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Extrapyramidal Side Effects

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Continuing Education Activity

Extrapyramidal side effects, sometimes referred to as medication-induced movement disorders, are significant adverse effects typically caused by antipsychotic medications and other dopamine receptor-blocking agents. While centrally acting dopamine receptor-blocking agents, such as antipsychotic medications, are the most common medications associated with extrapyramidal side effects, almost all antipsychotic medications can cause one or more of these effects in a dose-dependent manner. Acute manifestations of these adverse effects include but are not limited to dystonia, akathisia, tremor, and parkinsonism; typical chronic manifestations include tardive dyskinesia, tardive akathisia, and tardive dystonia. Extrapyramidal side effects can cause stigma and distress in patients and are associated with treatment nonadherence.

This educational activity for healthcare professionals reviews the current understanding of the neurobiology of extrapyramidal symptoms, elucidates the causal role of antipsychotic medications, explores treatment modalities, and emphasizes the pivotal role of interdisciplinary teams when delivering care to individuals with extrapyramidal side effects.

Objectives:

- Identify the signs and symptoms of various types of extrapyramidal symptoms.
- Develop strategies to mitigate the risk of extrapyramidal symptoms.
- Select appropriate treatments for extrapyramidal symptoms.
- Collaborate with the interprofessional team to educate, screen, treat, and monitor patients taking antipsychotic medications for extrapyramidal symptoms to improve patient outcomes.

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Introduction

Extrapyramidal side effects, also referred to as medication-induced movement disorders, are common adverse drug reactions caused by antipsychotic medications and other dopamine D2 receptor-blocking agents. These effects were first described in 1952 after chlorpromazine was recognized to produce side effects resembling Parkinson disease.[1] Acute manifestations include dystonia, akathisia, tremor, and parkinsonism, whereas chronic manifestations include tardive dyskinesia, tardive akathisia, and tardive dystonia. Extrapyramidal symptoms may be hyperkinetic or hypokinetic (parkinsonian) movement disorders, with varying pathophysiology.[2] These symptoms may arise due to medication use, but they can also occur without any medication exposure. Extrapyramidal symptoms are debilitating

and interfere with social functioning and communication, motor tasks, and activities of daily living. As a result, individuals may experience an impaired quality of life, treatment nonadherence, increased morbidity, caregiver burden, and increased utilization of healthcare resources.[3][4]

Movement disorder specialists contend that the term *extrapyramidal* is outdated and discourages accurate diagnosis. They argue that it is more helpful to describe the observed clinical motor phenomena, pursue the differential diagnosis, ascertain whether the symptoms are related to a primary motor disorder or are medication-induced, and manage accordingly.

The spectrum of acute symptoms in extrapyramidal symptoms is distressing and can include painful torticollis, oculogyric crisis, slurred speech, drooling, and trouble chewing or swallowing. If left untreated, acute symptoms may cause dehydration, infection, pulmonary embolism, rhabdomyolysis, respiratory stridor, and obstruction.[5][6][7][8]

Etiology

Centrally acting dopamine receptor-blocking agents, such as antipsychotic medications, are the most common medications associated with extrapyramidal symptoms. Almost all antipsychotic medications can cause extrapyramidal symptoms in a dose-dependent manner.[9]

Although extrapyramidal symptoms are less common with second-generation antipsychotic medications, the underlying reason for this remains unclear. Some theories suggest that second-generation antipsychotic medications exhibit stronger binding to serotonin receptors compared to dopamine receptors, possess partial agonism, demonstrate mesolimbic selectivity, bind loosely to receptors, and have anticholinergic properties.[10][11][12][9]

According to *The American Psychiatric Association Textbook of Psychopharmacology* (Sixth Edition), extrapyramidal symptoms can be caused by a variety of medications, as outlined below:

