Drug-Induced Movement Disorders



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Videos; courtesy Toronto Western Hospital movement disorder clinic
video library

Learning Objectives

1. To recognise the clinical features of drug-induced movement disorders

2. To review prevention, treatment and management of drug-induced movement disorders

Drug-induced movement disorders

- Dopamine Receptor Antagonists–induced Movement Disorders
  - Tardive syndromes
  - Acute/Subacute syndromes

- Other Drug-induced parkinsonism
- Other Drug-induced akathisia
- Other Drug-induced tremor

Drug-induced movement disorders

- **Dopamine Receptor Antagonists–induced Movement Disorders**
  - Tardive syndromes
  - Acute/Subacute syndromes

- Other Drug-induced parkinsonism
- Other Drug-induced akathisia
- Other Drug-induced tremor

Tardive Dyskinesia: DSM-5

Tardive Dyskinesia: 333.85 (G24.01)

- Involuntary movements (lasting at least a few weeks)
- generally of the tongue, lower face and jaw, and extremities
- developing in association with the use of a neuroleptic medication for at least a few months.
  - Shorter exposure particularly in older individuals
  - Persistent movements after this time point consistent with Tardive dyskinesia
  - Withdrawal emergent dyskinesia can occur with dose reduction or discontinuation but resolve in 4-8 weeks

Tardive Dystonia 333.72 (G24.09) Tardive Akathisia (G25.71)

- Tardive syndrome involving other types of movement problems

American Psychiatric Association, 2013

Classical tardive dyskinesia: Signs and Symptoms



- Repetitive, rhythmical, purposeless movements in oro-buccal-lingual region
  - Suppression with eating/drinking



- Jaw – lateral, chewing, biting, clenching
- lip- pursing, smacking, grimacing
- ‘flycatchers tongue’
- Trunk – rocking, twisting
- Diaphragm – grunting, irregular respiration
- Limbs – choreoathetoid, tapping, “guitar-piano” fingers

Tardive dystonia

- Onset: up to years after exposure to drug
- Site of origin varies with age of onset:
  - Young starts legs to face ;
  - Older starts craniocervical
  - Trunk arching backwards, retrocollis, internal rotation of arms
    - May be better when walking
  - Pisa syndrome

Tardive Syndromes: Clinical Phenotypes

Table 1
Phenomenology of tardive syndromes.

Tardive syndrome	Description
Classic tardive dyskinesia	O-B-L stereotypy. Complex, repetitive, chewing movement, sometimes with lip smacking, pouting, opening and closing of the mouth, and tongue protrusion. May interfere with speaking, chewing, and swallowing and may cause social embarrassment. May lead to tongue hypertrophy (macroglossia). Trunk and limbs may be affected, usually in association with O-B-L stereotypy. Limb involvement is typically distal with a repetitive, stereotypic pattern.
Tardive dystonia	May occur as focal, segmental or generalized dystonia; more common in young men. Typically presents as blepharospasm, OMD, retrocollis, trunk hyperextension (opisthotonus), and arm extension and pronation with wrist flexion.
Tardive akathisia	An inner sense of restlessness with inability to be still. Body rocking movement, shifting weight from one foot to another, walking in place, crossing/uncrossing the legs, or body rocking. May be associated with moaning or repetitive touching. Often disabling and difficult to treat.
Tardive myoclonus	Prominent postural, spontaneous or stimulus-sensitive jerk-like movements, particularly in the upper extremities during sustained posture or during voluntary movement (intention myoclonus).
Tardive tremor	Postural and/or resting tremor, 3–5 Hz. Improves with dopamine depleters.
Tardive tics	Motor or phonic tics with onset in adulthood. Can be identical to tics associated with Tourette syndrome.
Tardive chorea	Random, jerk-like movements that flow from one body region to the next in an unpredictable, random, manner.
Tardive gait	Gait changes may be "dance-like," taking short steps on toes followed by longer strides, or "duck-like" with wide-based, unsteady gait with short stride length and steppage pattern.
Tardive parkinsonism	Rest tremor, bradykinesia, rigidity persisting for months/years after discontinuation of DRBAs. DaTscan is typically normal.
Withdrawal emergent syndrome	Generalized choreiform movements mainly of the neck, trunk, and limbs in children after sudden cessation of DRBAs. A self-limited condition.
Tardive ocular deviation	Conjugate eye deviations characterized by a fixed stare followed by conjugate spasmodic movements of the eyes, generally in an upward direction. Not typically painful, in contrast to oculogyric crises in acute dystonic reaction.
Tardive pain	Chronic, often burning, pain or unpleasant sensation in the oral or genital regions.

