Drug-Induced Movement Disorders

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Etiology

1. **Acute dystonic reactions**: oculogyric crisis
2. **Acute akathisia** (motor restlessness) – usually reversible.
3. **Drug-induced parkinsonism** – subacute; usually reversible; clinically cannot be distinguished from idiopathic Parkinson’s disease.

Etiology

Types

D2 receptor-blocking agents

1. **Metoclopramide**, **Phenazine**, **Cinnarizine**
2. **Neuroleptics** (phenothiazines and butyrophenones)

Types

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

A. **Acute disorders**

1. **Acute dystonic reactions**: oculogyric crisis
2. **Acute akathisia** (motor restlessness) – usually reversible.
3. **Drug-induced parkinsonism** – subacute; usually reversible; clinically cannot be distinguished from idiopathic Parkinson’s disease.

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 (THEORIDAZINE).
  b) newer “atypical” agents (CLOZAPINE, RISPERIDONE)!!! - predominantly block D3 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).
- **Oscillopsia crisis** – incapacitating dystonic conjugate upward eye deviation for minutes or hours.
- **Self-limited** within 24 hours.
- usually reversible with anticholinergics (e.g. BENZTROPINE 1-2 mg IM; DIPHENHYDRAMINE 25-50 mg IM/IV).
- dangerous laryngeal dystonia needs LORAZEPAM / HAZEPAM (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**

**Triage**

NMS is clinical diagnosis!

1. **Hypertension** (40% have > 40°C) – chronic cerebellar syndrome.
2. **Autonomic dysfunction** (e.g. palla, 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, D2C — mortality 5-30%)

**DIAGNOSIS**
- laboratory: myoglobinuria, elevation of enzymes (CK [95%], aldolase, alkaline phosphatase, LDH, ALT, AST), PMN leukocytosis [99%], hypocalcemia, hypomagnesemia, low iron, protnitiurna.
- diangosis 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 antagonist BROMOCRIPTINE (2.5-7.5 mg PO tid) or another dopamine antagonist (LEVODOPA, AMANTADINE),
  - DANTROLENE (1-3 mg/kg IV q4-hh)!!
  - nondepolarizing muscle relaxants
- N.B. rapidly 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 4-6 months 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 gait or drapes, 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 snap 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
  - Lids and perioral area
  - Jaw
  - Tongue
  - Extremity movements
  - Arms
  - Legs
  - Trunk movements
  - Neck, shoulders, hips
  - Global judgments
    - Severity of abnoraml movements
    - Incapacitation due to abnormal movements
    - Patient's awareness of abnormal movements

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.
  - reversing drug can suppress movements.

N.B. for diagnosis of tardive dyskinesia, symptoms should have started while patient was still taking.

**Dop-blocking drug or less than 6 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**

<table>
<thead>
<tr>
<th>Clinical Signs</th>
<th>Classic Tardive Dyskinesia</th>
<th>Meige syndrome</th>
<th>Huntington disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of involuntary movements</td>
<td>stereotopic</td>
<td>dystonic</td>
<td>choreic</td>
</tr>
<tr>
<td>Flowing movements</td>
<td>0</td>
<td>0</td>
<td>+++</td>
</tr>
<tr>
<td>Repetitive movements</td>
<td>+++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Sustained contractions</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Forehead chorea</td>
<td>±</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Blepharospasm</td>
<td>+</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Movements of mouth</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Masticatory muscles</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>

**Effect on:**
- talking, chewing | ± | +++ | + |
- swallowing | 0 | ++ | +++ |
- Platyoma | ± | ± | ± |
- Nuchal muscles | ± | + | + |
- Trunk, legs | ± | 0 | +++ |
- Akathisia | ± | ± | ± |
- Motor impersistence (tongue, grip) | 0 | 0 | +++ |
- Stuttering, ataxic gait | ± | 0 | +++ |

**Terminology**
Diag. Induced Movement Disorders
Mov 25 (2)
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 (torticollis); 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, TETRAHYDRONAZINE)** - 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, TRIEXYPHENIDYL, 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.
- 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 >>](#)