- Acute dystonic reactions can be caused by dopamine receptor-blocking medications, selective serotonin reuptake inhibitors (SSRIs), mood stabilizers or antiepileptic medications, opioids, methylphenidate, rivastigmine, and gabapentin.
- Akathisia can be caused by dopamine receptor-blocking medications, antidepressants, mood stabilizers or antiepileptic medications, buspirone, lithium, and tetrabenazine.
- Parkinsonism, including tremors, can be caused by dopamine receptor-blocking medications; dopamine-depleting agents, mood stabilizers or antiepileptic medications; antidepressants, such as SSRIs or monoamine oxidase inhibitors; and lithium.
- Tardive movements can be caused by dopamine receptor-blocking medications and SSRIs.
- Myoclonus and asterixis can be caused by all types of antidepressants, clozapine and other antipsychotic medications, and mood stabilizers or antiepileptic medications.

Other agents that block central dopaminergic receptors have also been identified as causes of extrapyramidal symptoms, including antiemetics such as metoclopramide, droperidol, and prochlorperazine.[5][13] As stated above, lithium,[14] SSRIs,[15] stimulants,[16] and tricyclic antidepressants can induce extrapyramidal symptoms.[15][17] [15] In rare cases, antivirals, antiarrhythmics, and valproic acid have been implicated in medication-induced movement disorders.[18]

Epidemiology

Rates of extrapyramidal symptoms are dependent on the class of medication administered. In a study involving institutionalized patients with schizophrenia, first-generation antipsychotic medications were associated with

extrapyramidal symptoms in 61.6% of patients.[19] Rates of extrapyramidal symptoms with the use of second-generation antipsychotic medications are lower, with clozapine having the lowest risk and risperidone the highest risk in this class.[20]

Antiemetics that are dopamine D2 receptor blockers have an incidence of extrapyramidal symptoms between 4% and 25% for metoclopramide [21][22][23] and between 25% and 67% for prochlorperazine.[24][25]

Risk factors for extrapyramidal symptoms include a history of prior extrapyramidal symptoms and high medication doses.[26] Older women are more susceptible to medication-induced parkinsonism and tardive dyskinesia,[27] [28] whereas young men are more likely to have dystonic reactions.[29]

In a meta-analysis, tardive syndromes were present in 30% of individuals treated with first-generation antipsychotic medications and 21% of individuals treated with second-generation antipsychotic medications.[30]

Pathophysiology

The mechanisms of various extrapyramidal symptoms are unknown. Extrapyramidal symptoms are believed to be the result of the blockade of dopaminergic D2 receptors within the mesolimbic and mesocortical pathways of the brain by antipsychotic and other medications. Dopamine receptor blockade in the caudate nucleus and other basal ganglia may also contribute significantly to extrapyramidal symptoms.[31][32]

Extrapyramidal symptoms are correlated with association rates to the D2 receptor, not dissociation rates. By measuring the kinetic binding properties of first-generation and second-generation antipsychotic medications, extrapyramidal symptoms were predicted by a rebinding model that contemplates the microenvironment of postsynaptic D2 receptors and integrates both association and dissociation rates in calculating the net rate of reversal of dopamine receptor blockade.[33]

History and Physical

Assessing extrapyramidal symptoms requires a history of the onset and course of the abnormal movements, especially relative to the timing of exposure to the medication. Information about current and previous medications and family history is crucial.

Extrapyramidal symptoms present with a broad spectrum of manifestations on physical examination.

Acute dystonia occurs within 48 hours of drug exposure in 50% of cases and within 5 days in 90% of cases.[34] On physical examination, dystonia manifests with involuntary muscle contractions resulting in abnormal posturing or repetitive movements. It may affect muscles in different body parts, including the back and extremities (opisthotonus), neck (torticollis), jaw (trismus), eyes (oculogyric crisis), abdominal wall, pelvic muscles (tortipelvic crisis), and facial and tongue muscles (buccolingual crisis).[6]

During a physical examination, dystonia presents as involuntary muscle contractions, which lead to abnormal postures or repetitive movements. This condition can impact various muscle groups throughout the body, including those in the back and limbs (causing opisthotonus), the neck (resulting in torticollis), the jaw (leading to trismus), the eyes (manifesting as an oculogyric crisis), the abdominal wall, the pelvic muscles (causing a tortipelvic crisis), and the facial and tongue muscles (resulting in a buccolingual crisis).

