

Drug-induced parkinsonism in an adolescent with first manic episode: Neuropsychiatric manifestations and diagnostic challenges

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SUMMARY

The rising number of child and adolescent psychiatry referrals, along with the growing use of medications for mental health problems, has led to an increased incidence of drug-induced parkinsonism (DIP). This report aims to document a patient with DIP, which is rarely seen in child and adolescent psychiatry clinical practice, and to present the successful treatment of this patient with amantadine. Amantadine represents an evidence-based pharmacologic option for treating drug-induced parkinsonism.

Key words: Drug-induced parkinsonism, bipolar disorder, amantadine

INTRODUCTION

Recent evidence indicates a substantial increase in the use of both antipsychotic and antidepressant medications among children and adolescents, reflecting trends toward more frequent initiation and longer-term treatment (1, 2). This growing use of psychotropic medications, particularly antipsychotics, has been accompanied by a noticeable increase in the incidence of drug-induced parkinsonism (DIP) (3). Despite its clinical significance, DIP remains under-recognized in youth, highlighting the need for heightened vigilance in monitoring extrapyramidal side effects in this vulnerable group (3). To better understand the clinical implications of DIP, it is essential to first define its core features and distinguish it from other movement disorders.

Parkinsonism is a clinical syndrome characterized by bradykinesia, rigidity, resting tremor, and postural instability (4). It is broadly classified into degenerative and secondary forms based on etiology (4). Among children, DIP represents the most common

cause of secondary parkinsonism and is typically associated with antipsychotic use, though other medications such as calcium channel blockers, antiemetics, and valproic acid may also be implicated (5). According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), DIP is defined by the emergence of resting tremor, muscular rigidity, akinesia, or bradykinesia within weeks of initiating or increasing the dosage of a causative medication (6). In the clinical assessment of DIP, it is essential to differentiate it from other antipsychotic-related movement disorders such as tardive dyskinesia, acute dystonic reactions, akathisia, and neuroleptic malignant syndrome (NMS) (7). Early recognition and appropriate management rely on a high index of suspicion and comprehensive knowledge of the diverse range of medications capable of inducing parkinsonism.

Most studies on DIP have focused on adult populations, resulting in a limited understanding of its prevalence, risk factors, and management in children and adolescents (3). The distinct clinical characteristics and psychotropic medication use pat-

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terns in pediatric patients reduce the applicability of adult-based findings. Recent data by Jeon et al. (2023) addressed this knowledge gap, reporting that the annual prevalence of DIP in children and adolescents increased approximately tenfold between 2010 and 2017 (3). This rise was largely driven by increased prescriptions of atypical antipsychotics, particularly risperidone and aripiprazole (3). These findings underscore the need for age-specific research, cautious prescribing practices, and vigilant monitoring for DIP in young patients (8).

This report aims to present a rare case of DIP in an adolescent experiencing her first manic episode, highlighting the diagnostic challenges and therapeutic considerations associated with this condition. By documenting the successful management of DIP with amantadine and detailing the clinical decision-making process, this case underscores the importance of early recognition and tailored intervention in pediatric neuropsychiatric practice.

CASE

Initial Psychiatric Presentation and Treatment

A 15-year-old female patient was referred to our hospital's pediatric emergency department with symptoms of aggression, insomnia, and increased activity over the past few days. She had no prior psychiatric or medical history, but her family history was notable for schizophrenia in her older brother. There was no history of substance or alcohol use. Approximately one week before symptom onset, she received a 3-day course of azithromycin for an upper respiratory infection. Following this, she presented to an emergency service with insomnia, agitation, aggression, and pressured speech. She was diagnosed with a bipolar manic episode with psychotic features and was administered two injections of haloperidol (5 mg) and biperiden (5 mg), along with oral olanzapine 5 mg twice daily. Due to the persistence of psychiatric symptoms and concerns about possible organic causes, she was referred to our hospital for further evaluation.

