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Pisa Syndrome with Metronome Pattern: A Rare Case Associated with Aripiprazole Treatment

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ABSTRACT

Introduction: Pisa syndrome is a drug-induced dystonia characterized by lateral truncal flexion. "A metronome-like pattern," a rare variant characterized by alternating directions of deviation, may offer insights into the pathophysiology of extrapyramidal symptoms. This case report describes a rare case of Pisa syndrome induced by aripiprazole, in which the direction of truncal deviation changed following biperiden administration.

Case: We describe a 41-year-old female with rapid-cycling bipolar disorder treated with aripiprazole and clozapine who presented with marked rightward truncal flexion. Given her acute manic state, the anticholinergic agent biperiden was added to manage the dystonia without reducing antipsychotic dosage. Surprisingly, this intervention coincided with a shift of the deviation to the left—a phenomenon consistent with a metronome-like pattern. The condition resolved completely following a reduction in aripiprazole dose.

Conclusion: This case may support the view that Pisa syndrome is a dynamic state sensitive to the equilibrium between dopaminergic and cholinergic systems. We hypothesize that the anticholinergic effect of biperiden, combined with aripiprazole's partial agonist activity, precipitated the directional switch. Clinicians should be aware of this "direction-switching" phenomenon when managing drug-induced movement disorders in complex polypharmacy regimens.

Keywords: Aripiprazole, biperiden, case report, drug-induced dystonia, metronome pattern, Pisa syndrome

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INTRODUCTION

Pisa syndrome (PS), also known as pleurothotonus, is a rare, frequently overlooked, and potentially drug-induced extrapyramidal syndrome characterized by a tonic lateral flexion of the trunk of at least 10 degrees (1,2). This postural abnormality is typically accompanied by mild axial rotation, becomes more pronounced during ambulation, and resolves completely in the supine position. Named for its resemblance to the Tower of Pisa's leaning posture, the syndrome can markedly impair patients' quality of life, social functioning, and treatment adherence (3). Delays in diagnosis are often attributable to limited clinician awareness and may result in unnecessary diagnostic investigations and treatments.

Although PS was first described by Ekbom et al. (1972) in patients receiving butyrophenone antipsychotics, it has subsequently been associated with both typical and atypical antipsychotic agents (3,4). While the pathophysiology of PS has not been fully elucidated, the most widely accepted hypothesis involves an imbalance between dopaminergic and cholinergic systems within the basal ganglia (2,5). Identified risk factors include advanced age, female sex, pre-existing brain pathology, long-term or combined antipsychotic treatment, and a history of extrapyramidal symptoms (1).

In a case reported by Bruneau and Stip (1998) involving clozapine treatment, the direction of lateral deviation was observed to alternate over the course of follow-up; this phenomenon was termed "Metronome syndrome," a variant of PS (6). Since this initial description, the literature on Metronome syndrome has remained scarce (7).

In this case report, we describe Pisa syndrome with a metronome-like pattern in a patient with rapid-cycling bipolar disorder and obsessive-compulsive disorder who was receiving clozapine, lithium, valproate, and aripiprazole. Given the temporal relationship with aripiprazole dose

Highlights

- **This case describes Pisa syndrome with a rare metronome-like pattern.**
- **Aripiprazole emerges as a highly plausible factor in Pisa syndrome.**
- **Biperiden treatment may have contributed to the reversal of truncal deviation.**
- **This case may support dopaminergic-cholinergic imbalance in Pisa syndrome.**

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escalation and subsequent resolution after dose reduction, aripiprazole was considered a likely contributing factor rather than the sole etiological agent. The concomitant psychotropic regimen may also have increased the patient's vulnerability to extrapyramidal adverse effects. In addition, the initiation of the anticholinergic agent biperiden may have contributed to the observed directional change in truncal deviation. The case presented below delineates these temporal and clinical relationships in detail.