The healthcare provider must evaluate these patients for pain and acute laryngeal dystonia, which can result in life-threatening airway obstruction with difficulty breathing, swallowing, and speaking.

Acute akathisia is characterized by a subjective feeling of internal restlessness and a compelling urge to move. In some but not all cases, this leads to the objective observation of repetitive movements comprising leg crossing, swinging, or shifting from one foot to another.[28] The onset is typically within 4 weeks of starting or increasing the

medication dosage. Due to its often vague and nonspecific presentation of nervousness and discomfort, akathisia is often misdiagnosed as anxiety, restless leg syndrome, or agitation. In an attempt to treat these incorrect diagnoses, the healthcare provider may subsequently increase antipsychotic medication or other offending medication, further exacerbating akathisia.[28][35] This failure to correctly diagnose can be detrimental as the severity of akathisia is linked to suicidal ideation, aggression, and violence.[36] The healthcare provider must also note that withdrawal akathisia may occur with discontinuation or dose reduction of antipsychotic medication and is typically self-limited for up to 6 weeks.[28]

Medication-induced parkinsonism presents as tremors, rigidity, and slowing of motor function in the truncal region and extremities. The classic appearance is an individual with masked facies, stooped posture, and a slow shuffling gait. Gait imbalance and difficulty rising from a seated position are often noted.[18][37]

Tardive dyskinesia manifests as involuntary choreoathetoid movements affecting orofacial and tongue muscles and, less commonly, the trunk and extremities. Although symptoms are typically not painful, they may impede social interaction and cause difficulty in chewing, swallowing, and talking.[38]

Evaluation

In most cases, laboratory and imaging tests are not required for the diagnosis of extrapyramidal symptoms, as the condition is primarily clinical and based on a detailed history and physical examination.

Treatment / Management

When initiating antipsychotic medications, it is crucial to obtain a baseline screening and routine follow-up screening using validated scales such as the Abnormal Involuntary Movement Scale, the Maryland Psychiatric Research Center involuntary movements scale, the Extrapyramidal Symptoms Rating Scale, or the Barnes Akathisia Rating Scale.[39]

Acute dystonic reactions are treated by discontinuing the offending medication. An intramuscular injection of 1-2 mg of benztropine provides rapid relief of an acute dystonic reaction, and additional injections may be necessary. The medication causing the reaction should be avoided, and a different medication should be substituted. When starting a new antipsychotic medication, an anticholinergic medicine such as benztropine can be used for the first week of treatment and then tapered slowly to prevent an acute dystonic reaction.

Laryngeal and pharyngeal dystonic reactions may cause respiratory arrest, and the healthcare provider must assess to see if an emergency airway intervention and intravenous treatment with anticholinergic medication are necessary.

In cases of tardive dystonia, additional treatment options include benzodiazepines; botulinum toxin for facial dystonia;[40][41] muscle relaxants, such as baclofen;[41] and dopamine-depleting agents, such as tetrabenazine;[41] For refractory cases, advanced interventions such as consideration of deep brain stimulation or pallidotomy should be considered.[41][42]

Strategies for treating akathisia include stopping or reducing the dosage of the offending medication and switching to clozapine, olanzapine, or quetiapine.[43] Additional strategies specific to akathisia include administering an ß-blocker (propranolol) or agents with marked postsynaptic serotonin 5-HT_{2a} receptor antagonism, such as ritanserin, cyproheptadine, trazodone, mianserin, or mirtazapine.

