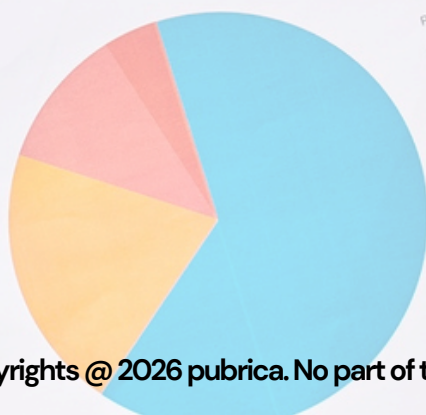


# CASE REPORTS

## DRUG-INDUCED PARKINSONISM: A CASE REPORT

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## Drug-induced parkinsonism: A case report

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### Abstract

#### Introduction

Drug-induced parkinsonism (DIP) is characterized by the emergence of parkinsonian symptoms following exposure to dopamine-blocking agents. Symptoms typically appear within days to weeks of treatment initiation, with nearly 90% of cases occurring within the first three months. Long-acting injectable (LAI) antipsychotics, including paliperidone, are widely used in psychiatric practice; however, their prolonged pharmacokinetic profile may increase the risk of sustained adverse effects.

#### Case presentation

A 68-year-old White man with a psychiatric history of bipolar I disorder versus cyclothymic disorder presented with pressured speech, flight of ideas, distractibility, delusions, and disorganized thinking. He was initially treated with risperidone and subsequently cross-tapered to olanzapine due to suboptimal response. divalproex was also initiated. The patient later received a loading dose of paliperidone LAI 234 mg, followed by 156 mg one week later. Following administration, he experienced progressive cognitive and functional decline. All neuroleptic medications were discontinued, and he was diagnosed with drug-induced parkinsonism. Despite supportive management, his hospital course was complicated, and he died approximately five months after receiving paliperidone LAI.

#### Discussion and conclusion

Although multiple confounding factors were present, the temporal association between paliperidone LAI administration and the onset of severe parkinsonism suggests a likely contributory role. The prolonged action of LAI antipsychotics may complicate the management of adverse extrapyramidal symptoms. Clinicians should carefully assess risk factors, particularly in older adults, and remain vigilant regarding the potential long-term consequences of paliperidone LAI therapy.

**Keywords:** parkinsonism, Parkinson disease, drug-induced parkinsonism, paliperidone, Invega Sustenna, long-acting injection, divalproex, antipsychotic

## Introduction

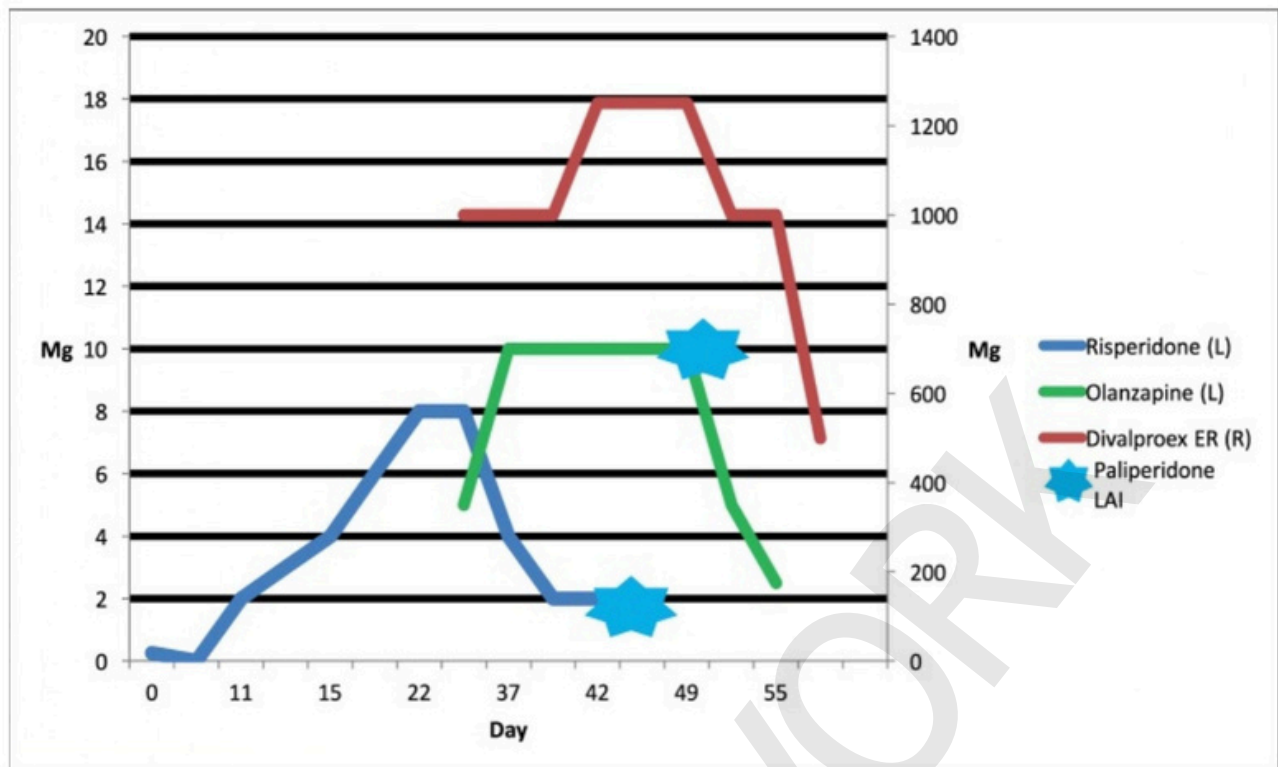
Drug-induced parkinsonism (DIP) is characterized by the development of parkinsonian features after exposure to certain medications. This phenomenon was first described as a complication of neuroleptic therapy in 1950. Symptoms of DIP tend to be bilateral and symmetrical in nature and often appear within days; however, the majority of patients with DIP will develop symptoms within three months of starting their medication. In contrast to Parkinson's disease, DIP does not result from degeneration of the substantia nigra, nor are there specific mechanisms associated with dopamine antagonist receptors (D2).[1]

