Medication-induced movement disorders
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**Introduction**
- Medication-induced movement disorders are most frequently associated with drugs that block dopamine (D2) receptors. Older (first generation) antipsychotics are more likely to cause these disorders, as newer second generation antipsychotics (atypicals) block dopamine receptors to a much lesser degree.
- The three most common drug-induced movement disorders are *parkinsonism, acute dystonia, and acute akathisia*.
- Antipsychotics with high dopamine blockade include fluphenazine, perphenazine, thiothixene, haloperidol, droperidol, pimozide, risperidone, and aripiprazole (as a partial agonist).

**I. Neuroleptic-induced parkinsonism**

**Presentation**
- Symptoms include:
  - muscle stiffness (“lead pipe” rigidity),
  - cogwheel rigidity,
  - shuffling gait,
  - stooped posture,
  - drooling, and
  - tremor (usually a course, regular tremor as opposed to typical pill-rolling type).
- Symptoms typically occur within 5-90 days after treatment initiation.
- Patients most at risk include elderly patients and females.

**Etiology**
- Neuroleptic-induced parkinsonism is caused by D2-receptor blockade in the caudate at the termination of nigrostriatal dopamine neurons. It can occur with any antipsychotics, but especially with high-potency agents with low levels of anticholinergic activity (such as haloperidol).

**Differential Diagnosis**
- Idiopathic Parkinson’s disease
- Organic Parkinsonism (tumors, toxins, hydrocephalus, degenerative disease, etc.)
- Depressive disorders
- Catatonia

**Treatment**
- First-line treatment is with **anticholinergic agents** (including benztropine, amantadine, diphenhydramine). Withdraw after 4-6 weeks to assess whether tolerance towards parkinsonian effects has developed. (50% of patients will require continuing treatment.)
- After discontinuation of antipsychotic, parkinsonism symptoms can continue for up to 2 weeks in adult patients and 3 months in elderly patients. Anticholinergic agent should be continued as needed.

**II. Neuroleptic malignant syndrome (NMS)**

**Presentation**
- NMS is a life-threatening complication that can occur at any time during treatment with antipsychotics. It presents with
  - muscular rigidity and dystonia,
  - hyperthermia,
  - diaphoresis,
  - hypertension,
  - tachycardia,
  - akinesia (loss of voluntary movement),
  - mutism,
  - obtundation, and
  - agitation.
- Lab findings include
  - elevated WBC,
  - elevated CPK,
  - elevated LFT’s,
  - elevated plasma myoglobin, and
  - myoglobinuria.
- NMS occurs in 0.01-0.02% of patients treated with antipsychotics. Risk factors include male gender, younger patients, and high potency neuroleptics (such as haloperidol).
- Symptoms evolve over **24-72 hours** and untreated it can last 10-14 days.
Treatment
Treatment requires supportive medical treatment (cooling down the patient, aggressive IV hydration, maintenance of cardiorespiratory function in ICU setting, etc.) as well as pharmacotherapy.
- **Dantrolene** is a direct-acting skeletal muscle relaxant that can be given 1-2.5 mg/kg IV (repeated up to max dose of 10mg/kg/day) for 8 days, then PO for 7 days.

III. Medication-induced acute dystonia
**Presentation**
Dystonias are brief or prolonged contractions of muscles that result in obviously abnormal movements or postures, which can be painful and frightening. These include
- oculogyric crises (upward gaze),
- tongue protrusion,
- trismus (“lockjaw”),
- torticollis,
- laryngeal-pharyngeal dystonia (vocal cord dystonia),
- dystonic postures of limbs and trunk,
- blepharospasm (closure of eyelids), and
- glossopharyngeal dystonia.
Onset occurs early during treatment. Higher risk in **male gender, patients < 30 years old, and high-potency neuroleptics** (i.e. haloperidol).

**Etiology**
Mechanism is thought to be dopaminergic hyperactivity in the basal ganglia that occurs when CNS levels of the antipsychotic medication begins to fall in-between doses.

IV. Medication-induced akathisia
**Presentation**
Akathisia is a subjective feeling of restlessness, objective signs of restlessness, or both, that has been associated with a wide range of psychiatric medications (antipsychotics, antidepressants, and sympathomimetics). Signs and symptoms include:
- a sense of anxiety,
- inability to relax,
- jitteriness,
- pacing,
- rocking motions while sitting, and
- rapid alteration of sitting and standing.
Increased risk in **middle-aged women**. Typically occurs within 5-90 days of starting treatment.

