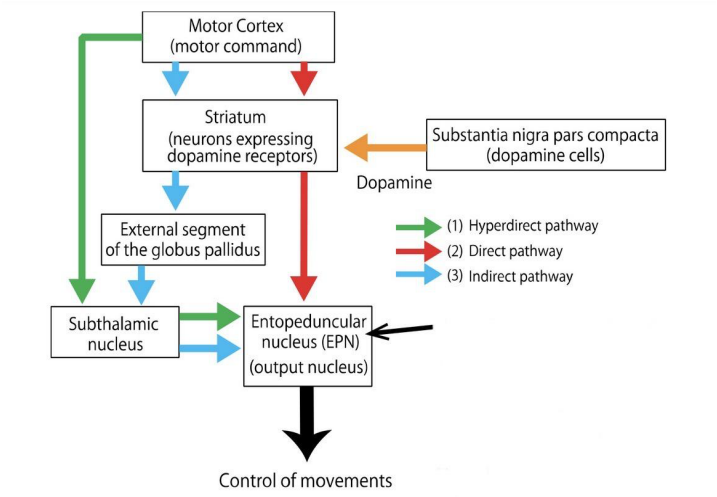
Clinical Pharmacology & Toxicology Pearl of the Week

Drug Induced Movement Disorders



Chiken, Satomi, 2015

Case: A 61 year old female who presented to hospital with increasing confusion admitted to neurology with a diagnosis of encephalitis who developed neck stiffness and increased tone while in hospital with exposure to haloperidol four days before symptom onset. The attending team was wondering if there were any medications that could account for her symptoms.

Physiology:

- Dopamine plays a major role in motor planning through the nigrostriatal pathway. The direct pathway is involved in the facilitation of wanted movements via D1 receptor in the caudate nucleus synapsing onto cells in the substantia nigra pars reticulata and internal segment of the globus pallidus which ultimately project to the thalamus.
- The indirect pathway involves D2 receptor activity in the caudate nucleus and putamen which synapse onto the cells in the external segment of the globus pallidus which then projects to the substantia nigra pars reticulata via the excitatory subthalamic nucleus. The ultimate effect of this pathway is inhibition of unwanted movements.
- Acetylcholine also plays an important role in the modulation of movement as well. The laterodorsal and pedunculopontine tegmental nuclei provide inputs to dopaminergic neurons. Muscarinic receptors have been shown to result in both excitation and inhibition of dopamine activity in the basal ganglia which suggests a complex modulatory role of acetylcholine.
- Ultimately, disruptions in the dopamine and acetylcholine balance are thought to play a role in the pathogenesis of movement disorders, with the hypothesis that dopamine deficiency and acetylcholine excess may lead to rigid dystonic states.
- There is also important GABA related neurotransmission that plays a role in these pathways.
- Medications that affect any one of these systems can lead to movement disorders.

Drug induced movement disorders can be classified based on the temporal time course, the type of reaction, or the type of pharmacological agent involved. The table below presents them based on the type of reaction arranged by time to onset.

Disorder	**Characteristics**	**Offending Medications**	**Time to Onset**	**Treatments**
Acute dystonic reactions	Characterized by involuntary contractions of muscles of the extremities, face, neck, abdomen, pelvis, or larynx in either sustained or intermittent patterns that lead to abnormal movements or postures	Dopamine receptor blockers. Reported with SSRIs, opioids, Methylphenidate, rivastigmine, albendazole, gabapentin, cetirizine, foscarnet, quinidine, and during or shortly after general anesthesia using propofol or fentanyl	50% within 48 hours and 90% within 5 days	Anticholinergics (diphenhydramine 25-50 mg IV or benztropine 1-2 mg IV)
Akathisia	Sense of internal restlessness, irritability and tension without necessarily manifesting with physical signs	Dopamine receptor blockers	Typically acute (a few days), subacute, to tardive phenomenon	Akathisia often improves following cessation of the offending drug. Can also be treated with anticholinergics, beta blockers, and benzodiazepines.
Tremor	Typically symmetrical. Can be intentional, postural, or resting depending on type of drug	SSRIs, lithium, TCAs, antiepileptics (valproate), cyclosporine, amiodarone, β-adrenergic agonists, tacrolimus, theophylline	Typically begins shortly after start of medication	Stop offending drug or reduce the dose. Propranolol can be trialed
NMS	Fever, autonomic instability, altered mental state, rigidity and other movement disorders including tremor, dystonia and myoclonus	Dopamine receptor blockers	Can develop soon after first dose or at any time after prolonged treatment. Usually 5-10 days after a neuroleptic has been started	Discontinue agent Supportive care Bromocriptine Dantrolene Benzodiazepines

Disorder	Characteristics	Offending Medications	Time to Onset	Treatments
Drug Induced Parkinsonism	Classically described as bilateral and symmetric parkinsonism without tremor at rest, but can present with unilateral symptoms and tremor making it difficult to distinguish from parkinsonism	Most commonly first generation antipsychotics and antiemetics such as metoclopramide, levosulpiride, and domperidone. Less commonly second generation antipsychotics, valproate acid, SSRIs	50-70% of patients will develop symptoms within 1 month and 90% within 3 months	Switch to a med with less EPS associated with it. Usually resolves within weeks to months after stopping the offending drug; however, parkinsonism may persist or progress in 10-50% of patients. Limited evidence for anticholinergic medications and amantadine
Tardive Dyskinesia	Spectrum of TD includes involuntary movements of the tongue, jaw, trunk, or extremities, and may be choreiform, athetoid, or stereotypic in nature	Dopamine receptor blockers	Typically exposure within 6 months of onset of symptoms, rarely up to 12 months	Use atypical antipsychotics where possible Tetrabenazine Amantadine Propranolol

Case resolution:

The haloperidol was stopped and the patient recovered. There was no need for any specific treatment such as anticholinergic agents to reverse the acute dystonia. Advice to avoid other dopamine blockers such as metoclopramide was also provided.

The Calgary Clinical Pharmacology physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA. Clinical Pharmacology consultation service is also available through the Netcare e-referral process and through Calgary Zone Specialist Link. Click HERE for more details.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK).

References:

1. Chiken, Satomi, et al. "Dopamine D1 receptor-mediated transmission maintains information flow through the cortico-striato-entopeduncular direct pathway to release movements." *Cerebral Cortex* 25.12 (2015): 4885-4897

2. Stahl SM, Davis KL, Berger PA. The neuropharmacology of tardive dyskinesia, spontaneous dyskinesia, and other dystonias. J Clin Psychopharmacol. 1982 Oct;2(5):321-8. PMID: 6127351.

3. Burkhard, Pierre R. "Acute and subacute drug-induced movement disorders." *Parkinsonism & related disorders* 20 (2014): S108-S112.

4. Aquino, Camila Catherine H., and Anthony E. Lang. "Tardive dyskinesia syndromes: current concepts." *Parkinsonism & related disorders* 20 (2014): S113-S117

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