## Case Presentation

An elderly male patient, aged 68 years, with a long-standing diagnosis of either bipolar disorder (type 1) or cyclothymic disorder; in addition, he was known to have other prior diagnoses including: hypertension, hyperlipidemia, allergic rhinitis, coronary artery disease, and previous positive purified protein derivative test for tuberculosis, presented to an acute care hospital (which was not a veteran's hospital) with the diagnosis of severe diarrhea. At the time of admission, he denied alcohol, tobacco, or illicit drug use; and was considered homeless. Following the involuntary medical authority granted by virtue of the Florida Mental Health Act of 1971, the patient was transferred to a veteran's hospital for psychiatric evaluation due to his presenting symptoms which included pressured speech, flights of ideas, distractibility, delusional thinking and disorganized thought process.

On the pioneering unit, the gastrointestinal complaints were resolved through supportive measures. The medication regimen on the psychiatry unit began with the initiation of risperidone (0.25 mg daily) and then increased in 8 mg increments to 8 mg daily, with intermittent non adherence. However, the medication was changed from a standard formulation to orally disintegrating tablet (ODT) to improve compliance. In addition, benztropine (0.5 mg daily) was added for extrapyramidal symptom prophylaxis due to stooped posture and shuffling gait.

Inadequate clinical efficacy led to the gradual switch of patient from oral risperidone to oral olanzapine (up to 10 mg/day) and initiation of divalproex extended-release at dosages of 1250 mg/day on day 34.(Figure)



Benzotropine was discontinued. One week following the switch to oral olanzapine, the patient was given a long-acting injection (LAI) of paliperidone (234 mg) and then a loading dose of (156 mg) one week later. Sedation began to increase after the first injection, then there was a progressive decline in cognitive and functional ability characterized by shuffling gait, bradykinesia, hypophonia, hypomimia, sialorrhea, cogwheel rigidity, and significant sedation after the second injection. There were no acute findings on MRI of the brain. Approximately one month after the first LAI was given, all neuroleptics were discontinued. He received a diagnosis of neuroleptic-induced parkinsonism. No labs were notable at time of LAI injection other than renal function (creatinine clearance approximately 60 mL/min) and factors within the metabolic panel were normal.

Management of the above symptoms proved to be quite difficult. High doses of diphenhydramine (daily doses of up to 275 mg) produced excessive sedation and delirium in the patient. Use of benzotropine (daily doses of up to 4 mg) provoked an extreme allergy with respiratory distress. Carbidopa-levodopa was initiated and increased to maximum tolerated level, however, this was subsequently discontinued due to dysphagia and obstruction of Dobhoff feeding tube. Due to these factors, amantadine (200 mg twice a day) and botulinum toxin type A injections for cervical dystonia were also administered.

