CASE REPORT

Flunarizine-induced Depression: A Case Report with Review of Literature

Gagandeep Ahuja[1], Anupama Arora[2], Simran Gupta[3]

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Abstract

Aim and background: Flunarizine, a cerebro-selective calcium channel blocker, prescribed worldwide for migraine prophylaxis, has demonstrated efficacy and safety in different migraine types and patient populations, comparable to other first-line antimigraine drugs used for migraines such as propranolol, topiramate, amitriptyline, and valproate.

Case description: A 35-year-old female primarily came to the outpatient department for treatment of headache and was started on Flunarizine 10 mg. Her headache significantly reduced but after 8 weeks she reported complaints of low mood, reduced sleep, reduced appetite, loss of interest in work, and crying spells. She was treated with adequate doses of Sertraline but showed no improvement in symptoms. Mental status examination revealed depressed affect, anhedonia, and negative cognition. After ruling out organic causes and medical work-up, drug-induced depression was considered, and flunarizine was stopped, and Sertraline was continued at the same dose. After she reported an improvement in depressive symptoms, the diagnosis was changed to drug-induced depression.

Conclusion: Flunarizine may induce depressive symptoms in susceptible patients. Patients receiving long-term flunarizine should be regularly monitored for any signs of depression. If a patient develops symptoms indicative of depression after the initiation of a given agent; another agent should be considered.

Clinical significance: As a clinician, we can never be too cautious of the adverse reactions of the prescribed drugs, hence, we should always be vigilant and prepared if the situation ever arrives.

Keywords: Adverse drug reactions, Case report, Depression, Flunarizine.

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Introduction

Depressive symptoms may be seen with several medications. This might occur due to alteration of neurotransmitter levels in the central nervous system (CNS) or due to adverse effects such as lethargy, reduced appetite, etc. causing subsequent irritation, dismal, or even a full depressive episode.[1] Depression is more prevalent in patients with physical illness as compared to the general population. Studies have shown that nearly 10–20% of patients having acute cardiac disease, diabetes, renal failure, or cancer suffer from major depressive disorder (MDD), while clinically significant, subsyndromal depressive symptoms are seen more frequently.[2–5] Thus, assessing the causal or spurious relationship between medication and depression can be challenging. A few case reports and small studies report the association of medicine with the onset of depressive symptoms. Here, we outline the case of Flunarizine-induced depression in a 35 years old female.

Case Description

A 35 years married female, Mrs D, with nil significant past medical illness or psychiatric illness, presented with 4 month history of recurrent right-sided unilateral moderate to severe pulsating headache associated with nausea and photophobia. There were no other associated symptoms of aura or signs of raised intracranial tension. There was no family history of mental illness, seizures, thyroid dysfunction, asthma, or migraine. General physical examination and systemic examination including fundus examination was within normal limits. On the mental status examination, her general appearance was appropriate, psychomotor activity was average, speech was relevant and coherent with normal volume, and affect was euthymic. Thought content was a preoccupation with the episodes of headache with no depressive cognition. There were no perceptual abnormalities. Higher cognitive functions were intact and insight was good.

Her metabolic parameters including complete hemogram, random glucose levels, kidney function test, hepatic function, lipid panel, and thyroid profile, were within normal limits. She was diagnosed with "Migraine without aura" as per The International Classification of Headache Disorders 3rd Edition (ICHD-3) criteria.[6] She was started on tablets naproxen 500 mg si opus sit (SOS) and amitriptyline 25 mg, which was gradually increased to 100 mg in the next follow-ups spanning over 7–8 weeks as the patient showed only slight improvement. When the patient showed no significant improvement even on 100 mg Amitriptyline, she was switched to

[1–3]Department of Psychiatry, Dr. Yashwant Singh Parmar Government Medical College Nahan, Himachal Pradesh, India

Corresponding Author: Anupama Arora, Department of Psychiatry, Dr. Yashwant Singh Parmar Government Medical College Nahan, Himachal Pradesh, India, Phone: +91 9805607093, e-mail: dr.aarora07@gmail.com

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Table 1: Summary of events and management as per the timeline

Timeline	*Event*	*Management*
Day 0	Recurrent right sided unilateral moderate to severe pulsating headache, with nausea and photophobia	Tab. Naproxen SOS Tab. Amitriptyline 25 mg
At 7–8 weeks	Slight improvement in headache	Tab. Amitriptyline increased upto 100 mg Tab. Naproxen SOS
~10 weeks	No significant improvement	Tab. Flunarizine 10 mg/d started Tab Headset SOS Tab. Amitriptyline gradually tapered off and stopped
~14–16 weeks	Reduction in severity and frequency of episodes of migraine. Depressive symptoms reported HAM-D score 21	Tab. Sertraline 50 mg/d, increased upto 100 mg/d Tab. Clonazepam 0.5 mg HS Tab. Flunarizine 10 mg/d and Tab. Headset SOS continued Cognitive therapy and supportive sessions taken
~20–21 weeks	No improvement in depressive symptoms	Tab. Flunarizine 5 mg/d Tab. Sertraline 100 mg/d
~22–23 weeks	~15–20% improvement in depressive symptoms	Flunarizine was stopped Rest treatment was continued
~26–27 weeks	Significant improvement seen HAM-D score 8	

10 mg flunarizine and tablet headset SOS (Sumatriptan 85 mg and naproxen 500 mg).