**Bromocriptine** is a dopamine agonist that is given 2.5 mg through NGT q6-8h (max dose 40 mg total/day) for 10 days, then taper slowly.
**Amantadine** is a dopaminergic and anticholinergic agent that can be given 100 mg to 200 mg PO q12h.
**ECT** has also been used, although there are no large randomized control studies.

**Differential Diagnosis**
- Seizure disorder
- Tardive dyskinesia
- Neuroleptic malignant syndrome
- Conversion disorder
- Tetanus

**Treatment**
Symptoms can fluctuate spontaneously and respond to reassurance; this does not indicate that the movement is under conscious control. Dystonias can be prevented with prophylactic treatment, and acute dystonias are treated with IM or IV medications:
- **Benztropine** can be given 1-2 mg IM or IV for acute dystonia and 0.5-2 mg PO TID for prophylaxis.
- **Diphenhydramine** can be given 25-50 mg IM or IV for acute dystonia and 25 mg PO QID for prophylaxis.
- **Diazepam** 10 mg IV is also effective in acute dystonia.
- **Clonazepam** 1 mg PO BID is also effective in prophylaxis.

**Akathisia** is associated with poor treatment outcome.
V. Tardive dyskinesia

Presentation
Tardive dyskinesia (TD) is an abnormal, involuntary, irregular choreathetoid movement of the muscles of the head, limbs, and trunk that is a delayed effect from antipsychotic medications (rarely occurring until after 6 months of treatment). Symptoms can include:
- darting, twisting, protruding tongue movements,
- chewing and lateral jaw movements,
- lip puckering,
- facial grimacing,
- finger and hand clenching,
- torticollis,
- retrocollis,
- trunk twisting, and
- pelvic thrusting.

TD develops in 10-20% of patients treated with antipsychotics for > 1 year. Risk factors include female gender, children, elderly patients (>50 years), patients with brain damage, and patients with mood disorders.

Prevention entails using lowest effective antipsychotic dose and choosing an appropriate antipsychotic. Atypicals are less associated with TD. Clozapine is the only antipsychotic to have a very minimal risk and can potentially improve preexisting TD symptoms (it has a low D2 receptor affinity and high 5HT receptor antagonism).

Diagnosis is important and patients on antipsychotics should be examined regularly, preferably using an AIMS score.

Management of TD includes 1) consideration of dose reduction, 2) changing to another antipsychotic such as clozapine or an atypical, or 3) adding lithium, carbamazepine, or benzodiazepines to reduce symptoms.

Prognosis
5-40% of all TD cases eventually remit, with 50-90% of mild cases remitting. TD is less likely to remit in elderly patients.

Tardive dystonia and akathisia
In some patients, dystonia and akathisia symptoms can emerge late in the course of treatment and persist for months or years, despite drug dose reduction or discontinuation.

VI. Medication-induced postural tremor

Presentation
Tremors are rhythmic alterations in movement that are usually faster than one beat per second. Typically, tremors will decrease during relaxation and sleep, and increase with stress and anxiety.

Etiology
A range of psychotropic medications can cause tremor, including antipsychotics, lithium, stimulants, antidepressants, caffeine, and valproate.

Treatment involves four principles:
- Use the lowest possible dose of psychiatric medication.
- Patients should minimize caffeine intake in order to prevent tremor exacerbation.
- The psychiatric medication can be taken at bedtime to minimize daytime tremors.
- Beta-adrenergic receptor antagonists such as propranolol can be given to treat drug-induced tremors.

VII. Other medication-induced movement disorders

Nocturnal myoclonus
Nocturnal myoclonus consists of highly stereotypes, abrupt contractions of leg muscles during sleep to which patients are unaware. It is a rare side effect of SSRI’s, and causes frequent awakenings, unrefreshing sleep, and daytime sleepiness. Possibly effective treatment includes benzodiazepines, levodopa, quinine, and opioids.

Restless leg syndrome (RLS)
In RLS, patients feel deep creeping sensations in their calves when sitting or lying down. These are rarely painful but are relentless and cause irresistible urge to move the legs, thus interfering with sleep. This is also a rare side effect of SSRI’s. Treatment includes leg massage and ropinirole or pramipexole (dopamine receptor agonists).