Onset of Extrapiramidal Symptoms

Upon admission, she was uncooperative, disoriented, and exhibited elevated mood, religious delusions, rapid speech, and psychomotor agitation. Haloperidol 5 mg/day IM, biperiden 5 mg/day IM, and olanzapine 5 mg twice daily were continued. Extensive investigations, including autoimmune and rheumatological panels (e.g., anti-NMDA, ANA, anti-dsDNA, ANCA), cerebrospinal fluid analysis, EEG, and cranial imaging were performed, all yielding normal results.

Despite treatment, her agitation worsened. Zuclopenthixol acuphase (50 mg IM) and zuclopenthixol decanoate depot (200 mg) were administered alongside biperiden (2 mg twice daily). During hospitalization, she developed extrapyramidal symptoms including akathisia, echolalia, negativism, severe bradykinesia, sialorrhea, and postural instability. Due to the progression of dystonia affecting her jaw, which led to difficulties in speech and swallowing, a nasogastric tube was inserted for nutritional support. In addition, midazolam infusion (0.2 mg/kg/h) was initiated to manage severe dystonic reactions and provide sedation. Her bradykinesia was profound and she exhibited marked facial hypomimia. Muscle rigidity was significant, and she demonstrated considerable difficulty with voluntary movements, including ambulation and oromotor control. Treatment was switched to lorazepam 2.5 mg twice daily and biperiden 2 mg daily due to suspected catatonia.

Diagnostic Evaluation and Differential Diagnosis

The patient's complex clinical picture necessitated consideration of several differential diagnoses, including catatonia, NMS, and autoimmune encephalitis.

The patient began to exhibit disorganized behavior and insomnia, accompanied by bradykinesia, bradymimia, muscular rigidity, distal tremors, postural instability, and an inability to ambulate without assistance. As there was no observable clinical improvement with lorazepam treatment, it was discontinued, and the patient was subsequently trans-

ferred to the pediatric neurology ward. Given the lack of response to lorazepam and the absence of hallmark catatonic features such as catalepsy and waxy flexibility, catatonia was considered unlikely. Due to the emergence of dysphagia secondary to jaw dystonia, nasogastric feeding was initiated. Neurological examination revealed marked rigidity, cogwheel phenomenon, and tremors in the upper extremities, along with difficulty in voluntary eye opening and oromandibular movement. Given the deterioration in speech and swallowing functions attributable to dystonia, a continuous infusion of midazolam was commenced at a dose of 0.2 mg/kg/hr, and biperiden was added to the treatment regimen at a dosage of 2.5 mg three times daily.

The patient, sedated with a continuous midazolam infusion, continued to exhibit disorganized behavior throughout hospitalization. She responded to questions with inappropriate, single-word utterances, frequently incorporating offensive language, and her speech was characterized by echolalia. Although muscle strength was reduced, she was able to stand with support. Follow-up laboratory tests revealed elevated creatine kinase (CK) levels—707 U/L, 964 U/L, and 784 U/L, respectively—peaking at 964 U/L before beginning to decline. Due to concerns regarding malignant hyperthermia, bromocriptine was initiated at a dose of 2.5 mg twice daily. However, as clinical improvement was not observed, bromocriptine was discontinued. Since no significant benefit was achieved with midazolam either, it was subsequently stopped. Oral clonazepam drops (2.5 mg/mL, 5 drops three times daily) and propranolol 40 mg twice daily were then initiated to manage the patient's dystonia and tremor. During continued follow-up, CK levels declined to 404 U/L and subsequently returned to within normal limits. The normalization of CK levels, stable body temperature (36.5–37.0°C), and normal arterial blood gas results were reassuring. Moreover, there were no clinical or laboratory findings typically associated with malignant hyperthermia, such as tachypnea, hypercapnia, acid-base imbalance, rhabdomyolysis, myoglobinuria, renal dysfunction, hyperkalemia, or cardiac arrhythmias. Therefore, the likelihood of malignant hyperthermia was considered low.