CASE

A 41-year-old female patient with diagnoses of rapid-cycling bipolar disorder and obsessive–compulsive disorder (OCD) presented to our clinic. Her history revealed numerous mixed and psychotic manic and depressive episodes beginning at the age of 19, with a history of hospitalizations due to these episodes. She had previously been treated with aripiprazole, risperidone, lithium, valproate, carbamazepine, and clozapine, and had also received electroconvulsive therapy (ECT). Clozapine was observed to be the most effective agent in terms of controlling psychotic symptoms and stabilizing mood.

At presentation, she exhibited racing thoughts, irritability, pressured speech, increased libido, mood lability, persecutory delusions, ideas of reference, and auditory hallucinations described as a humming sound. She also reported a tactile hallucination of feeling her deceased father's hand on her back, along with worsening obsessive-compulsive symptoms centered on uncertainty and checking. Passive suicidal ideation was also present. Young Mania Rating Scale (YMRS) score at presentation was 24. Given the severity of the manic episode with mixed features, inpatient treatment was considered necessary. Review of the outpatient records revealed that in the days preceding hospitalization, the clozapine dose had been increased from 250 mg/day to 350 mg/day, and the aripiprazole dose from 5 mg/day to 15 mg/day due to worsening manic symptoms.

Review of the outpatient records revealed that the patient had been receiving clozapine therapy since 2018 and aripiprazole since 2022, with no prior history of extrapyramidal or postural adverse effects. Due to a recent worsening of manic symptoms, a sequential dose escalation was performed in the outpatient setting. First, the clozapine dose was increased from 250 mg/day to 350 mg/day, which did not precipitate any truncal deviation or postural changes. Two weeks after this adjustment, the aripiprazole dose was escalated from 5 mg/day to 15 mg/day. Notably, the symptoms of Pisa syndrome emerged five days after the aripiprazole dose increase. At admission, her treatment regimen consisted of clozapine 350 mg/day, lithium 900 mg/day (0.83 mEq/L), valproic acid 2000 mg/day (62.9 mg/L), and aripiprazole 15 mg/day.

On mental status examination at admission, in addition to her psychiatric symptoms, the patient was observed to have a marked rightward deviation of the trunk (clinically estimated to be well above the 10° diagnostic threshold, although objective goniometric measurement was not performed) while both sitting and walking (tonic truncal flexion). This postural abnormality resolved completely when the patient was placed in the supine position. No other extrapyramidal signs –such as rigidity, resting tremor, or bradykinesia– were detected on clinical observation during the routine examination; however, no standardized extrapyramidal symptom scale was applied. A review of her medical records revealed no structural brain pathology, neuromuscular or neurodegenerative disorders, history of head trauma, or substance use that could account for the postural disturbance. Furthermore, routine biochemical evaluations, along with the detailed clinical history and physical examination, excluded potential organic, metabolic, intoxication, or substance-related causes for both the tactile hallucinations and the acute psychotic presentation. Consequently, a diagnosis of drug-induced PS was considered.

As the patient was in an acute manic exacerbation and was benefiting from her current antipsychotic treatments, it was decided to add biperiden at a dose of 2 mg/day to manage extrapyramidal side effects rather than reducing the antipsychotic dosage. With biperiden treatment, a reduction in the degree of lateral trunk deviation was observed. Following a substantial improvement in manic symptoms, with a reduction in the YMRS score to 8, the patient was discharged within 14 days. Before discharge, the antipsychotic doses were gradually reduced. She was discharged on clozapine 200 mg/day, aripiprazole 10 mg/day, lithium 900 mg/day (0.87 mEq/L), valproic acid 2000 mg/day (63.6 mg/L), and biperiden 2 mg/day.

One week after discharge, the patient returned for follow-up, at which time a striking change in posture was noted: the truncal deviation, although milder, had shifted to the left side. The leftward lean persisted even while she was seated. This directional change was considered consistent with a metronome-like pattern of PS; however, it was based on a single follow-up observation rather than recurrent alternating cycles.

Given the marked reduction in manic and obsessive-compulsive symptoms, we decided to reduce the dose of the agent presumed to be contributing to the postural abnormality. Aripiprazole was considered a likely contributing factor, and its dose was gradually tapered to 5 mg/day. At the follow-up visit two weeks after the aripiprazole dose reduction, the patient's lateral trunk flexion had resolved completely, and her posture had returned to normal. Biperiden was subsequently tapered and discontinued without recurrence of postural changes.

