepressants (particularly tetracyclic), anticholinergics, anticonvulsants, antihistamines, decongestants, stimulants, antimalarials, antiparkinson agents, anxiolytics, mood stabilizers and biogenic agents (Cornett, et al., 2017)
Tardive dyskinesia: offending agents

Antipsychotics

• First and second generation are both implicated in causing TD, though it is most common to see emergence with FGAs
• Incidence with FGAs between 5-6 percent annually and 5 to 10 year risk approximately 25-30 percent
• Incidence with SGAs 4 percent annually but increases in geriatric population
  • Highest incidence with paliperidone and risperdone
  • Intermediate incidence for aripiprazole, lurasidone, olanzapine, ziprasidone
  • Lowest incidence with clozapine, quetiapine and pimavanserin

(Deik & Tarsy, 2021)
Tardive dyskinesia: offending agents

Antiemetic

• Metoclopramide has D2 blocking mechanism (D2 receptor antagonist)
• Most commonly used in gastroparesis and is a frequent cause of TD in adults
• Implicated in a vast spectrum of movement disorders including drug-induced parkinsonism
• Carries black box warning since 2009
• Also associated: Prochlorperazine, Chlorpromazine, promethazine
Tardive dyskinesia: Risk factors

• Causative agent and length of treatment
• Age (increased risk in older adults over age 55)
• Gender (more common in females)
• Previous development of extrapyramidal symptoms
• Higher doses of DRBAs
• Hx of psychotic and or mood disorders, intellectual disability, cognitive impairment, substance abuse, ECT hx
• Historically children at lower risk but this is changing. Increased r/f withdrawal TD after abrupt discontinuation of DRBA
## Risk factors for tardive dyskinesia

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Drug exposure characteristics*</th>
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<tbody>
<tr>
<td>Older age</td>
<td>First &gt; second-generation antipsychotics*</td>
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<tr>
<td>Female sex</td>
<td>Cumulative duration</td>
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<td>Higher dose</td>
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<td>Early occurrence of drug-induced movement disorders</td>
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<tr>
<td>Comorbidities</td>
<td>Schizophrenia and other psychotic disorders</td>
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<td>Intellectual disability</td>
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<td>Preexisting mood disorder</td>
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<td>Alcohol or substance use disorder</td>
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<td>Dementia</td>
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<td>Diabetes</td>
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<td>Others</td>
<td>Prior electroconvulsive therapy</td>
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</tbody>
</table>

* All dopamine receptor-blocking agents have the potential to cause tardive dyskinesia. The most commonly implicated drugs are first-generation antipsychotic drugs, second-generation antipsychotic drugs, and metoclopramide.

* Not as great a difference as once thought.
Tardive dyskinesia: Course, assessment and management

- Appear as early as 1 month to 6 months after initial exposure to offending agent
- Symptoms can worsen during times of emotional distress, illness, physical exertion, and will often diminish and remit during rest, sedation or sleep
- Severe impact on quality of life, especially for the cognitively intact and psychiatrically stable client who is cognizant of the movements
  - Feelings of hyperawareness, depression, impaired functioning with IADLs/ADLs, lowered self esteem, anxiety
  - RE-KINECT study with patient reported outcomes, though tools used not validated in pts with TD, demonstrated psychosocial impact and real world implications of disease process on pt QOL and ADLs (Caroff, et al., 2020)
FIGURE 3
Impact of involuntary movements on daily activities (cohort 2). Patient-reported impact of involuntary movements on daily activities for the past 4 weeks. It includes patients who were aware of involuntary movements in the past 4 weeks that they could not control (n = 110). (Caroff, et al, 2020)
Tardive dyskinesia: Course, assessment and management

• Prevention, early diagnosis and rapid intervention are paramount in lessening morbidity and severity of disease

• Routine assessment using standardized assessment tools (AIMS) upon beginning of DBRA and every 3 to 6 months with consideration to complexity and chronicity of treatment

• Consideration and ruling out of other drug-induced movement disorders

• Limiting the use of unnecessary DBRAs

• Remaining vigilant of prescribing practices- “start low go slow”

• Educating the patient on possible risks of medications and clearly delineating risk to benefit ratio when beginning therapies
Abnormal involuntary movement scale

Public Health Service  
Alcohol, Drug Abuse, and Mental Health Administration  
National Institute of Mental Health

**KEY:**  
0 = None  
1 = Minimal, may be extreme normal  
2 = Mild  
3 = Moderate  
4 = Severe

**NAME:**  
**DATE:**  
Prescribing practitioner: _______________________

**MOVEMENT RATINGS:** Rate highest severity observed. Rate movements that occur upon activation one less than those observed spontaneously. Circle movement as well as code number that applies.

