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Case Series

When Antidepressants Mimic Antipsychotics, Fluoxetine induced Extrapyramidal Syndrome: A Case Series

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ABSTRACT

Serotonin-specific reuptake inhibitors (SSRIs) are widely used for a variety of clinical conditions due to their relatively safe side-effect profile. Among the various classes of antidepressants, SSRIs are the common offenders producing extrapyramidal symptoms (EPSs). The SSRIs produces reversible or irreversible motor disturbances through pathophysiological changes in basal ganglion motor system by altering the dopamine receptors post synaptically. Among the SSRIs, Fluoxetine has been associated with most case reports of EPS, though other SSRI, particularly, Paroxetine and Sertraline has also been reported in certain cases. Most of these reports are from other countries, and relevant searches have not found any case report from India. Here we are presenting three cases of Fluoxetine-induced EPS.

Keywords*: Extrapyramidal symptoms, SSRI, Fluoxetine, Antidepressants.*

INTRODUCTION

Fluoxetine is one of the most widely prescribed selective serotonin reuptake inhibitors (SSRIs), with a favorable safety profile and tolerability making it a cornerstone in psychiatric care for diverse age groups, from children to older adults, thus often used as first-line pharmacotherapy for depression and numerous other psychiatric disorders.[1] Among the SSRIs, Fluoxetine has been associated with most case reports of EPS. Fluoxetine use is associated with significantly higher risk of EPS compared to citalopram (Hazard Ratio ≈ 8.2) with presentations ranging from acute dystonia in adolescents to parkinsonism in adults.[2] Because of this wide use even low-frequency adverse effects are becoming more prevalent, and reports of extrapyramidal symptoms (e.g. dystonia, dyskinesia, akathisia, parkinsonism and neuroleptic malignant syndrome) associated with SSRI use have been accumulating in the literature.[3] Epidemiological studies suggest that EPS occur in about 1 per 1000 adult patients treated with SSRIs.[4] EPS have been reported with different classes of antidepressants, are not dose related, and can develop with short-term or long-term use.[5]The pathophysiology underlying antidepressant-induced EPS remains multifactorial and incompletely understood. Proposed mechanisms include alterations in dopaminergic neurotransmission, serotonin-dopamine interactions, and individual susceptibility factors.[6] Moreover, genetic predispositions and pharmacokinetic properties of specific antidepressants may contribute to the variability in EPS susceptibility across patient populations.[7]

CASE 1

Mr. A, 39 yrs old married male, graduate, working as clerk in bank, residing in nuclear family of middle socio economy status of urban ground of Delhi presented with symptoms of low & irritable mood, anxiety, disturbed sleep, lack of interest & energy and heaviness overhead. There was no precipitating factor or stressor was found. He had no history of medical illness, substance use, or family history of psychiatric or neurological disorders. After detail assessment patient was diagnosed with Moderate Depressive Episode (F32.1) as per ICD 10 criteria. Laboratory investigations including CBC, thyroid profile, liver function, renal function, and electrolytes were within normal limits. Patient was prescribed 20mg of Fluoxetine OD with 0.5mg of clonazepam HS for two weeks after that patient reported slight improvement so Fluoxetine

was increased to 40mg with same dose of clonazepam for next two weeks. Patient follow up after two weeks. Patient reported significant improvement but this time during interview slight tremor was observed when inquired about the same patient also reported increased salivation although it was not significant. There was no rigidity or dystonia was found during neurological examination. Again, fluoxetine was increased to 60mg in divided doses this time patient was also asked to follow up with family member as all the time patient was coming alone. On next visit patient reported that within 10days of dose escalation he developed stiffness of the neck, slowness of movement with marked tremor and drooling of saliva. As mentioned earlier there was no past history of antipsychotic use or other medications that could explain the symptoms. Fluoxetine induced EPS was suspected. 2mg of Trihexyphenidyl was introduced to treatment for symptomatic relief. Fluoxetine was also discontinued. Within a week all of his extrapyramidal symptoms resolved. Patient was later started with Amitriptyline on which he responded well and within 3 months patient was symptom free.

CASE 2

A 22-year-old unmarried female, studied up to 12th, belonging to Muslim joint family of middle socio economy status of rural background of Aligarh, UP presented to the psychiatry outpatient department with a 2-year history of intrusive, repetitive thoughts of contamination and compulsive handwashing rituals, significantly impairing her social and academic functioning. She had no history of medical illness, substance use, or family history of psychiatric or neurological disorders. During the detail assessment she was found to be a drug naïve patient.