O-B-L = oral-buccal-lingual, *DaTscan* = dopamine transporter scan, *DRBA* = dopamine receptor blocking agent.

Dopamine D2 Receptor blocking agents causing movement disorders

- **'Typical' and 'atypical' antipsychotics**

- Typicals >> Risperidone > Olanzapine > Quetiapine > Clozapine

- Substituted benzamides:
  - Metoclopramide
  - Tiapride, sulpiride, amisulpiride

Epidemiology

- Percent by phenomenology
  - Tardive dyskinesia: 30% of pts on antipsychotics (20-50%)
  - Tardive akathisia: 20%
  - Tardive dystonia: 5-15%
  - Others are rare

- Long term risk
  - 25% in 5 years
  - 49% in 10 years
  - 68% in 25 years

Acquino and Lang. Parkinsonism Rel Disord 2014
Lerner et al. Psychiatr Clin Neurosci 2015

TD: risk factors

- Risk factors
  - Increasing age (except for tardive dystonia)
    - Increased incidence, prevalence
    - Worse severity
    - Less likely to resolve
  - Female gender especially for oral-lingual buccal movements
  - Longer duration of exposure
  - More potent DRBAs: High affinity for D2 receptors
  - Dose (chlorpromazine equivalents)

Citrome et al. Neuropsych Dis Treatment 2021

Antipsychotic use in the elderly

- Up to 35% of patients residing in nursing home or assisted living receive antipsychotic agents
  - Predominantly for off-label indications
    - Aggressive behavior
    - Insomnia
    - Anxiety
- Cumulative TD incidence of 26% (year 1), 30% year 2) and up to 60% after 3 years

Citrome et al. Neuropsychiatric Disease and treatment. 2021

Pathophysiology of Tardive syndromes

- **Increased affinity to D2 receptors**
  - "fast v slow OFF" (no change in number of receptors)
- **Genetic factors**
  - Dopamine D3 receptor gene Ser9Gly polymorphism is associated with 2.5 increased risk for TD
  - Multiple studies D1, D2, 5HT2C, VMAT
  -
- **Non dopaminergic**
  - **Cholinergic – likely cholinergic interneurons (loss of inhibition),**
  - Opioid, GABA, 5HT, Glutamate

Management of Tardive Syndromes

Canadian Recommendations for Long-Term Effects of antipsychotic (AP) drugs

- **Examine for movement disorder prior to AP treatment**
- **Examine for movement disorder every 6 months during AP treatment**
- **Results must be recorded (standard rating scales helpful)**
- **If TD:**
  - Evaluate symptoms
  - Switch to Atypical
  - Clozaril trial if persistent symptoms
  - **No evidence based medicine treatment formally indicated**
  - Prevention is preferred strategy

Canadian Clinical Practice Guidelines for the Treatment of Schizophrenia. *Can J Psychiatry.* 2005;50(suppl 1)

Examine for presence of TD using Abnormal Involuntary Movement Scale **AIMS**

- 5 point scale – rate 7 body regions

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

- Global Judgment rating

1. Muscles of facial Expression (e.g., movement of forehead, eyebrows, periorbital area, cheeks; include frowning, blinking, smiling, grimacing)

2. Lips and Perioral Area (e.g., puckering, pouting, smacking)

3. Jaw (e.g. biting, clenching, chewing, mouth opening, lateral movement)

4. Tongue (Rate only increase in movement both in and out of mouth, NOT inability to sustain movement.)

5. Upper (arms, wrists, hands, fingers). Include choreic movements (i.e., rapid, objectively purposeless, irregular, spontaneous), athetoid movements (i.e., slow, irregular, complex, serpentine). Do NOT include tremor (i.e., repetitive, regular, rhythmic).