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</table>

**Facial and oral movements**

1. Muscles of facial expression  
   - movements of forehead, eyebrows, periorbital area, cheeks, including frowning, smiling, smiling, grooving  
   0 1 2 3 4

2. Lips and perioral area  
   - puckering, pouting, smacking  
   0 1 2 3 4

3. Jaw  
   - clenching, chewing, mouth opening, lateral movement  
   0 1 2 3 4

4. Tongue  
   - Rate only increases in movement both in and out of mouth. NOT instability to sustain movement.  
   0 1 2 3 4

**Extremity movements**

3. Upper (arms, wrists, hands, fingers)  
   - include choreic movements (ie, rapid, objectively purposeless, irregular, spontaneous) athetoid movements  
   - include tremor (ie, repetitive, regular, rhythmic). DO NOT INCLUDE TETANY.  
   0 1 2 3 4

6. Lower (legs, knees, ankles, toes)  
   - eg, lateral gaze movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot  
   0 1 2 3 4

**Trunk movements**

7. Neck, shoulders, hips  
   - eg, rocking, twisting, squirming, pelvic gyrations  
   0 1 2 3 4

**Global judgments**

8. Severity of abnormal movements overall  
   0 1 2 3 4

9. Incapacitation due to abnormal movements  
   0 1 2 3 4

10. Patient's awareness of abnormal movements  
    - rate only patient's report  
    - No awareness 0  
    - Aware, no distress 1  
    - Aware, mild distress 2  
    - Aware, moderate distress 3  
    - Aware, severe distress 4  
   0 1 2 3 4

**Dental status**

11. Current problems with teeth and/or dentures?  
    - No  
    - Yes  

12. Are dentures usually worn?  
    - No  
    - Yes

13. Edentia?  
    - No  
    - Yes

14. Do movements disappear in sleep?  
    - No  
    - Yes
Tardive dyskinesia: Course, assessment and management

Initial management of new onset TD

- Discontinue offending agent if possible
- Antipsychotics should be slowly withdrawn over a period of months to prevent unmasking or withdrawal TD, abrupt discontinuation can significantly worsen TD
- Educating patient of expected prognosis- time to remission can take months or years depending on severity
- Need for reintroduction of DBRA after discontinuation can cause reoccurrence of TD
Review dopamine receptor-blocking agents (DRBAs)*

Ongoing treatment necessary?

- **Yes**
  - Continue DRBA
    - Use lowest effective dose
    - Switch to agent with lower risk of perpetuating/worsening TD (eg, from first- to second-generation antipsychotic), if possible

- **No**
  - Discontinue DRBA
    - Taper gradually over weeks to months
    - TD may worsen during taper; if severe, slow taper or begin concurrent symptomatic therapyΔ
    - TD may take weeks to months to improve, if at all
    - Avoid DRBAs in future

Persistent moderate to severe TD

Is focal dystonia present (eg, cervical dystonia, blepharospasm)?

- **Yes**
  - First line:
    - Botulinum toxin
  - Second line:
    - VMAT2 inhibitor
    - Anticholinergic therapy
  - Refractory:
    - Deep brain stimulation

- **No**
  - First line:
    - VMAT2 inhibitor◊
  - Second line:
    - Benzodiazepines
  - Refractory:
    - Deep brain stimulation
Tardive dyskinesia: Course, assessment and management

Considerations for those requiring chronic antipsychotic or antiemetic therapies

- Closely monitor patients on multiple/combination DBRA therapies
- Consider swapping from FGA to SGA
- Consider RVB of continuing vs discontinuing long acting injectable antipsychotics
- Consider agents with less D2 affinity- clozapine (preferred agent in setting of severe TD, but not without risks!!) quetiapine, iloperidone
Tardive dyskinesia: Course, assessment and management

Symptomatic therapy

• BNZ- clonazepam, initiated 0.5mg/day and titrated to maximum of 3-4mg/day in divided doses
• Amantadine- 200-300mg/day in divided doses
• Benztpoine/Trihexyphenidyl- can worsen TD sx by exacerbating choreiform dyskinesias but may aid in dystonias
  • benztropine dosing initiated at 0.5mg po daily and titrated to 4mg/day divided doses
  • Trihexyphenidyl dosing initiated at 1mg daily and titrated to 6mg/day in divided doses.
• Botulinum toxin for focal dystonias
• Deep brain stimulation
• VMAT2 inhibitors
• Referral to movement specialist
Tardive dyskinesia: Course, assessment and management

