

Drug-Induced Movement Disorders

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ETIOLOGY

Dopamine-depleting drug **RESERPINE** can induce ACUTE AKATHISIA and DRUG-INDUCED PARKINSONISM.

D₂ receptor-blocking agents:

- 1) **METOCLOPRAMIDE, FLUNARIZINE, CINNARIZINE.**
- 2) **NEUROLEPTICS** (phenothiazines and butyrophenones)

TYPES

D₂ receptor-blocking agents can cause **extrapyramidal side effects** (due to D₂ blockade in nigrostriatal pathway):

Evolution of EPS:

4 hours: Acute dystonia
4 days: Akinesia
4 weeks: Akathisia
4 months: Tardive dyskinesia

A. Acute disorders:

1. ACUTE DYSTONIC REACTIONS, oculogyric crisis
2. ACUTE AKATHISIA (motor restlessness) – usually **reversible**. see p. Mov1 >>
3. DRUG-INDUCED PARKINSONISM – subacute; usually **reversible**; clinically cannot be distinguished from idiopathic Parkinson's disease. see p. Mov11 >>
4. NEUROLEPTIC MALIGNANT SYNDROME

B. Chronic disorders:

1. WITHDRAWAL EMERGENT SYNDROME
2. TARDIVE DYSKINESIA SYNDROMES (persistent dyskinesias):
 - 1) classic tardive dyskinesia (oral-buccal-lingual)
 - 2) tardive dystonia
 - 3) tardive akathisia see p. Mov1 >>
 - 4) tardive tics
 - 5) tardive myoclonus
 - 6) tardive tremor.

- **most common** with drugs that exhibit **weak anticholinergic activity** (**HALOPERIDOL, FLUPHENAZINE**).
- **less common** with:
 - a) drugs that exhibit **strong anticholinergic activity** (**THIORIDAZINE**).
 - b) **newer "atypical" agents** (**CLOZAPINE, RISPERIDONE**)!!!! - predominantly block D₄ receptors; almost free of motor side effects (except for ACUTE AKATHISIA).

ACUTE DYSTONIC REACTIONS

- dramatic severe twisting of limbs, trunk, neck, tongue, and face.
- occur within **first few days** (usually within 48 hours)* – idiosyncratic reaction.
 - *often seen following single parenteral dose of neuroleptics
- predominantly affect children and young adults (males > females).
- extremely frightening reactions (**oculogyric crises, opisthotonic posturing, torticollis**).
 - OCULOGYRIC CRISIS** – incapacitating dystonic conjugate upward eye deviation for minutes or hours.
- **self-limited** within 24 hours.
- **easily reversible with** anticholinergics (e.g. **BENZTROPINE** 1-2 mg IM; **DIPHENHYDRAMINE** 25-50 mg IM/IV).
 - dangerous **laryngeal dystonia** needs **LORAZEPAM / DIAZEPAM** (5-7.5 mg IM) & intubation.

NEUROLEPTIC MALIGNANT SYNDROME

- PREVALENCE (among patients receiving neuroleptics) < 2%; most commonly young adults.
- pathogenesis is not completely understood (believed to be **blockade of D₂ receptors**).
- associated with all groups of neuroleptics (esp. **high-potency** agents [**HALOPERIDOL, FLUPHENAZINE**] and **depot forms**), even **CLOZAPINE**.
- **men** > women 5-fold!
- can develop at **any time** during exposure to medication, but usually:
 - a) **within first 30 days** (≈ 0.5-3% of all patients) – idiosyncratic reaction.
 - b) after **dosage increase** (agitated male who received large and rapidly increased doses).
 - rare during maintenance treatment unless other condition such as dehydration, dopamine agonist withdrawal occurs.

CLINICAL FEATURES

TRIAD:

NMS is clinical diagnosis!

- 1) **HYPERTHERMIA** (40% have > 40°C) → chronic cerebellar syndrome.
- 2) **AUTONOMIC dysfunction** (e.g. pallor, diaphoresis out of proportion to temperature, blood pressure instability, tachycardia, pulmonary congestion, tachypnea).
- 3) **MOVEMENT disorder** (e.g. **akinesia**, “lead pipe” **rigidity, dystonia**) → CK↑, myoglobinuria → renal failure.