Autoimmune encephalitis was also evaluated because of the acute onset of psychiatric symptoms. Nevertheless, negative cerebrospinal fluid autoimmune panels and imaging results excluded this possibility.

Final Diagnosis

As part of the follow-up evaluation, the patient continued to exhibit severe rigidity, bradykinesia, and resting tremor. Based on the clinical presentation, a preliminary diagnosis of DIP was considered, and treatment with amantadine was initiated at a dose of 25 mg twice daily. In addition, the patient continued to receive clonazepam oral drops (2.5 mg/mL; 5 drops three times daily) and propranolol 40 mg twice daily as part of her ongoing treatment regimen. Over time, the amantadine dose was gradually titrated to 100 mg/day, resulting in a significant reduction in rigidity and tremor, with noticeable improvement occurring within approximately five days of treatment initiation. As clinical improvement progressed, nasogastric feeding was discontinued and oral intake was re-established. Upon further psychiatric evaluation, the patient, who was found to be in partial remission from manic symptoms, was started on lithium at a dose of 300 mg once daily. Both extrapyramidal and affective symptoms showed gradual improvement.

Parkinsonian symptoms emerged shortly after the initiation of antipsychotic treatment for a manic episode. Additionally, there was no personal or family history suggestive of idiopathic Parkinson's disease. These findings further supported the diagnosis of DIP. By the fourth week of hospitalization, her neurological symptoms had resolved, and she was deemed clinically stable for discharge.

Treatment and Outcome

At the time of discharge, the patient's mental status examination revealed orientation to person, place, and time. Attention was impaired, and she exhibited minimal psychomotor agitation along with mild rigidity, consistent with residual extrapyramidal side effects. Her mood was slightly elevated with mood-congruent affect, and both insight and judgment were moderately impaired. She was dis-

Table 1. Timeline of Case Report

Step (with Day)	Description
Initial Presentation and Diagnosis (Day 1)	Acute onset of mania with psychotic features; treated with haloperidol and olanzapine.
Referral to Tertiary Hospital (Day 3)	Transferred due to persistent agitation and suspected organic etiology.
Inpatient Evaluation (Day 5)	Continued psychotic symptoms; extensive workup (EEG, MRI, CSF, autoimmune panel) was normal.
Onset of Extrapyrimal Symptoms (Day 7)	Developed dystonia, bradykinesia, sialorrhea, and swallowing difficulties; midazolam infusion and NG tube initiated.
Differential Diagnosis	Catatonía, NMS, and autoimmune encephalitis considered but ruled out; lorazepam and bromocriptine were ineffective.
Diagnosis of Drug-Induced Parkinsonism (Day 21-)	Amantadine started; clonazepam and propranolol added; marked motor improvement followed.
Discharge and Early Follow-Up (Week 4)	Discharged with mild residual symptoms; maintained on lithium and antiparkinsonian medications.
Long-Term Outcome (Month 2-12)	Full resolution of parkinsonian symptoms by week 6; one-year remission with good functional recovery.

EEG: Electroencephalography; MRI: Magnetic Resonance Imaging; CSF: Cerebrospinal Fluid; NMS: Neuroleptic Malignant Syndrome

charged on a treatment regimen consisting of lithium 300 mg once daily, amantadine 50 mg twice daily, clonazepam oral drops (2.5 mg/mL) three times daily, and propranolol 40 mg twice daily. She was subsequently followed at regular intervals in the outpatient clinic.

At the one-month follow-up, her mobility had returned to normal, and parkinsonian symptoms had completely resolved. Subsequently, amantadine and propranolol were gradually tapered and discontinued by the sixth week of treatment. Clonazepam was also discontinued, and the lithium dose was adjusted to 300 mg twice daily. During the follow-up period, melatonin 3 mg was temporarily added to address sleep difficulties. The patient has continued outpatient treatment with lithium 300 mg twice daily for the maintenance of bipolar disorder. At the one-year follow-up, she remained in remission with favorable social and academic functioning (Table 1).