VMAT2 inhibitors
- Main symptomatic drugs for TD
- Indicated for moderate to severe disease
- Three current medications available for use
  - Tetrabenazine
  - Valbenazine
  - Deutrebanazine
Tardive dyskinesia: Course, assessment and management

Tetrabenazine

- Been around for decades, rec indication for HC in 2008, not currently indicated for TD but has been used OL
- 50 mg/day in divided doses; if needed, may increase daily dose by 50 mg every 2 weeks up to maximum of 150 mg/day in divided doses (Uptodate, 2021).
Valbenazine

- Approved based on efficacy demonstrated in KINECT-2 and KINECT-3 clinical trials (Liang & Tarsy, 2021)
- Recommended starting dose is 40mg/day and titrated as indicated/tolerated to 80mg/day
- Those with hepatic impairment or concurrent CYP34A or CYP2D6 inhibitors such as paroxetine, fluoxetine or bupropion should not exceed 40mg/day
Deutetrabenazine
- Initial starting dose 6mg BID and titrated to 36mg/day to remission of sx. Dose can be increased every 7 days.
- Those taking CYP2D6 inhibitors should not exceed 36mg/day, however continued remission is usually seen at this dose. Some patients require upwards of 48mg/day in divided doses.
- Effects were demonstrated to be maintained over time through two years (Liang & Tarsy, 2021)
- Can cause akathisia and early discontinuation of treatment
## Cytochrome P450 2D6 (CYP2D6) inhibitors

<table>
<thead>
<tr>
<th>Strong inhibitors</th>
<th>Moderate inhibitors</th>
<th>Strong inducers</th>
<th>Moderate inducers</th>
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<tr>
<td>Bupropion</td>
<td>Abrameivos</td>
<td>Apalidin</td>
<td>Bencaridine</td>
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<td>Dextromethorphan</td>
<td>Cinacalcet</td>
<td>Carbovirnophene</td>
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<td>Fluoxetine</td>
<td>Darifenacin</td>
<td>Carbamazepine</td>
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<td>Paroxetine</td>
<td>Darunavir</td>
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<td>Duloxetine</td>
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<td>Mirtazapine</td>
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<td>Nizatidine</td>
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<td>Varenicline</td>
<td>Carboprostell</td>
<td>Betnovate</td>
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### References
2. US Food and Drug Administration. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Available at: FDAtexts website.
Drug-Induced Parkinsonism
Drug-induced parkinsonism

- Most common DIMD
- Most common cause of non-degenerative parkinsonism
- Caused by any drug or agent that affects D2 directly or indirectly
- Clinically is often indistinguishable from Parkinson’s disease, other than by scan
  - Single photon emission computed topography (SPECT)
  - Positron emission tomography (PET)
- Important for clear identification as it is reversible when offending mediation/agent is discontinued or removed.
Drug-induced parkinsonism

• Prevalence is unclear as symptoms are frequently underrecognized by clinicians or is misdiagnosed as Parkinson’s disease

• Risk
  • increases with age and highest rates are among those ages 60-80 years
    • Theoretically d/t physiologic decrease in dopamine transport associated with age
  • Patients previously dx with PD or subclinical PD sx
  • Type of medication/agent and dose
Drug-induced parkinsonism

- Pathophysiology
  - Interruption in transmission of dopamine among receptors usually by a structural or functional blockade of D2 in striatum
Dopamine feedback loop as presented in the normal brain vs Parkinson’s disease brain/DIP

Of note: STN primary function of movement regulation as fundamental circuit for the basal ganglia

TH function serves as the center of motor control - receives input from cerebellum, striatum, and cortex and projects to primary motor cortex.