+ **altered mental status** resembling **catatonia** (eventually leading to **stupor** or **coma**).

- full-blown syndrome develops rapidly over 1-2 days after period of gradual progressive rigidity.
- ≈ 40% patients develop life threatening medical complications (MI, aspiration pneumonia, respiratory failure, acidosis, rhabdomyolysis → renal failure, DIC) - **mortality 5-30%!**

DIAGNOSIS

- laboratory: **myoglobinuria**, elevation of enzymes (**CK** [95%], aldolase, alkaline phosphatase, LDH, ALT, AST), PMN **leukocytosis** [98%], hypocalcemia, hypomagnesemia, low iron, proteinuria.
- diagnosis confirmation - **muscle biopsy** (abnormal augmentation of in vitro muscle contraction after pretreatment with halothane).
- head CT and lumbar puncture are done if CNS cause is suspected.

TREATMENT

- in ICU:

- stop immediately offending medication (most often HALOPERIDOL).
- intravenous **rehydration & cooling**, antipyretics.
- maintain blood pressure; monitor serum [K⁺].
- **dopamine agonist BROMOCRIPTINE** (2.5-7.5 mg PO tid) or another dopamine agonist (LEVODOPA, AMANTADINE).
- **DANTROLENE** (1-3 mg/kg IV q4-6h)!!!
- **nondepolarizing muscle relaxants**.
N.B. rigidity can be blocked with muscle relaxants (vs. malignant hyperthermia)!
- supportive measures (ABC, evaporative cooling, alkaline diuresis); **HEPARIN** (to avoid pulmonary embolism).

- recovery generally occurs over 2-3 weeks (most survivors recover completely).
- NMS recurrence on restart ≈ 33%; if necessary to continue neuroleptics – switch to **atypical agent**.

TARDIVE DYSKINESIA (TD) syndromes

- most feared complications because persistent and often permanent* (persists after discontinuation of therapy and is **irreversible** in 66% patients – due to increased number of D receptors in response to long-term D receptor blockade).

* treatment with neuroleptics requires signed informed consent because of risk of irreversible tardive dyskinesia! (such consent is not required for antidepressants)

Classic tardive dyskinesia, tardive dystonia, and tardive akathisia may occur together!

- appears after several months ÷ years of treatment (**never before 3 months**; monitor patient at least q6mo with *Abnormal Involuntary Movement Scale*).
- produced to same degree and frequency by all neuroleptics when used in equieffective doses!???
- once TD has appeared, its peak severity is reached rapidly and is often maintained.

Abnormal Involuntary Movement Scale:

1. Observe gait on way into room.
2. Have patient remove gum or dentures, if ill-fitting.
3. Determine if patient is aware of any movements.
4. Have patient sit on firm, armless chair with hands on knees, legs slightly apart, and feet flat on floor. Now and throughout examination, look at entire body for movements.
5. Have patient sit with hands unsupported, dangling over knees.
6. Ask patient to open mouth twice. Look for tongue movements.
7. Ask patient to protrude tongue twice.
8. Ask patient to tap thumb against each finger for 15 sec with each hand. Observe face and legs.
9. Have patient stand with arms extended forward.

Rate each item on 0 to 4 scale for greatest severity observed. 0 = none; 1 = minimal, may be extreme normal; 2 = mild; 3 = moderate; 4 = severe. Movements that occur only on activation merit 1 point less than those that occur spontaneously.

Facial and oral movements	Muscles of facial expression	0 1 2 3 4
	Lips and perioral area	0 1 2 3 4
	Jaw	0 1 2 3 4
	Tongue	0 1 2 3 4
Extremity movements	Arms	0 1 2 3 4
	Legs	0 1 2 3 4
Trunk movements	Neck, shoulders, hips	0 1 2 3 4
Global judgments	Severity of abnormal movements	0 1 2 3 4
	Incapacitation due to abnormal movements	0 1 2 3 4
	Patient's awareness of abnormal movements	0 1 2 3 4
	(0 = unaware; 4 = severe distress)	

Classic TD (oral-buccal-lingual) see p. Mov1 >>

- prevalence increases with age and duration of treatment; more severe among **elderly women**.
- requires exposure for at least 6 months and may persist indefinitely.
N.B. tardive dyskinesia does not always occur!
- **time of onset is difficult to discern** because these drugs mask movements!
 - reducing dosage / discontinuing drug can unmask disorder.
 - reinstating drug can suppress movements.