DISCUSSION

This case report describes a rare presentation of DIP in an adolescent during treatment for a first manic episode of bipolar disorder. DIP risk is influenced by factors such as drug type, dosage, patient age, and sex, with a higher susceptibility reported in females (9). To the best of our knowledge, this is the first reported case of DIP in the pediatric population in our country. In our case, parkinsonian symptoms developed gradually after the initiation of antipsychotic medication and became prominent within approximately one week. Given the subacute progression, the differential diagnosis inclu-

ded primary movement disorders, encephalitis/encephalopathy, catatonía, and NMS.

In a clinical study involving 97 patients, DIP was reported as the most frequently observed movement disorder associated with dopamine receptor-blocking agents (10). This finding underscores the need for early recognition, as DIP not only represents a common complication of antipsychotic therapy but can also mimic or coexist with other serious neurological conditions, potentially delaying appropriate management. Movement disorders associated with the use of antipsychotic medications include tardive dyskinesia, acute dystonic reactions, akathisia and DIP (7). Unlike tardive dyskinesia, DIP occurs earlier in the course of antipsychotic treatment, with approximately 50–75% of cases appearing within the first month and 90% within the first three months (7). Akathisia may occur either with or without DIP. Reducing the antipsychotic dose can improve both conditions, but anticholinergics are ineffective in treating akathisia (11). In our case, beta-blockers were used to address the akathisia accompanying DIP, and a beneficial response was observed. When rigidity and altered consciousness occur after antipsychotic drug use, NMS must also be considered. According to recent expert guidance, NMS is characterized by hyperthermia, altered mental status, muscle rigidity, and autonomic instability, supported by laboratory findings such as leukocytosis and elevated creatine kinase (12). In our patient, severe bradykinesia and bradyphrenia were accompanied by rigidity but without fever or autonomic dysfunction, and laboratory evaluation revealed no leukocytosis or metabolic acidosis. These findings argued strongly against NMS. Similarly, catatonía was considered

because of the patient's psychomotor slowing and rigidity; however, the absence of catalepsy or waxy flexibility—core features in DSM-5 diagnostic criteria—made catatonia unlikely (6). The lack of response to benzodiazepines at standard therapeutic doses further reduced the likelihood of this diagnosis (13). Encephalitis and encephalopathy were also evaluated. The absence of abnormal findings in brain MRI, cerebrospinal fluid analysis, and autoimmune panels effectively excluded these possibilities (14).

Due to the patient's increased rigidity, bradykinesia, and a marked degree of bradyimia, a diagnosis of DIP was considered, and treatment with amantadine was initiated. Although amantadine is Food and Drug Administration (FDA) approved for adults with DIP, its pediatric use is off-label (15). Nevertheless, pharmacological evidence supports its dopaminergic action—particularly through indirect dopamine release and receptor stimulation (16), and limited pediatric data suggest acceptable tolerability and functional improvement in neurologic conditions (17). Following treatment, our patient experienced rapid improvement, particularly in motor function, which allowed for the introduction of lithium amid partial remission of affective symptoms. In mild to moderate cases of DIP, discontinuation of the causative drug alone is often sufficient to achieve symptom resolution; however, in this case, the severity of parkinsonian features warranted initiating amantadine as adjunctive therapy (18). The rapid response observed may have been facilitated by the absence of comorbid medical conditions and a negative family history of Parkinson's disease—factors that could be favorable for recovery—though this remains speculative given the paucity of pediatric data. A similar outcome was reported in a previous pediatric case, where amantadine treatment led to marked clinical improvement within 72 hours (19).