Over the next 2 weeks, the patient showed improvement; as the frequency of her headache episodes reduced from once daily to once per week. Flunarizine was continued at the same dose for the next 4 weeks and the frequency of her episodes was reduced even further. After around 7–8 weeks on Flunarizine 10 mg, upon her usual follow-up, for the first time patient reported the complaints of sadness of mood, disturbed sleep, reduced appetite, anhedonia, and easy fatiguability with routine work. No recent stress factors were elicitable. General physical and systemic examinations was within normal limits at this point too. Mental status examination showed her to be adequately kempt, and cooperative. She spoke in a reduced tone and volume. Depressed affect was observed during the interview. Thought content revealed preoccupations regarding her illness, worthlessness, and helplessness. No ideations or plans of self-harm, illusions, or hallucinations could be elicited. Higher mental functions and insight were intact. Hamilton depression rating scale (HAM-D) was applied according to which moderate depression was noted with a score of 21.[7] Tablet sertraline 50 mg was started which was increased to 100 mg on the next follow-up after 1 week. Flunarizine 10 mg and Headset were continued as such. Clonazepam 0.5 mg Hora Somni (HS) was also started for the complaint of reduced sleep.

This treatment was continued for the next 4–5 weeks along with cognitive therapy and supportive sessions but the patient reported no improvement in depressive symptoms. At this point, after detailed medical work-up and ruling out organic causes, the likelihood of drug-induced depression was considered. So, Flunarizine was reduced to 5 mg and Sertraline was kept at the dose of 100 mg. After 2 weeks, the patient reported around 15–20% of subjective improvement after which flunarizine was stopped while other drugs were continued. She showed consistent improvement over the next 1 month as her mood almost reached baseline, appetite and sleep improved, and she commenced her household duties. Her HAM-D score also reduced to 8. Considering the substantial reduction in symptomatology seen once the medication flunarizine was stopped, the final diagnosis was concluded to drug-induced depression (Table 1).

Discussion

Depression and migraine have a strong, bidirectional relationship. Patients with migraine are at a 2–4 fold increased risk of depression, and patients with a depressive disorder are 3 times more likely to get migraine; suggestive of a common pathophysiology, probably comprising serotonergic and gamma-aminobutyric acid (GABA) ergic neurotransmitter systems.[8–10]

Quality of life as well as holistic treatment of migraine is adversely affected in such patients.[11] Therefore, while determining the course of therapy, especially for vulnerable individuals, it is noteworthy to regard the potential of antimigraine medications to produce depressive symptoms.

A randomized, double-blind, prospective study of migraine prophylaxis showed that 8% of patients treated with flunarizine developed depressive symptoms leading to discontinuation of the treatment.[12] Calcium channel blockers may cause depression by blocking the slow entry of calcium into cells, which prevents the release of calcium-dependent neurotransmitters, thus reducing neurotransmitter amplification through the second-messenger system.[13]

Prophylactic treatment of migraine can also be accomplished by using anticonvulsants (e.g., topiramate, valproic acid), tricyclic antidepressants (TCAs) (e.g., amitriptyline), and ß-blockers (e.g., propranolol). Topiramate appears to increase the risk of depression, while valproic acid does not.[14] Ten percent of patients treated with topiramate developed depression; history of depression and rapid escalation of dose being significant factors in increasing the risk of depression.[14–16] Depression and even comorbid migraine is effectively treated with Amitriptyline and other TCAs.[11] Lastly, although ß-blockers were previously thought to cause depressive symptoms,[17–19] latest research (including a large meta-analysis) has shown that they do not.[20,21]

More than a dozen different classes of drugs have been found to have possible depressive and other psychiatric adverse drug reactions (ADR). The limitation is that scientific evidence linking certain medications to depressive disorder is not extensive and the information offered in reference sources might not be well supported by research.

Conclusion

Patients receiving long-term flunarizine should be regularly monitored for any signs of depression. However, in prospective studies flunarizine does not usually cause depression in the majority of patients and depression is rarely an absolute contraindication for the use of this medication. Many factors should be contemplated before starting treatment such as understanding the possible advantage of the medication on the medical complaint, the presence of non-depression inducing drugs to treat the disorder, and the history of depression in the patient, must be considered by the attending for prescribing the best course of action.

Finally, one last remark: even though a particular medicine may not generally result in a depressive state, idiosyncratic responses might happen due to genetic predispositions and environmental stressors. Hence, if a patient develops symptoms indicative of depression upon commencement of a given medication; alternative medication should be taken into consideration.

Clinical Significance

As a clinician, we can never be too cautious of the adverse reactions of the prescribed drugs, hence, we should always be vigilant and prepared if the situation ever arrives. As Hippocrates said 'do no harm', it is our solemn duty to understand the implications of the prescribed medications and outweigh the benefits over the risks.

Orcid

Gagandeep Ahuja https://orcid.org/0009-0006-0181-0605
Anupama Arora https://orcid.org/0009-0007-6179-8633
Simran Gupta https://orcid.org/0009-0003-1866-143X

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