Of this group, 7.5 mg or 15 mg of mirtazapine once daily has shown the greatest efficacy in alleviating akathisia symptoms.[44][45][46]

Medication-induced parkinsonism is managed by discontinuing or reducing the dosage of the causative medication, switching to another medication less likely to cause parkinsonian symptoms, and administrating antiparkinsonian medications, including amantadine, anticholinergic medications, L-dopa, and selegiline.[37]

Tardive dyskinesia and other tardive syndromes are treated by gradually tapering or discontinuing the causative medication. There may be transient worsening of symptoms during withdrawal of the causative medication. Anticholinergic medications and antiparkinsonian medications should be discontinued, as they may worsen tardive dyskinesia.[47] Patients may be switched to second-generation antipsychotic medications such as quetiapine or clozapine with a lower risk of tardive movements. Dopamine-depleting medications known as vesicular monoamine transporter 2 (VMAT2) inhibitors are the first medications approved by the Food and Drug Administration to treat tardive syndromes. These medications include valbenazine and deutetrabenazine.[48] Tetrabenazine was a VMAT2 inhibitor approved for dyskinesias in Huntington's disease and has been used off-label for tardive syndromes.[49][50]

Studies on prophylactic anticholinergic medications to prevent or reduce extrapyramidal symptoms have been performed. Authors have cautioned that prophylactic anticholinergic medications have distressing peripheral adverse effects, such as dry mouth, urinary disturbances, and constipation, and undesirable central effects, such as cognitive dysfunction and delirium.[51] This long-term prophylactic administration of anticholinergic medications in schizophrenia patients taking antipsychotics may worsen underlying cognitive impairment and subsequently worsen the quality of life.[51] Thus, current guidelines generally do not recommend the prophylactic or long-term use of anticholinergics in schizophrenic patients taking antipsychotics. Decisions regarding their use should be made on a case-by-case basis with meticulous risk-benefit analysis. In the emergency medicine realm, a meta-analysis demonstrated that prophylactic diphenhydramine reduces extrapyramidal symptoms in patients receiving bolus administration of antiemetic (with a dopamine D2 antagonist effect), but not when the antiemetic was given as an infusion; thus, this meta-analysis concluded that the most effective strategy is to administer the antiemetic as an infusion without anticholinergic prophylaxis.

Differential Diagnosis

Extrapyramidal symptoms may be challenging to distinguish from other idiopathic movement disorders, making it essential to consult neurology if there is any uncertainty about the diagnosis.

- Muscle rigidity and tension are nonspecific symptoms that may be observed in neuroleptic malignant syndrome,[52] serotonin syndrome, and other movement disorders outside the scope of this topic.
- Chorea and athetosis are also present in Huntington's disease (diagnosed based on family history and genetic testing), Sydenham chorea (sequela of streptococcal infection), Wilson disease (adolescent-onset due to a defect in copper metabolism), and cerebrovascular lesions.[53][54]
- Bradykinesia, tremor, and rigidity may be the result of medication-induced parkinsonism but are difficult to distinguish from idiopathic Parkinson's disease. Any new case of parkinsonism should prompt a thorough neurologic evaluation. Dopamine transporter single-photon emission computed tomography scanning can be used to distinguish medication-induced parkinsonism from Parkinson disease.[55] In addition, restlessness in akathisia may also appear similar to anxiety and psychotic agitation.[56]
- If there is a decline in cognitive function from the previous level of performance, the individual should be assessed for major neurocognitive disorders, such as Lewy body disease, vascular disease, frontotemporal dementia, and Alzheimer's disease, which can all include parkinsonian signs.[54]
- Up to one-third of individuals with new-onset schizophrenia who are medication-naive may present with parkinsonian signs.[57]

Pertinent Studies and Ongoing Trials

Several receptors, including 5-hydroxytryptamine, glutamate, γ-aminobutyric acid, acetylcholine receptors, and norepinephrine, play a role in the development of schizophrenia. New antipsychotic medications that modulate these

symptoms may help reduce adverse effects and provide better treatments.