Green: excitatory
Red: inhibitory
GPe: globus pallidus externa
GPi: globus pallidus interna
SNc: substantia nigra pars compacta
SNr: substantia nigra pars reticulata
STN: subthalamic nucleus
TH: ventrolateral nucleus of the thalamus
(Wyant & Chou, 2021)
Drug-induced parkinsonism: Causative agents

- DRBAs including FGA and SGA
- Antiemetic agents
- Prokinetic agents
- Dopamine depleting agents
- Mood stabilizers
- Antidepressants
- Some Ca+ channel blockers
# Drugs that reduce the effect of dopamine in the brain

<table>
<thead>
<tr>
<th>Type of drug</th>
<th>Antidopaminergic mechanism</th>
<th>Examples</th>
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<tbody>
<tr>
<td><strong>First-generation antipsychotics</strong></td>
<td>D2R antagonism (high potency)</td>
<td>● Droperidol</td>
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<tr>
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<td>● Risperidone</td>
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<td>● Fluphenazine</td>
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<td>● Haloperidol</td>
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<td>● Loxapine</td>
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<td>● Perphenazine</td>
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<td>● Pimozide</td>
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<td>● Trihexyphenidyl</td>
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<td>● Trifluopropazine</td>
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<td></td>
<td>D2R antagonism (low potency)</td>
<td>● Chlorpromazine</td>
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<td>● Chlorprothixene</td>
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<td>● Levomepromazine</td>
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<td>● Mepazine</td>
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<td>● Mesoridazine</td>
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<td>● Metoclopramide</td>
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<td>● Perazine</td>
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<td>● Promazine</td>
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<td>● Thioridazine</td>
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<td><strong>Second-generation antipsychotics</strong></td>
<td>D2R antagonism</td>
<td>● Asenapine</td>
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<td>● Clozapine*</td>
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<td>● Iloperidone</td>
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<td>● Quetiapine*</td>
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<td>Partial D2R agonism</td>
<td>● Anzapirazone</td>
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<td>● Brexpiprazole</td>
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<td><strong>Antipsychotic/promility agents</strong></td>
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<td>● Metoclopramide</td>
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<td>● Promethazine*</td>
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<td><strong>Calcium channel blockers</strong></td>
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<td><strong>Dopamine-depleting agents</strong></td>
<td>Presynaptic dopamine depletion</td>
<td>● Deuterobenzamine</td>
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<td>(no D2 activity)</td>
<td>● Reserpine</td>
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<td>● Tetrabenazine</td>
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<td>● Valbenazine</td>
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D2R: dopamine D2 receptor; D1R: dopamine receptor.
* = weak antidopaminergic properties.
Drug-induced parkinsonism: Causative agents

Antipsychotics- FGA and SGA

• Potency, route of administration and dose affect onset and acuity of drug induced parkinsonism
• Administration routes other than parenteral can increase the risk
  • IM (long acting injectables, short acting antipsychotics frequently used in acute settings)
  • Suppositories
• SGA thought to have less risk
  • Usually higher affinity for 5HT2A and modulation at D receptors
  • Risperdal, olanzapine, ziprasidone, lurasidone, paliperidone most often implicated
  • Quetiapine and clozapine with lowest risk
Drug-induced parkinsonism: Causative agents

Antipsychotics- FGA and SGA continued:

- Aripriprazole and brexpriprazole
  - Agonist and antagonist action at D2
  - Carry lower risk of DIP
  - Pharmacovigilance database of WHO indicates aripriprazole caused DIP more frequently than Zyprexa (Wyant & Chou, 2021)

- Primavanserin
  - Inverse agonist for 5-HT2A receptor
  - No affinity for D2 and is drug of choice of PD related psychosis/psychosis in LBD
  - Alternative to clozapine and quetiapine for PD patients
Drug-induced parkinsonism: Causative agents

Antiemetic agents

• Prochlorperazine
• Metoclopramide
• Well documented evidence of dystonias, movement disorders, DIP and TD
Drug-induced parkinsonism: Causative agents

VMAT2 inhibitors

• inhibit dopamine storage in presynaptic vesicles which impairs or inhibits vesicular transport of dopamine
• Reserpine irreversible VMAT2 and 10-20 times more potent than tetrabenazine (Wyant & Chou, 2021)
• Includes tetrabenazine (HC/HD), Deutrabenazine, valbenazine
  • The latter two have least evidence of worsening parkinsonism compared with placebo in trials
Drug-induced parkinsonism: Causative agents

Mood stabilizers/antiepileptics
  • Valproate
    • GABA theory of reduced dopamine transport likely
  • Lithium

Selective serotonin reuptake inhibitors (SSRIs)
  • Citalopram, fluoxetine, sertraline, fluvoxamine, paroxetine
  • Not well understood why but risk thought to be low
  • Many reports indicate concurrent use of antipsychotic

Ca+ Channel blockers
  • Flunarizine, amlodipine, diltiazem, verapamil
Drug-induced parkinsonism: Clinical presentation and assessment