Over the next few months after starting paliperidone LAI therapy, his condition declined. Due to poor oral intake, a gastrostomy tube was inserted approximately 2.5 months after starting the paliperidone LAI. Four months later, he underwent tracheostomy for prolonged

respiratory failure. He experienced multiple complications during his hospital stay: multiple infections, thromboembolic events, gastrointestinal bleeding, pneumothorax, heart failure, acute hypoxic respiratory

failure, acute renal failure, and ventilator-associated pneumonia. He died about five months after beginning paliperidone LAI therapy due to cardiorespiratory failure.

## Discussion

The loading strategy for paliperidone long-acting injection (LAI) is intended to achieve therapeutic plasma concentrations quickly without oral supplementation. Systemic exposure following initiation generally corresponds to that observed with 6–12 mg of extended-release oral paliperidone. [2] Before starting the LAI, the patient had received up to 8 mg of oral risperidone, and available evidence indicates that 6–12 mg of oral paliperidone offers efficacy comparable to 4–6 mg of risperidone. Although he demonstrated a limited response and possible parkinsonian features while on risperidone, concerns about medication adherence supported the decision to transition to paliperidone LAI.

Prescribing guidance recommends administering the first two injections in the deltoid muscle, as deltoid administration produces approximately 28% higher peak plasma concentrations than gluteal injection. [3] In this case, the initial dose was administered in the gluteal muscle and the second in the deltoid, potentially resulting in lower early peak exposure. However, the patient's creatinine clearance was approximately 60 mL/min. For individuals with creatinine clearance between 50 and 79 mL/min, a reduced loading regimen—156

mg on day 1 and 117 mg one week later, both in the deltoid—is recommended. Instead, he received 234 mg followed by 156 mg, which likely resulted in elevated serum concentrations relative to renal function.

Pharmacokinetic data demonstrate that coadministration of extended-release oral paliperidone with divalproex extended release increases paliperidone peak levels and overall exposure by approximately 50%. Although this interaction has not been specifically evaluated with the LAI formulation and is considered unlikely to be clinically significant due to bypass of first-pass metabolism, a contributory effect cannot be excluded. [4]

Paliperidone LAI has been associated with parkinsonism, though reports of such severe manifestations are rare. Clinical trials have documented parkinsonism rates of 8.7% in a 23-week open-label study and 3% in a 15-month double-blind study, compared with 1.8% for placebo. Valproic acid has also been implicated in parkinsonism among older adults, with uncertain pathophysiology and variable response to dopaminergic therapy. [5] Based on the Naranjo probability scale, the adverse reaction was considered possibly related to paliperidone LAI. [6]

Given the temporal association and prolonged pharmacologic activity of the formulation, paliperidone LAI is regarded as the most probable precipitating factor, although prior exposure to risperidone, divalproex, and olanzapine remains confounding.

While the patient had no documented features of Parkinson disease (PD) before

admission, undiagnosed early PD cannot be ruled out. A dopamine transporter single-photon emission computed tomography scan could have assisted in distinguishing degenerative PD from drug-induced parkinsonism;<sup>[7]</sup> however, it was deferred due to cost and the expectation that results would not alter clinical management.

### Conclusion:

Despite multiple confounding variables, the close temporal association between paliperidone LAI administration and symptom progression suggests that it likely contributed to the development of severe, persistent parkinsonism, which ultimately played a role in the patient's death. Supratherapeutic paliperidone exposure secondary to reduced renal clearance (CrCl approximately 60 mL/min) may have been a contributing factor. The potential influence of divalproex in increasing susceptibility to parkinsonism remains uncertain. Furthermore, although olanzapine was being tapered at the time of paliperidone initiation, its concurrent use may have compounded the risk of drug-induced parkinsonism.

Clinicians and pharmacists should exercise heightened vigilance regarding appropriate renal dose adjustments when prescribing paliperidone LAI. Incorporating electronic alerts to flag the need for dosage modification in patients with estimated creatinine clearance below 80 mL/min may enhance medication safety. Caution is also warranted when combining oral antipsychotics or divalproex with long-acting injectable antipsychotics. Awareness of the potential for serious and prolonged adverse effects with paliperidone LAI is essential in clinical practice.

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