In managing DIP, the causative drug should be discontinued whenever possible, with subsequent clinical monitoring (18). If discontinuation is not feasible, dose reduction and, if needed, substitution with an alternative agent is recommended (18). Additional pharmacologic options include a levodopa-benserazide combination, anticholinergic agents, and amantadine in appropriate candidates

(18,20,21). Symptom resolution generally occurs within weeks to months after discontinuation of the causative drug, but the course can vary from days to years, and symptoms may persist or progress in up to 50% of patients, with approximately 10% experiencing permanent deficits (5). As in our patient, cases with symptom resolution are classified as "pure DIP," whereas those without symptom improvement are referred to as "toxic DIP" (22). Persistence or recurrence of parkinsonian symptoms—whether through gradual progression or reappearance after a complete remission—may point to an underlying, previously unrecognized idiopathic Parkinson's disease or another neurodegenerative parkinsonian syndrome triggered by drug exposure (22). Conversely, non-progressive persistent symptoms may indicate irreversible injury to the nigrostriatal dopaminergic pathway due to toxic pharmacologic effects, as was the case in our patient (22).

In conclusion, this case highlights the importance of considering DIP in adolescents with acute or subacute movement disorders during antipsychotic treatment. The rapid clinical improvement observed suggests that early recognition and timely intervention can reduce unnecessary investigations and prevent functional impairment. While amantadine has a long-standing role in Parkinson's disease, robust evidence for its use in DIP—particularly in pediatric cases—remains scarce, warranting cautious patient selection and close monitoring (16). Based on this case, clinicians should be cautious when initiating high-dose antipsychotics in first-time users and, whenever feasible, consider starting with oral regimens unless rapid symptom control necessitates parenteral administration.

The findings should be interpreted in light of key limitations, including the inherent constraints of a single case report, the inability to establish causality, the absence of standardized long-term follow-up, the lack of objective severity assessment using validated parkinsonism rating scales, and the omission of neuroimaging—which some studies recommend as part of the diagnostic work-up (22). Future research could include the use of structured movement disorder rating scales to systematically screen patients receiving antipsychotics—particularly those on long-term treatment—for early

detection of extrapyramidal symptoms.