Ethical approval was obtained from the Institutional Review Board of Ege University (Application No: 2025-5844, Decision No: 25-10T/12). Written informed consent was obtained from the patient for the publication of this case report.

DISCUSSION

Although the etiology of PS has not been fully elucidated, a principal proposed mechanism involves dopaminergic-cholinergic imbalance in the basal ganglia following D2 receptor blockade (2,5). While PS cases associated with atypical antipsychotics have been reported, alternating or metronome-like patterns remain exceedingly rare in the literature (6). A true metronome syndrome typically involves recurrent alternations of lateral flexion. Because our patient exhibited a single directional switch rather than continuous alternations, we opted to describe this presentation as a 'metronome-like' pattern or a direction-switching variant. This case is one of the few to provide a longitudinal description of the clinical course of this uncommon phenomenon.

The presence of known risk factors in our patient, including female sex and long-term and/or combined use of antipsychotics, is consistent with previous reports (1). The concomitant use of clozapine, lithium, valproate, and aripiprazole may have increased her vulnerability to extrapyramidal adverse effects by creating a complex neurochemical milieu involving the dopaminergic, cholinergic, and serotonergic systems (8).

In this case, due to a recently experienced episode, a centrally acting anticholinergic agent biperiden was added initially rather than reducing the antipsychotic dosage. The subsequent change in the direction of postural deviation after initiation of biperiden may suggest that PS may represent a dynamic condition susceptible to changes in the underlying neurotransmitter balance. The initial rightward deviation may have been related to aripiprazole's partial agonist activity at D2 receptors, potentially disrupting the dopamine-acetylcholine balance beyond a critical threshold (9). However, given the concomitant use of clozapine, lithium, and valproate, aripiprazole

should be interpreted as a likely contributing factor rather than the sole etiological agent. The anticholinergic intervention may have suppressed cholinergic tone, triggering a compensatory overshoot that may have clinically contributed to the reversal of the lateralization. Although this interpretation warrants further validation due to being a single observation, it reinforces the hypothesis that bidirectional interplay between the dopaminergic and cholinergic systems drives the metronomic pattern. Following the reduction of the aripiprazole dose, the patient's symptoms resolved within two weeks. A causality assessment using the Naranjo algorithm yielded a score of 5, indicating a "probable" drug-related adverse effect**;** however, this result should be interpreted with caution because the algorithm has limited ability to disentangle causality in the context of polypharmacy and sequential medication changes (10).

Furthermore, the prominent serotonergic properties of aripiprazole and clozapine (5-HT2A antagonism and, regarding aripiprazole, partial agonism at 5-HT1A receptors) merit consideration (11,12). Since serotonin can inhibit dopamine release in the striatum, serotonergic modulation may have amplified temporal and drug-dependent fluctuations in dopaminergic tone, thereby facilitating an asymmetric dystonic response.

Notably, the literature contains reports in which aripiprazole has been implicated both as a cause of PS and as a therapeutic agent for the condition (13). This apparent paradox is consistent with the context-dependent pharmacodynamics inherent to partial agonism. Similarly, clozapine has been reported to both precipitate PS and exert beneficial effects in its treatment (14). These bidirectional observations suggest that PS cannot be attributed to a single receptor or neurotransmitter system; rather, the interplay between dopamine, acetylcholine, and serotonin pathways must likely be considered.

Previous studies suggest that approximately 40% of drug-induced PS cases respond to anticholinergic agents (2). In our case, biperiden was associated with a reduction in the degree of truncal deviation as well as a directional switch, whereas the subsequent reduction of aripiprazole led to complete resolution. This clinical course may be compatible with the hypothesis that dopaminergic-cholinergic disequilibrium contributes to the clinical phenotype, with aripiprazole acting as one of the key modulators of this balance. The absence of a standardized extrapyramidal symptom scale and the single documented directional change should be considered limitations when interpreting this case.