6. Lower (legs, knees, ankles, toes). (E.g., lateral knee movement, foot taping, heel dropping, foot squirming, inversion and eversion of foot.)

7. Neck, shoulders, hips (e.g., rocking, twisting, squirming, pelvic gyrations)

UK Guidelines for the Treatment of Tardive Dyskinesia

Withdraw any prescribed anticholinergic agent

↓

Consider reducing dose of antipsychotic or withdraw (may worsen symptoms initially)

↓ *Antipsychotic required*

Switch to Atypical (quetiapine, then clozapine)

↓ *Ineffective/Metabolic side-effects*

Consider use of tetrabenazine 25–100 mg/day

↓ *Ineffective*

Consider clonazepam 1–4 mg/day

↓ *Ineffective*

Consider vitamin E (widely used but doubtful efficacy)

Adapted from *The Maudsley 2003 Prescribing Guidelines*, 7th ed. Taylor D, Paton C, Kerwin R, eds.

VMAT2 inhibitors for Tardive Dyskinesia

- Tetrabenazine
- Valbenazine
- Deutetrabenazine

Vesicular monoamine transport inhibitors: current uses and future directions

Liana S Rosenthal, Mena Farag, N Ahmad Aziz, Jee Bang

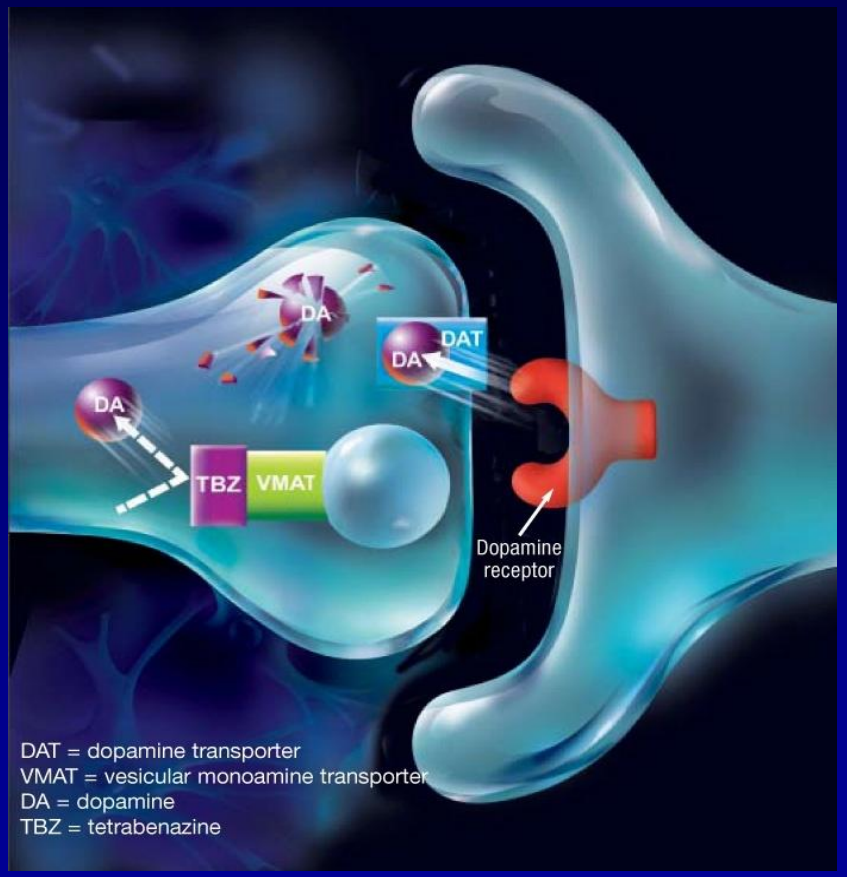
Tetrabenazine Mechanism of Action

- **TBZ selectively inhibits central vesicular monoamine transporter type 2 (VMAT2) in the striatum**
  - Reversible and selective binding
- **TBZ reduces dopamine transmission in the brain**
  - Avoids peripheral nervous system side effects seen with reserpine
  - Depletes 5HT and NA