Prognosis

Extrapyramidal symptoms often resolve spontaneously or with the discontinuation of the causative medication. In cases where symptoms persist, pharmacologic interventions can provide significant relief.

Acute dystonic reactions are typically transient, but in late-onset and persistent tardive dystonia, symptoms can persist for years.[58] A study involving 107 cases of tardive dystonia reported that only 14% of patients achieved remission over a mean follow-up period of 8.5 years.[59]

Acute akathisia may spontaneously resolve or improve with appropriate medication; however, there are reported cases of tardive akathisia persisting over many years.[60]

Tardive dyskinesia may be unable to be reversed, with a cumulative persistence rate as high as 82% in a study involving patients with schizophrenia.[61]

Complications

Medication-induced laryngeal dystonia can result in life-threatening airway obstruction and requires emergency treatment.[62] Rhabdomyolysis is a rare complication of drug-induced dystonia, especially if prolonged dystonia is present.[63]

A dystonic storm is a life-threatening situation that manifests with fever, tachycardia, tachypnea, hypertensive crisis, diaphoresis, dysphagia, and respiratory failure.[64] Dystonic storm typically occurs in patients with a primary known dystonia such as Wilson disease, dystonic cerebral palsy, or DYT1 dystonia. Common triggers include infection and medication adjustments.[64]

Extrapyramidal symptoms in patients with schizophrenia are associated with poor compliance with antipsychotic medications, which may lead to relapse and increased morbidity.[3] Failure to correctly diagnose and treat akathisia is linked to self-harm, suicidal ideation, aggression, and violence.[36]

Consultations

Although some drug-induced movement disorders may last within a few minutes, others may last long-term and may lead to contractures, bony deformities, or significant motor impairment. Early neurological consultation is essential for diagnostic clarification and appropriate treatment.

Physical medicine and rehabilitation consultations can provide valuable therapeutic strategies to alleviate dystonia, including relaxation training, biofeedback, transcutaneous electrical nerve stimulation, and percutaneous dorsal column stimulation.[65] Physical therapy may help gait and mobility. Occupational therapy may assist with fine motor skills and activities of daily living. In patients with oromandibular or laryngeal involvement, speech therapy may assist with dysphagia and communication barriers.

When extrapyramidal symptoms are refractory to medication discontinuation or pharmacologic management, neurosurgical consultation may be beneficial to explore deep brain stimulation, thalamotomy, and pallidotomy.

Deterrence and Patient Education

Extrapyramidal symptoms are iatrogenically caused, and it is critical to inform patients of the risk of developing movement disorders from antipsychotic medications and other dopamine receptor-blocking agents. Patient and family education about abnormal movements should be provided to aid in recognition, and routine screening of patients on these medications is necessary for early intervention.

Pearls and Other Issues

Key thoughts to consider regarding extrapyramidal side effects include those below.

- Acute laryngeal dystonia caused by dopamine receptor-blocking medications can result in life-threatening airway obstruction and requires emergency treatment.
- Clozapine causes fewer extrapyramidal symptoms compared to other antipsychotic medications and is preferred in patients with psychosis and parkinsonian symptoms.[66]
- Approving VMAT2 inhibitors to treat patients with tardive dyskinesia is a significant advance.[67]
- Antipsychotic medications administered at doses higher than the minimum dosage that causes extrapyramidal symptoms are likely to increase adverse effects without additional therapeutic benefit.
- Although anticholinergic medications can be effective for medication-induced parkinsonism and dystonia, they are not recommended for tardive dyskinesia, akathisia, or neuroleptic malignant syndrome. Anticholinergic medications have a high adverse effect burden and should be prescribed for appropriate reasons at the lowest effective dose for only a limited period.[68]