Pisa syndrome is a rare, potentially drug-induced extrapyramidal postural disorder that is frequently overlooked in routine clinical practice. Although its pathophysiology remains incompletely understood, a dopaminergic-cholinergic imbalance within the basal ganglia is widely regarded as the most plausible mechanism. In the present case, a direction-switching variant of PS –consistent with metronome-like pattern– was observed, wherein a shift in the direction of lateral deviation occurred following the addition of biperiden, with complete resolution achieved after aripiprazole dose reduction. This clinical trajectory underscores the dynamic nature of PS and its sensitivity to alterations in neurotransmitter balance. Presence of ongoing polypharmacy suggests that aripiprazole likely served as a contributing factor within a broader context of medication-related vulnerability. Such cases highlight the importance of carefully reviewing medication history when establishing a diagnosis of PS, as well as the need for systematic and close monitoring of the temporal relationships between postural changes and pharmacological interventions.

Ethics Committee Approval: Ethical approval was obtained from the Institutional

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Informed Consent: Written informed consent was obtained from the patient for the publication of this case report.

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REFERENCES

1. Santos H, Dornelles E, Pereira J, Vieira A. What is the Pisa syndrome? A review. Eur Psychiatry. 2022;65:S725. [Crossref]
2. Suzuki T, Matsuzaka H. Drug-induced Pisa syndrome (pleurothotonus). CNS Drugs. 2002;16:165–174. [Crossref]
3. Pitton Rissardo J, Murtaza Vora N, Danaf N, Ramesh S, Shariff S, Fornari Caprara AL. Pisa syndrome secondary to drugs: a scope review. Geriatrics. 2024;9:110. [Crossref]
4. Ekbom K, Lindholm H, Ljungberg L. New dystonic syndrome associated with butyrophenone therapy. Z Neurol. 1972;202:94–103. [Crossref]
5. Villarejo A, Camacho A, García-Ramos R, Moreno T, Penas M, Juntas R, et al. Cholinergic-dopaminergic imbalance in Pisa syndrome. Clin Neuropharmacol. 2003;26:119–121. [Crossref]
6. Bruneau MA, Stip E. Metronome or alternating Pisa syndrome: a form of tardive dystonia under clozapine treatment. Int Clin Psychopharmacol. 1998;13:229–232. [Crossref]
7. Pellene A, Saenz-Farret M, Micheli F. Recurrent and alternating pisa syndrome. Clin Neuropharmacol. 2015;38:252–254. [Crossref]
8. Walder A, Greil W, Baumann P. Drug-induced Pisa syndrome under quetiapine. Prog Neuropsychopharmacol Biol Psychiatry. 2009;33:1286–1287. [Crossref]
9. Mamo D, Graff A, Mizrahi R, Shammi CM, Romeyer F, Kapur S. Differential effects of aripiprazole on D2, 5-HT2, and 5-HT1A receptor occupancy in patients with schizophrenia: a triple tracer PET study. Am J Psychiatry. 2007;164:1411–1417. [Crossref]
10. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30:239–245. [Crossref]
11. Seeman P. Clozapine, a Fast-Off-D2 antipsychotic. ACS Chem Neurosci. 2014;5:24–29. [Crossref]
12. Kikuchi T, Maeda K, Suzuki M, Hirose T, Futamura T, McQuade RD. Discovery research and development history of the dopamine D2 receptor partial agonists, aripiprazole and brexpiprazole. Neuropsychopharmacol Rep. 2021;41:134–143. [Crossref]
13. Shan JC, Tseng MCM. Improvement in Pisa syndrome and tardive dyskinesia following aripiprazole treatment. J Neuropsychiatry Clin Neurosci. 2009;21:350–351. [Crossref]
14. Weise J, Schomerus G, Speerforck S. Add-on cariprazine in patients with long-term clozapine treatment and treatment resistant schizophrenia: two cases of psychotic deterioration and Pisa syndrome. Clin Psychopharmacol Neurosci. 2022;20:398–401. [Crossref]