Potential side-effects

- Parkinsonism
- Depression
- Sedation

- May respond to reducing dose



Extensive first pass metabolism via CYP2D6 – bioavailabilty is <5%

Summary: VMAT2 inhibitors

	Tetrabenazine	Valbenazine	Deutetrabenazine
Half Life	Short (T ½ = 4.8 hours)	Long (T ½= 20 hours)	Medium (T ½ = 8.6 hours)
Efficacy	++	+++	+++
Dosing	tid	nightly	bid
Side effects	++++	+	+
	Sedation Depression Suicidal ideation Akathisia Parkinsonism Prolonged QTc Orthostatic hypotension	Sedation **reduce to 40 mg/day in patients who are concomitantly receiving a potent CYP3A4 inhibitor (e.g., ketoconazole, itraconazole, clarithromycin).**	Headache Sedation v. small risk of parkinsonism and depression Hauser et al j Clin Psych 2024

Other Treatment Options for Tardive dyskinesia

- Alpha-receptor modulators
  - Clonidine
- GABA modulators
  - Benzodiazepines (clonazepam), Baclofen
  - Valproate, Levetiracetam; piracetam
- Beta blockers
- Vitamin E, Vitamin B_6
- Acetylcholinesterase inhibitors
  - Donepezil; Galantamine
- NMDA antagonists
  - Amantadine
- Opioid antagonists
  - Naltrexone

Treating Tardive Dystonia

- Dopamine depletors
  - Tetrabenazine
- Anticholinergics
  - care can exacerbate co-existent tardive chorea
- Clonazepam
- Switch to Clozapine
- Botulinum toxin for focal dystonia
- Surgery - Bilateral Globus Pallidus stimulation

Systematic Review

Association des psychiatres du Canada

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Treatment Recommendations for Tardive Dyskinesia

Recommandations sur le traitement de la dyskinésie tardive

Lucia Ricciardi[1], Tamara Pringsheim[2], Thomas R.E. Barnes[3], Davide Martino[4], David Gardner[5], Gary Remington[6], Donald Addington[7], Francesca Morgante[1], Norman Poole[8], Alan Carson[9], and Mark Edwards[1]

Results: Preventing tardive dyskinesia is of primary importance, and clinicians should follow best practice for prescribing antipsychotic medication, including limiting the prescription for specific indications, using the minimum effective dose, and minimising the duration of therapy. The first-line management of tardive dyskinesia is the withdrawal of antipsychotic medication if clinically feasible. Yet, for many patients with serious mental illness, the discontinuation of antipsychotics is not possible due to disease relapse. Switching from a first-generation to a second-generation antipsychotic with a lower D2 affinity, such as clozapine or quetiapine, may be effective in reducing tardive dyskinesia symptoms. The strongest evidence for a suitable co-intervention to treat tardive dyskinesia comes from tests with the new VMAT inhibitors, deutetrabenazine and valbenazine. These medications have not been approved for use in Canada.

CNS Drugs (2024) 38:239–254
https://doi.org/10.1007/s40263-024-01078-z

CURRENT OPINION

An Evidence-Based Update on Anticholinergic Use for Drug-Induced Movement Disorders

Nora Vanegas-Arroyave[1] · Stanley N. Caroff[2,3] · Leslie Citrome[4] · Jovita Crasta[5] · Roger S. McIntyre[6,7] · Jonathan M. Meyer[8] · Amita Patel[10,9] · J. Michael Smith[11] · Khody Farahmand[12] · Rachel Manahan[12] · Leslie Lundt[12] · Samantha A. Cicero[12]