Enhancing Healthcare Team Outcomes

Abouzaid and colleagues recently evaluated the economic burden of extrapyramidal symptoms due to atypical antipsychotics in patients with schizophrenia. During a 12-month follow-up period, 12.6% of patients experienced extrapyramidal symptoms. Compared to patients without extrapyramidal symptoms, those who did experience extrapyramidal symptoms had more schizophrenia-related and all-cause hospitalizations, schizophrenia-related emergency room visits, and higher schizophrenia-related and all-cause total healthcare, inpatient, and prescription medication costs.[69]

The interprofessional healthcare team enhances patient care and outcomes when addressing adverse reactions from antipsychotic medications and other dopamine receptor-blocking medications. Clinicians, advanced practice providers, nurses, pharmacists, and other allied healthcare professionals collaborate seamlessly to ensure a well-coordinated response to any abnormal movements. Clinicians provide expertise to routinely monitor, promptly diagnose, and treat abnormal movements, tailoring interventions based on the patient's needs. Nursing staff routinely monitor and observe for early signs of adverse reactions, immediately reporting any concerns. Pharmacists offer valuable insights into medication management. Effective communication and collaboration within the team are fundamental, allowing for a swift and comprehensive response to minimize patient harm and optimize outcomes. This coordinated effort ensures that patient safety remains at the forefront of medication management.

Review Questions

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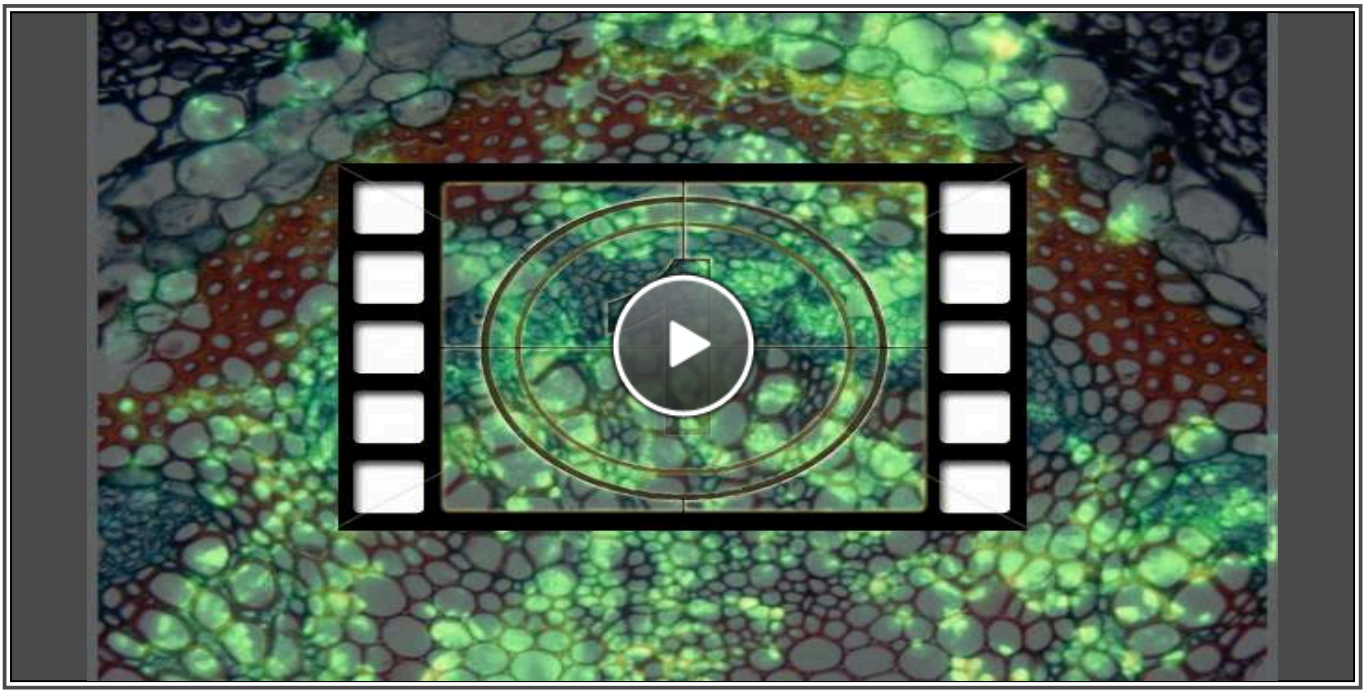
Figures