- Bradykinesia, muscle rigidity, cogwheeling, resting tremor, shuffling of feet and psychomotor retardation, mask like appearance/flat affect
- Usually clinically indistinguishable from idiopathic PD
- Onset of sx within hours to weeks after exposure to offending medication/agent
  - 90 percent of patients rec antipsychotics demonstrated PD within first 72 hours of administration
  - Can present more acutely with non-parenteral forms of administration
- Rigidity followed by bradykinesia and resting tremor are most frequent sx
- PD cannot be ruled out or diagnosed while exposed to possible offending medication/agent
Drug-induced parkinsonism: Clinical presentation and assessment

• Suspicions for diagnosis
  • concurrent presentation of various movement disorders can indicate the presence of DIP
    • Tardive syndromes, akathisia, bradykinetic movements
  • Imaging studies such as SPECT testing in case where the offending medication/agent cannot be stopped or if sx persist after stopping the offending medication/agent
    • Dopamine transmission scan (DaTscan): striatal dopamine transporter imaging
  • Presence of reoccurring or irreversible DIP
    • When sx persist after the offending medication/agent is discontinued
    • May indicate presence of preclinical/premorbid PD in which the offending medication/agent “unmasked” PD
Drug-induced parkinsonism: Management

- Avoidance/Discontinuing offending medication/agent
  - Avoid known medications especially in hx of DIP/subclinical PD
  - Limit or avoid use in high risk populations (older adults)
- If DBRA required for management of sx
  - “start low go slow” vs reduce dose to least, most effective strength for tolerability
- Psychosis in presence of PD
  - Quetiapine, clozapine, pimavanserin- latter being first line
- Symptomatic management
  - Principal of delaying use unless absolutely necessary for the improvement of motor function/QOL due to s/e profiles especially in older populations
  - Levodopa- usually contraindicated in presence of psychosis but is often first line outside of psychiatry
    - Dosing of 25/100mg carbidopa-levodopa TID and titrated to efficacy
Drug-induced parkinsonism: Management

- Symptomatic management continued:
  - Amantadine- anecdotal reports of worsening psychosis with this medication
    - 100mg BID to TID, usually preferred to Cogentin dt less s/e profile
  - Benztropine- longstanding hx of use in EPS/DIP with limited high-quality data to support effectiveness (Wyant & Chou, 2021)
    - 0.5mg po daily and titrated to efficacy, usually 1-2mg/day in divided doses
  - Electroconvulsive therapy (ECT)
    - Numerous case reports suggest improving PD through possible upregulation of D1 receptors
    - Anecdotally supports use in DIP as well
    - May be indication for patients with clinical psychiatric indication such as refractory depression who develop DIP from adjunctive antipsychotic treatment
Acute drug-induced movement disorders
Akathisia

- Common and frequently underrecognized/misdiagnosed
- Presents most often as “anxiety” and is diagnosed as such
- Sense of internal restlessness *, irritability, tension sometimes without objective clinical signs
- “ants in your pants feeling” urge to move, pace “like running from the feeling”
- Reported with DBRAs, SSRIs, antiepileptics
  - Antipsychotics, Fluoxetine, paroxetine, valproate, lithium
- Improves with cessation of offending medication
- Alternative adjunctive tx: anticholinergics, beta blockers (propranolol)*, BNZ, amantadine, mirtazepine
Tremor

• Postural and/or kinetic
• Usually symmetrical in presentation
• Presents acutely following induction or dose titration of medications
• Can be associated with TD (tardive tremor)
• Can present in valproate even at therapeutic or low doses
• Occurs with some SSRIs, lithium, TCAs, antiepileptics (predominantly valproate), bronchodilators, amiodorone, immunosuppressives (corticosteroids)
• R/O thyroid/PD
• Management through dose alteration or addition of propranolol
Acute dystonic reactions

- Occurs after exposure to DBRA
- Most common in younger patients*
  - Children, adolescents, younger adults
- Acute and sustained dystonia of larger muscle groups
  - Cervical muscles typical
  - Lower extremities*
- Management by stopping offending medication/agent, IM/IV anticholinergic, antihistamine, BNZ administration, muscle relaxers
Parkinsonism-hyperpyrexia disorder

- Syndrome of clinically worsening PD in patients who have recently reduced or abruptly stopped taking anti-PD medications
- Can occur with/without encephalopathy
- Elevated temperature, autonomic instability, elevated creatine kinase
- Overlap with NMS sx
- Resuming anti-PD medications main treatment, apomorphine injections
- Recovery within hours to weeks
Serotonin syndrome