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REFERENCES

1. Altuwairqi Y. Trends and Prevalence of Psychotropic Medication Use in Children and Adolescents in the Period Between 2013 and 2023: A Systematic Review. *Cureus*. 2024 Mar 3;16(3):e55452. doi: 10.7759/cureus.55452. PMID: 38571846; PMCID: PMC10987897.
2. Radoj i MR, Pierce M, Hope H, Senior M, Taxiarchi VP, Trefan L, Swift E, Abel KM. Trends in antipsychotic prescribing to children and adolescents in England: cohort study using 2000-19 primary care data. *Lancet Psychiatry*. 2023 Feb;10(2):119-128. doi: 10.1016/S2215-0366(22)00404-7. Epub 2023 Jan 10. PMID: 36638816.
3. Jeon SM, Lee YJ, Kwon JW. Prevalence and causative drugs of drug-induced Parkinsonism in pediatric patients. *Eur Child Adolesc Psychiatry*. 2023 Sep;32(9):1805-1814. doi: 10.1007/s00787-023-02207-7. Epub 2023 Apr 11. PMID: 37039890.
4. Wichmann T. Changing views of the pathophysiology of Parkinsonism. *Movement Disorders*. 2019 Jun 19;34(8):1130-43.
5. Erkeko lu P, Baydar T, ahin G. Ters ilaç reaksiyonu olarak ilaçlarla indüklenen parkinsonizm. *Marmara Pharm J*. 2011;15(3):110-7.
6. American Psychiatric Association, D.S. Diagnostic and statistical manual of mental disorders: DSM-5 (Vol. 5, No.5). Washington, Dc. 2013
7. Ward KM, Citrome L. Antipsychotic-Related Movement Disorders: Drug-Induced Parkinsonism vs. Tardive Dyskinesia-Key Differences in Pathophysiology and Clinical Management. *Neurol Ther*. 2018 Dec;7(2):233-248. doi: 10.1007/s40120-018-0105-0. Epub 2018 Jul 19. PMID: 30027457; PMCID: PMC6283785.
8. Byun JH, Cho H, Kim YJ, Kim JS, Baik JS, Jang S, Ma HI. Trends in the Prevalence of Drug-Induced Parkinsonism in Korea. *Yonsei Med J*. 2019 Aug;60(8):760-767. doi: 10.3349/ymj.2019.60.8.760. PMID: 31347331; PMCID: PMC6660437.
9. Keener, A. M., & Bordelon, Y. M. (2016, August). Parkinsonism. In *Seminars in neurology* (Vol. 36, No. 04, pp. 330-334). Thieme Medical Publishers.
10. Chouksey A, Pandey S. Clinical Spectrum of Drug-Induced Movement Disorders: A Study of 97 Patients. *Tremor Other Hyperkinet Mov (N Y)*. 2020 Oct 26;10:48. doi: 10.5334/tohm.554. PMID: 33178486; PMCID: PMC7597587.
11. Pringsheim T, Gardner D, Addington D, Martino D, Morgante F, Ricciardi L, Poole N, Remington G, Edwards M, Carson A, Barnes TRE. The Assessment and Treatment of Antipsychotic-Induced Akathisia. *Can J Psychiatry*. 2018 Nov;63(11):719-729. doi: 10.1177/0706743718760288. Epub 2018 Apr 23. PMID: 29685069; PMCID: PMC6299189.
12. Orsolini L, Volpe U. Expert guidance on the differential diagnosis of neuroleptic malignant syndrome. *Expert Rev Neurother*. 2025 Feb;25(2):125-132. doi: 10.1080/14737175.2024.2417414. Epub 2024 Oct 18. PMID: 39425495.
13. Pelzer AC, van der Heijden FM, den Boer E. Systematic review of catatonia treatment. *Neuropsychiatr Dis Treat*. 2018 Jan 17;14:317-326. doi: 10.2147/NDT.S147897. PMID: 29398916; PMCID: PMC5775747.
14. Davies E, Connolly DJ, Mordekar SR. Encephalopathy in children: an approach to assessment and management *Archives of Disease in Childhood* 2012;97:452-458.
15. Hubsher G, Haider M, Okun MS. Amantadine: The journey from fighting flu to treating Parkinson disease. *Neurology*. 2012; 78:1096-9.
16. Pelzer AC, van der Heijden FM, den Boer E. Systematic review of catatonia treatment. *Neuropsychiatr Dis Treat*. 2018 Jan 17;14:317-326. doi: 10.2147/NDT.S147897. PMID: 29398916; PMCID: PMC5775747.
17. Hosenbocus S, Chahal R. Amantadine: a review of use in child and adolescent psychiatry. *J Can Acad Child Adolesc Psychiatry*. 2013 Feb;22(1):55-60. PMID: 23390434; PMCID: PMC3565716.
18. Shin HW, Chung SJ. Drug-induced parkinsonism. *J Clin Neurol*. 2012 Mar;8(1):15-21. doi: 10.3988/jcn.2012.8.1.15. Epub 2012 Mar 31. PMID: 22523509; PMCID: PMC3325428.
19. Patel H, Patel A, Mushtaq S, Haq F, Raza S. Aripiprazole-induced parkinsonism in a child: a case report. *Prim Care Companion CNS Disord*. 2011;13(3):PCC.10101081. doi: 10.4088/PCC.10101081. PMID: 21977366; PMCID: PMC3184558.
20. Fann WE, Lake CR. Amantadine versus trihexyphenidyl in the treatment of neuroleptic-induced parkinsonism. *Am J Psychiatry* 1976;133: 940-943.
21. Jankovic J. Tardive syndromes and other drug-induced movement disorders. *Clin Neuropharmacol* 1995; 18:197-214.
22. López-Sendón J, Mena MA, de Yébenes JG. Drug-induced parkinsonism. *Expert Opin Drug Saf*. 2013 Jul;12(4):487-96. doi: 10.1517/14740338.2013.787065. Epub 2013 Mar 31. PMID: 23540800.