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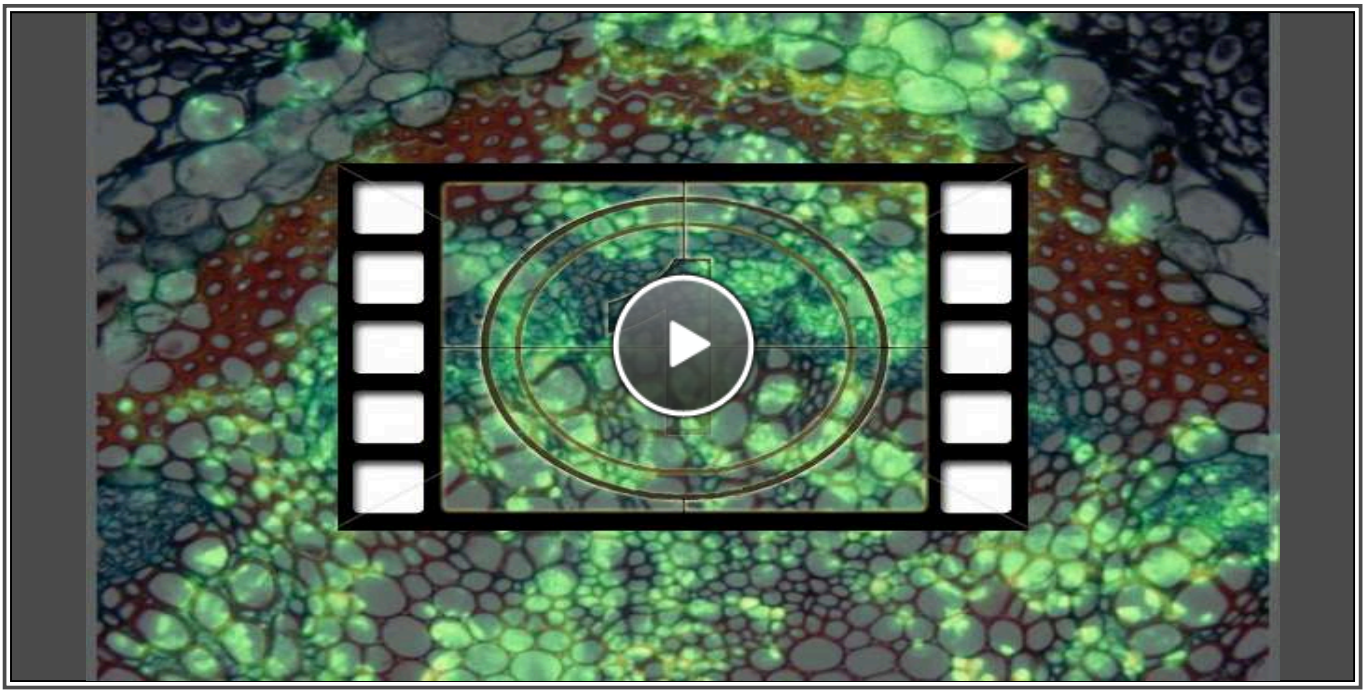
Parkinson Gait, Involuntary Movement, Festinant Gait, Video. This video describes different gaits and involuntary movements. Contributed by RS Kumar, MD



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Simulation of Cogwheel Rigidity, Parkinson's Disease, Tremor, Stop and Go effect during a range of motion maneuver Contributed by Dr. Raju S. Menon (https://www.youtube.com/watch?v=8xxe2WWWoYI)

Shuffling Gait Seen in Parkinson Disease. This image illustrates the shuffling gait characteristic of Parkinson disease. Contributed by S Bhimji, MD

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