Prophylactic Use of Anticholinergics

- Anticholinergics are not recommended for preventing DIMDs as they are generally unnecessary and have significant central nervous system and peripheral adverse effects
- Short-term prophylactic use of anticholinergics may be considered in patients with risk factors for acute dystonia (e.g., current intramuscular treatment with a first-generation antipsychotic)
- Duration of prophylactic anticholinergic use should be limited, and discontinuation (if possible) should be gradual

Acute movement disorders with dopamine blocking drugs

Acute dystonia within hours - days

- Craniofacial - Oculogyric crisis; limb dystonia; laryngeal
  - Increased risk - young men; rapid dose escalation

- **Treatment**
  - Stop offending drug
  - Antihistamine/Anti-cholinergic eg biperiden 5 mg IV, followed by PO maintenance for 7d). Or promethazine 25-50 mg IM
  - Clonazepam 2 mg PO

Sub acute movement disorders with Dopamine blocking drugs

- **Subacute (days – weeks)**

- Parkinsonism
- Akathisia
- Neuroleptic Malignant syndrome

NMS v Serotonergic Syndrome v MH

Table 2. Comparison of features and management of neuroleptic malignant syndrome, serotonergic syndrome, and malignant hyperthermia

	Neuroleptic malignant syndrome	Serotonergic syndrome	Malignant hyperthermia
Age/sex prodisposition	Young men	None	Children, young adults
Triggering factor	Idiosyncratic	Drug combination/ overdose	Gene mutation
Onset	Acute	Subacute	Acute
Causative agents	Classic/newer antipsychotics, antiemetics, L-dopa withdrawal	SSRIs, SNRIs, tricyclic antidepressants, MAOIs, L-tryptophan, amphetamines, cocaine	Volatile anesthetics, succinylcholine
Fever	+++	++	+++
Confusion	+++	+++	+
Dysautonomia	+++	+++	+++
Motor features	Tremor, rigidity	Myoclonus, rigidity, stereotypies, hyperreflexia	Rigidity
Diaphoresis	+++	++	+++
Elevated serum creatine kinase	+++	++	+++
Elevated serum transaminases	+++	+	–
Metabolic acidosis	+	+	++
Pharmacologic treatment[a]	Bromocriptine, amantadine, dantrolene	Cyproheptadine, methylsergide	Dantrolene

MAOIs, monoamine oxidase inhibitors; NMS, neuroleptic malignant syndrome; SNRIs, serotonin–norepinephrine inhibitors; SSRIs, selective serotonin reuptake inhibitors.

[a]Prior to any form of pharmacological treatment, patients should be stabilized and withdrawn of causative agent.

Drug-induced movement disorders

- Dopamine Receptor Antagonists–induced Movement Disorders
  - Tardive syndromes
  - Acute/Subacute syndromes

- **Other Drug-induced parkinsonism**
- **Other Drug-induced akathisia**
- **Other Drug-induced tremor**

Drug-induced parkinsonism

- Usually present with bilateral symptoms; bradykinesia, rigidity, slow gait and less commonly tremor

- If symptoms persist or progress after removal of offending drug; maybe idiopathic PD ‘unmasked’ by use of dopamine-blocking agent (10% of cases)

- Conn and Jankovic Drug-Induced Parkinsonism. Exp Opn Drug Safety Dec 2024

Causes of drug-induced PD

1) Antipsychotics (50%)
- Typical >> atypical
- Occurs within 3m of starting drug
- 2/3 resolve on stopping drug
- Can co-exist with tardive dyskinesias

2) Metoclopramide (30%)
- F > M

3) Dopamine depletory - Tetrabenzine

4) Lithium
- More likely postural tremor

5) Sodium Valproate
- More likely to cause a postural tremor; rarely causes parkinsonism

6) Calcium channel blockers

7) Toxins/drugs: eg MPTP, Manganese

Drug-induced Akathisia

- Definition; Subjective inner restlessness and inability to sit still, relieved by moving about. When sitting, the patient usually has repetitive movements that involve primarily the legs and trunk

- Can be acute or tardive

Barnes Akathisia Rating Scale

Instructions: Patient should be observed while they are seated, and then standing while engaged in neutral conversation (for a minimum of two minutes in each position). Symptoms observed in other situations, for example while engaged in activity on the ward, may also be rated. Subsequently, the subjective phenomena should be elicited by direct questioning.