The patient was diagnosed with Obsessive–Compulsive Disorder (OCD) as per ICD-10 criteria and was initiated on Tab fluoxetine 20 mg/day, titrated to 40 mg/day after two weeks due to partial response. Within three weeks of dose escalation, she developed stiffness of the neck, tremors of the hands, slowness of movement, and restlessness. Neurological examination revealed rigidity, tremor, and bradykinesia, consistent with extrapyramidal symptoms. There was no past history of antipsychotic use or other medications that could explain the symptoms. Laboratory investigations including thyroid profile, liver function, renal function, and electrolytes were within normal limits. Considering the temporal relationship, fluoxetine-induced EPS was suspected. Fluoxetine was discontinued, and the patient was managed with Tab Trihexyphenidyl 2 mg/day for symptomatic relief. Within one week, her extrapyramidal symptoms markedly reduced, and by the third week, they had completely resolved. She was later started on clomipramine, which was well tolerated and led to gradual improvement in her OCD symptoms.

CASE 3

A 10-year-old male child, student of Std 5th, belonging to Hindu nuclear family of middle socio economy status of urban background of Delhi who was brought to the psychiatry outpatient department with complaints of persistent sadness, irritability, and academic decline for the past 3 months. The onset of symptoms followed a recent change of school, where the child faced repeated incidents of bullying by peers. Family history revealed that the child's mother had an episode of major depressive disorder 5 years ago and was successfully treated(no documentation avilable), while his father had a longstanding history of alcohol dependence. These psychosocial stressors led to poor adjustment, social withdrawal, loss of interest in play, and sleep disturbances. Based on clinical evaluation, a diagnosis of Adjustment disorder was made as per ICD 10 criteria. After psychoeducation and counseling, pharmacological management with 10mg of fluoxetine was initiated considering the persistence and severity of symptoms. Within 2 weeks of starting fluoxetine, the child developed extrapyramidal symptoms (EPS) in the form of tremors, rigidity, and restlessness. Neurological examination and other systemic evaluations ruled out organic causes. Fluoxetine was discontinued, and the EPS symptoms gradually subsided over the next 10 days without the need for additional medications. This case highlights the occurrence of fluoxetine-induced EPS in a pediatric patient, a relatively rare but clinically significant adverse effect, especially in the context of psychosocial vulnerability and positive family psychiatric history.

DISCUSSION

This case series documents fluoxetine-induced EPS across a spectrum of patients, emphasizing that while fluoxetine is widely considered a safe and effective SSRI, rare motor adverse effects may still occur. The observed EPS, including tremors, rigidity, and bradykinesia, reflect disturbances within the basal ganglia motor circuits. The underlying mechanism likely involves fluoxetine's serotonergic enhancement leading to indirect dopaminergic inhibition in the nigrostriatal pathway.[8] Specifically, increased serotonin activity at 5-HT2 receptors modulates dopamine release, resulting in relative dopamine insufficiency akin to that produced by classic dopamine receptor antagonists.[9]

Several risk factors have been identified from previous studies, including higher SSRI doses, rapid dose escalation, age extremes (pediatric or elderly populations), female sex, genetic predispositions such as polymorphisms in serotonin transporter or dopamine receptor genes, and underlying medical or neurological vulnerabilities.[10] In the presented case series, dose escalation appeared to be a critical precipitating factor, with symptoms manifesting shortly after increasing fluoxetine doses.[11] Additional vulnerability in the pediatric case may have been compounded by psychosocial stressors and family psychiatric history, whereas, in adult patients, individual neurobiological sensitivities and pharmacodynamic responses possibly contributed.[12,13]

Our first case involved a 39-year-old male with depression who developed EPS after fluoxetine initiation. Age-related decline in dopaminergic reserve may have contributed to increased susceptibility.[14] The second case, a 22-year-old female with obsessive–compulsive disorder (OCD), developed EPS while on fluoxetine. Higher SSRI doses often required for OCD compared to depression may elevate risk.[15] The third case, a 10-year-old boy with adjustment disorder, presented with EPS in the context of family history of depression and alcohol dependence, suggesting a possible genetic or neurodevelopmental vulnerability.[16] This case also indicate that fluoxetine induced EPS may be not dose dependent.
The mechanism of SSRI-induced EPS is thought to involve excessive serotonergic activity in the basal ganglia, leading to secondary inhibition of dopaminergic neurotransmission.[14] Although the incidence is considered rare, misdiagnosis is common, with symptoms sometimes attributed to psychiatric illness progression or noncompliance. Timely identification and discontinuation of the offending agent usually result in symptom resolution.

CONCLUSION

This case series underscores the importance of vigilant monitoring for extrapyramidal symptoms in patients on fluoxetine, especially during dose escalation. Early recognition and prompt discontinuation often lead to complete resolution, highlighting the reversible nature of this adverse effect. Systematic documentation of such adverse effects can inform practice guidelines, improve early detection, and encourage personalized prescribing strategies that take into account genetic and individual vulnerabilities.

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