• Occurs from exposure to drugs that increase 5-HT activity
• Can range in severity from mild to life threatening
• Assessment reveals AMS, CNS hyperexcitability, myoclonus, tremor, akathisia, hyporeflexia, clonus, rigidity, autonomic instability, fever, tachycardia, can have elevated CK
• Sx overlap with NMS
• Management through d/c offending medication/drug first line, supportive care, cyproheptadine in less severe cases, BNZ, chlorpromazine, olanzapine
• Resolves in hours to days in acute phase, sequelae for weeks
Neuroleptic malignant syndrome

- Potentially life-threatening
- Occurs after exposure or acute withdrawal from DRBA
- Occurs often with antipsychotics, tetrabenazine, lithium, antiemetics
- DX criteria/assessment: exposure to DRBA or acute withdrawal within last 72 hours, hyperthermia on 2 occasions >100.4, rigidity, AMS, ^CK, autonomic instability
- Differentiation - leukocytosis, abnormal CMP, abnormal RF, abnormal LFTs, altered coag studies
  - Rigidity in NMS, where as myoclonus/hypereflexia with clonus, mydriasis with SS
  - Parkinsonism hyperpyrexia can be ruled out if no prior hx of PD/ingestion of antiPD agents
Neuroleptic malignant syndrome

• Management
  • Acute hospitalization warranted
  • Cessation of offending medications/drugs
  • Bromocriptine initiation
  • SQ apomorphine
  • BNZ

• Course
  • Plateaus and improves over 2-3 weeks
    • Bromocriptine should be continued over this time to ensure syndrome completely subsided
<table>
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<tr>
<th>Movement disorder</th>
<th>Implicated drugs</th>
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| Akathisia                                                                        | Dopamine receptor blocking drugs  
Selective serotonin reuptake inhibitors  
Antiepileptics                                                                      |
| Tremor                                                                           | Selective serotonin reuptake inhibitors  
Lithium  
Tricyclic antidepressants  
Antiepileptics (e.g. valproate)  
Bronchodilators  
Amiodarone  
Immunosuppressive drugs (tacrolimus, ciclosporin) |
| Serotonin syndrome (usually due to overdose or combinations of serotonergic drugs)| Selective serotonin reuptake inhibitors  
Serotonin noradrenaline reuptake inhibitors  
Tricyclic antidepressants  
Monoamine oxidase inhibitors  
Lithium  
Linezolid  
Opioids (pethidine, tramadol, propentadol)  
Antiepileptics (valproate, lamotrigine)  
St John’s wort |
| Acute dystonic reaction | Dopamine receptor blocking drugs (e.g. antipsychotics, metoclopramide)  
Selective serotonin reuptake inhibitors  
Opioids  
Methylphenidate  
Rivastigmine  
Albendazole  
Gabapentin  
Cetirizine  
Cetirizine  
Foscarnet  
Quinine  
Propofol  
Sevoflurane |
| --- | --- |
| Neuroleptic malignant syndrome | Antipsychotics (e.g. haloperidol, fluphenazine, chlorpromazine)  
Prochlorperazine  
Metoclopramide  
Droperidol  
Promethazine  
Tetrabenazine  
Tetranemine  
Lithium |
| Parkinsonism                                    | Dopamine receptor blocking drugs (e.g. antipsychotics)  
|                                                | Calcium channel antagonists (e.g. flunarizine, cinnarizine)  
|                                                | Antiepileptics (e.g. phenytoin, valproate, levetiracetam)  
|                                                | Antidepressants (e.g. selective serotonin reuptake inhibitors, monoamine oxidase inhibitors)  
|                                                | Lithium  
|                                                | Chemotherapeutic drugs (e.g. cystosine arabinoside, cyclophosphamide, vincristine, adriamycin, doxorubicin, paclitaxel, etoposide)  
|                                                | Immunosuppressive drugs (e.g. ciclosporin, tacrolimus)  
|                                                | Toxins (e.g. 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), organophosphate pesticides, manganese, methanol, cyanide, carbon monoxide and carbon disulphide)  
| Tardive drug-induced movement disorders        | Antipsychotics  
|                                                | Antiemetics (e.g. metoclopramide)  

(Duma & Fung, 2019)
References


Questions and Comments? Thank you!

Amelia Kelley, FPMHNP
amkelleypmhnp@gmail.com
(662)803-0883