Objective

0 Normal, occasional fidgety movements of the limbs
1 Presence of characteristic restless movements: shuffling or tramping movements of the legs/feet, or swinging of one leg while sitting, *and/or* rocking from foot to foot or "walking on the spot" when standing, but movements present for less than half the time observed
2 Observed phenomena, as described in (1) above, which are present for at least half the observation period
3 Patient is constantly engaged in characteristic restless movements, *and/or* has the inability to remain seated or standing without walking or pacing, during the time observed

Subjective

Awareness of restlessness
0 Absence of inner restlessness
1 Non-specific sense of inner restlessness
2 The patient is aware of an inability to keep the legs still, or a desire to move the legs, *and/or* complains of inner restlessness aggravated specifically by being required to stand still
3 Awareness of intense compulsion to move most of the time *and/or* reports strong desire to walk or pace most of the time

Distress related to restlessness
0 No distress
1 Mild
2 Moderate
3 Severe

Global Clinical Assessment of Akathisia

0 *Absent.* No evidence of awareness of restlessness. Observation of characteristic movements of akathisia in the absence of a subjective report of inner restlessness or compulsive desire to move the legs should be classified as pseudoakathisia
1 *Questionable.* Non-specific inner tension and fidgety movements
2 *Mild akathisia.* Awareness of restlessness in the legs *and/or* inner restlessness worse when required to stand still. Fidgety movements present, but characteristic restless movements of akathisia not necessarily observed. Condition causes little or no distress.
3 *Moderate akathisia.* Awareness of restlessness as described for mild akathisia above, combined with characteristic restless movements such as rocking from foot to foot when standing. Patient finds the condition distressing
4 *Marked akathisia.* Subjective experience of restlessness includes a compulsive desire to walk or pace. However, the patient is able to remain seated for at least five minutes. The condition is obviously distressing.
5 *Severe akathisia.* The patient reports a strong compulsion to pace up and down most of the time. Unable to sit or lie down for more than a few minutes. Constant restlessness which is associated with intense distress and insomnia.

Drug-induced causes of akathisia

- Antipsychotics
- Tetrabenazine
- Antidepressants – SSRIs, SNRIs, TCAs
- Illegal/recreational drugs – GHB, Amphetamines, MDMA

Management of Akathisia

- Remove offending drug
- Anticholinerigcs ? No good evidence
- Beta blockers - may help
- Case reports - Mirtazapine; high dose Vit B6

Drug-induced tremor

- **Bilateral action limb tremor most typical**
  - May have pre-existing essential tremor that is worsened by tremorgenic drugs
  - May settle over time
  - Does not progress, unlike ET

- **Rest tremor -** drug-induced parkinsonism
- Perioral ‘rabbit tremor’ – with antipsychotics

Thuy-Uyen Huynh, MD, and Ethan H. Beckley, MD, PhD

Neurology® 2024;102:e209275. doi:10.1212/WNL.0000000000209275

Causes of Drug-induced tremor

- **Mood stabilisers-** Lithium, Valproate, Lamotrigine
- **Antidepressants -** SSRIs; SNRIs; amitryptiline
- Drugs of misuse **;** Ethanol, Cocaine, Nicotine, MDMA
- Hormones - Thyroxine, Calcitonin, Medroxyprogesterone
- **Chemotherapy** - Cytarabine
- **Immunosuppressants**- Tacrolimus, Cyclosporin, a-Interferon
- Methylxantines - Theophylline, Caffeine
- Beta agonists - Salbutamol inhalers
- Antipsychotics
- Gastrointestinal drugs -metoclopramide
- Antiarrhythmic drugs - amiodarone

Conclusions

- Drug-induced movement disorders are common
- Antipsychotic drugs are usual culprit
- Regular examination of patients on AP drugs is required for recognition of tardive syndromes
- Postural tremor, parkinsonism and akathisia usually remit on removal of offending drug

Reading

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