N.B. for diagnosis of tardive dyskinesia, symptoms should have started while patient was **still taking D₂-blocking drug** or **less than 3 months after** discontinuing drug.

If oral dyskinesia is induced by **other types of drugs**, it is not, by definition, tardive dyskinesia!

Major differential diagnoses of ORAL DYSKINESIAS:

Clinical Signs	Classic Tardive Dyskinesia	Meige syndrome	Huntington disease
Type of involuntary movements	stereotypic	dystonic	choreic
Flowing movements	0	0	+++
Repetitive movements	+++	+	±
Sustained contractions	+	+++	±
Forehead chorea	±	±	++
Blepharospasm	+	+++	±
Movements of mouth	+++	+++	+
Masticatory muscles	+++	+++	±
Effect on:			
talking, chewing	±	+++	+
swallowing	0	++	+++
Platysma	±	+++	±
Nuchal muscles	+	++	±
Trunk, legs	++	0	+++
Akathisia	++	0	0
Motor impersistence (tongue, grip)	0	0	+++
Stuttering, ataxic gait	±	0	+++

Clinical Signs	Classic Tardive Dyskinesia	Meige syndrome	Huntington disease
Postural instability	0	0	+++
Effect of:			
antidopaminergics	decrease		
anticholinergics	increase	decrease	±

Tardive dystonia

- younger individuals have more severe generalized form.
- begins focally in **face** (blepharospasm, oromandibular dystonia) or **neck** (retrocollis); may spread to **arms** (typically rotated internally, elbows extended, and wrists flexed) and **trunk** (arches backward); legs are affected infrequently.
- resolves spontaneously in children or young adults but frequently persists in older individuals.

N.B. **Wilson disease** must be excluded in any patient with *psychiatric symptoms + dystonia!*

TREATMENT OF TARDIVE DYSKINESIAS

Treatment of established disorder is often unsatisfactory!

- 1) if possible, **stop offending drug** (dyskinesia may slowly subside in months or years); if offending drug is required **change to atypical neuroleptic** or **increase dosage** (to suppress dyskinesia - temporary improvement by increasing dopamine-receptor blockade, however, this ultimately causes further progression of TD).
- 2) add dopamine-depleting drug (**RESERPINE, TETRABENAZINE**) - most effective drugs for symptomatic treatment!!!; with time, may be tapered and discontinued; **VALBENAZINE** (Ingrezza®) – FDA approved for tardive dyskinesia.
- 3) **TARDIVE DYSTONIA** may be treated with **anticholinergics!**
vs. **TARDIVE DYSKINESIA** and **AKATHISIA** – with **cholinergics**.

N.B. TD may worsen following neuroleptic withdrawal or addition of anticholinergic drug! H: dopamine depleters.

PROPHYLAXIS OF TARDIVE DYSKINESIAS

- 1) use neuroleptics only when necessary and with minimal effective dosages.
- 2) interrupt long-term use with periodic DRUG HOLIDAYS:
 - to determine whether treatment is still required;
 - to unmask incipient dyskinesias.
- 3) **anticholinergic drug** (**BENZTROPINE, TRIHEXYPHENIDYL, PROCYCLIDINE, DIPHENHYDRAMINE**) - fewer extrapyramidal effects in exchange for side effects of parasympathetic blockade; may be used with neuroleptics prophylactically.

WITHDRAWAL EMERGENT SYNDROME

- **variant of tardive dyskinesia.**
- occurs in children upon sudden cessation of chronic drug use.
- *flowing** movements ≈ Sydenham chorea.
*rather than *repetitive* (as in classic tardive dyskinesia).
- syndrome is self-limiting (may take weeks to resolve).
- H: reintroduce drug and then taper dosage slowly.

BIBLIOGRAPHY for ch. “Movement disorders, Ataxias” → follow this [LINK >>](#)