A Unique case of Flunarizine Induced Extrapyramidal Syndrome and Depression

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ABSTRACT
Flunarizine is one the cerebroselective calcium channel blocker, commonly prescribed for migraine prophylaxis in neurology clinic. It is considered as non inferior to propranolol and amitriptyline to reduce the frequency of migraine attacks. Here we report a case flunarizine induced extrapyramidal syndrome and depression. A 37 year old female on tablet flunarizine 15 mg daily for her migraine signs of depression and restlessness, propensity to bend, slow reactions and mask face. Depression was rated using patient health questionnaire and extrapyramidal syndrome was diagnosed by modified simpson angus scale and Barnes akathisia rating scale. Considering nil organic lesion and improvement of all symptoms with the cessation of flunarizine, case was diagnosed as flunarizine induced depression and extrapyramidal disorder.

Key words: Adverse drug reaction, Flunarizine, Drug induced depression, Extra pyramidal Syndrome, Pharmacovigilance.

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CASE REPORT
A 37 year old married female with nil significant past medical illness or psychiatric illness presented with one month history of disturbed sleep, crying spells, decreased psychomotor activity, lack of interest in day to day activities. The patient also complained of pain in the neck with difficulty in moving her neck sideways freely. Her family members noted that her walking pace was slow and facial expression was restricted during the above mentioned period. Her major concern at the time of presentation was restlessness and inability to stand still with a tendency to move. She was also concerned that the present state is not her usual self and there was no other precipitating factors or stressors or life events that could have precipitated these symptoms.

The patient had consulted a psychiatrist who started her on Escitalopram 10 mg with clonazepam 0.5 mg once daily, to lisopam 50 mg twice daily and busiprone 5 mg thrice daily. The patient was on above medicines for almost 15 days when she presented to us with minimal improvement in sleep. There was no improvement in subjective sadness, restlessness in legs and slowness in psychomotor activity.

Past medical history revealed that the patient was on treatment with Flunarizine 15 mg once daily for the past one month for complaints of recurrent right sided unilateral headache associated with nausea and vomiting. There were no other associated symptoms of aura or signs of intracranial tension.

There was no family history of mental illness or seizures, thyroid dysfunction or asthma or migraine. General examination and systemic examination was within normal limit except for mask like facies, decreased arm swing and restricted movement at the neck.

On Mental state examination, her general appearance was appropriate; She was unable to sit for awhile with a tendency to keep alternating her feet, speech was relevant and coherent with normal volume. Thought content was preoccupation with her current state with no depressive cognitions. Her mood was reportedly sad and affect was restricted with decreased range and reactivity. There were no perceptive abnormalities and insight was good. Higher cognitive functions were intact.

Her blood investigations gave the following values hemoglobin–12. gm%, WBC count-5600 cells/mm³; platelet count–3.2 lakhs/mm³; random blood sugar-122 mg/dl. His metabolic parameters including renal function, liver function, lipid profile were within normal limits. On Modified Simpson angus scale for extra pyramidal symptoms, she scored 7 which indicates clinically significant degree of movement disorder. On Barnes akathisia rating scale, she scored 7 again which indicates moderately severe akathisia with distress.

After ruling out organic and medical work up, the possibility of drug induced depression with EPS was thought of. After admission, the patient was continued on T Escitalopram 10 mg with clonazepam 0.5 mg combination and other drugs were stopped. She was started on T. lorazeepam 2 mg BD in view of insomnia and agitation. The patient was admitted on 28th May 2015. The patient reported improvement in sleep and restlessness and a tendency to move and also 40% improvement in subjective mood state within 2 days of admission. There was no objective restlessness or squarming in seat noted during review. The informant reported improvement in terms of sleep, movements of neck and restlessness. There was a significant improvement noted objectively in terms of neck movement and patient reported decrease in pain. As her slowness in walking, restricted affect persisted, she was also started on T. Trihexyphenidyl 2 mg once daily. Considering the improvement that happened with stopping Flunarizine (the major change in drug prescription) and the fact that Flunarizine is likely to produce EPS, the final diagnosis was made as flunarizine induced extra pyramidal disorder and depression.

DISCUSSION
Drug induced extra pyramidal symptoms varies from parkinsonism, akathisia to severe neuroleptic malignant syndrome. These disorders are commonly seen with potent dopamine receptor (D2) blockers like neu-
roleptics, prokinetics like metaclopromide etc. Drug induced parkinsonism is more common in females and neurological deficits is likely to be more in drug induced parkinsonism.¹

Flunarizine is cerebroselective, non dihydropyridine calcium channel blocker given as prophylactic treatment of migraine. Flunarizine is devoid of major cardiovascular effects unlike other drugs given for same purpose including beta adrenergic blocker (propranolol), tricyclic antidepressants (amitriptyline). There are few documented cases of extra pyramidal disorder by flunarizine, however flunarizine induced extra pyramidal symptoms (parkinsoniam, akathisia) as well as depression is rarely encountered in the literature.²

Possible mechanisms by which flunarizine produces EPS are chemical and structural similarity to that of neuroleptic agents. Other postulated mechanisms are flunarizine exhibit significant dopamine receptor binding in radio ligand assay. Phenotypic expression of extrapyramidal features gets accentuated if patients receive concomitant medication that affect dopamine synthesis or block dopamine receptors in nigrostraital pathway. In a case series reported among fifteen patients who were all receiving flunarizine along with antivertigo drug cinnarizine, eleven patients developed parkinsonism and one patient had akathisia as well.³⁴

Our case is unique in the way that our patient developed depression apart from mixed symptoms of extrapyramidal disorder. Exact mechanism of flunarizine induced depression is not understood. Commonly onset of these symptoms varies from three months to twenty months after starting treatment with flunarizine;³ whereas in our case symptoms were seen within first month of treatment. Depression was evident even when patient was on other antidepressants prescribed by a psychiatrist, namely esicitalopram and buspirone. Symptoms improved only after cessation of flunarizine from the prescription.

CONCLUSION
Flunarizine is prone to induce extrapyramidal syndrome and depression episodes in susceptible patients, the same must be looked for whenever patient is on long term treatment with flunarizine. Concomitant treatment with antidopaminergic drugs and flunarizine should be given with caution.

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CONFLICT OF INTEREST
None.

ABBREVIATION USED

REFERENCES