



# Calcium channel blocker-induced depression: a case report from South India

## Abstract

Flunarizine is a cerebro-selective calcium channel blocker, commonly prescribed for migraine prophylaxis and is considered as non-inferior to propranolol to reduce the frequency of migraine attacks. A 50-year-old female with history of headache for last seven years was using analgesics on and off. As frequency of headache increased, she consulted a doctor one year back and was started on flunarizine 15 mg. She used the medication for eight months without follow-ups and there was moderate improvement. She came to us four months back with complaints of sad mood, decreased sleep, decreased appetite, decreased interest to do work, crying spells, death wishes, and was treated with adequate doses of amitriptyline but had no improvement in symptoms. No medical comorbidities were found. Mental status examination revealed sad mood, anhedonia, negative cognition. After ruling out organic causes and medical work-up, drug-induced depression was considered and flunarizine was stopped, and amitriptyline dose was continued. She reported amelioration in depressive features; following which, diagnosis was revised to drug-induced depression.

**Keywords:** Flunarizine. Migraine. Propranolol. Analgesics. Amitriptyline.

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## INTRODUCTION

Medications can lead to depressive symptoms. These effects can be directly due to altering levels of neurotransmitters in the central nervous system (CNS). Alternatively, they can also be indirect, by causing fatigue, diminished appetite, sedation, or other side effects, leading to subsequent frustration, demoralisation, or even a full depressive episode.[1]

However, it is often difficult to ascertain whether a medication has caused depression in any given patient.[1] The literature supporting an association of drugs with depression is largely comprised of case reports and retrospective observational studies, making the case for causality difficult. Flunarizine is a cerebro-selective calcium channel blocker, commonly prescribed for migraine prophylaxis and is considered as non-inferior to propranolol to reduce the frequency of migraine attacks.[2] We report a case of flunarizine-induced depression from rural South India.

## CASE REPORT

A 50-year-old female, Mrs. X, hailing from rural South India, belonging to Hindu faith, reported history of headache for seven years and was using analgesics, mostly paracetamol intermittently without consulting a doctor. As frequency of headache increased, she consulted a doctor one year back and was started on flunarizine 10 mg for 2 weeks following which the dosage was increased to 15 mg, and she had improvement in the frequency and severity of headache. Mrs. X continued taking the medication without follow-up for eight months.

She was brought to the psychiatry outpatient department (OPD) with complaints of sad mood, decreased sleep, decreased appetite, lack of interest to do work, easily fatigued with routine work, crying spells, death wishes, occasional headache for the past four months. Patient and family members did not report any stressors in the recent past. No significant past or family history of mental illness, medical or surgical comorbidities were noted. Physical and systemic examination were within normal limits. Mental status examination found her to be moderately kempt, cooperative, and elaborative in her complaints with crying spells noted during the interview. She spoke in a reduced tone and volume. She was preoccupied with her illness and harboured negative cognitions and death wishes. Her mood was reportedly sad with objective corroboration of low mood. She did not harbour suicidal ideas/plans and perceptual abnormalities were not found. Higher mental functions were intact with insight recorded as grade four. A provisional diagnosis of moderate depressive episode was made as per the tenth revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10).[3] Beck's Depression Inventory (BDI)[4] and Hamilton Rating Scale for Depression (HAM-D)[5] scales were applied at the time of admission and the scores were 24 and 17 respectively indicating moderate depression.

She was advised admission and was initiated on tablet amitriptyline 25 mg twice daily along with continuation of tablet flunarizine 10 mg. Her blood investigation reports were: haemoglobin=12.7 g/dl, white blood cells=10600/microlitre,

neutrophils=66.6%, lymphocytes=23.1%, monocytes=6.1%, eosinophils=3.9%, basophils=0.3%, red blood cells=4.36 million, mean corpuscular volume=89.7 fl, mean corpuscular haemoglobin=29.1 pg/cell, mean corpuscular haemoglobin concentration=32.5 g/dl, platelet count=359000/microlitre, platelet distribution width=16.2%, triiodothyronine=0.97 ng/ml, tetraiodothyronine=6.37 microgram/dl, thyroid stimulating hormone=1.95 micro IU/ml, serum total cholesterol=158 mg/dl, serum triglycerides=112 mg/dl, serum high density lipoprotein=30 mg/dl, serum low density lipoprotein=105 mg/dl, random blood sugar=91 mg/dl, total serum bilirubin=0.4 mg/dl, direct bilirubin=0.02 mg/dl, total serum protein=6.7 g/dl, serum albumin=3.4 g/dl, globulin=3.2 g/dl, serum alkaline phosphatase=82 IU/L, blood urea=9.6 mg/dl, serum creatinine=0.7 mg/dl.

The dose of amitriptyline was increased to 150 mg in divided doses per day over eight days; but, she reported minimal improvement in her symptoms. After ruling out organic causes and detailed medical work-up and physician review, the possibility of drug-induced depression was considered. She was advised to stop tablet flunarizine on day 12 and tablet amitriptyline 150 mg in divided doses was continued. The patient reported improvement in mood, decreased crying spells, and no death wishes within one week and continued to show consistent improvement over one month. The patient presented the following month for review with mood almost having reached baseline, no crying spells, and having commenced her household duties and no further episodes of headache. Considering the significant improvement noted in all symptomatology with the discontinuation of flunarizine (the major change in drug prescription), the final diagnosis was revised to drug-induced depression.

## DISCUSSION

The text revision of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) defines substance-induced depression as a prominent and persistent disturbance of mood that occurs during use of a medication causally related to depression, or within

one month of intoxication or withdrawal of therapy with a medication.[6] Symptoms must be severe enough to result in clinically significant distress in social, occupational, or other areas of functioning.[6]

Depression and migraine headaches frequently co-occur. Patients with migraine headaches have a two- to four-fold increased risk for depression, while patients with depression are at a three-fold increased risk for developing a migraine headache.[1] This bi-directionality suggests that these disorders share a common pathophysiology, most likely involving the serotonergic and gamma-Aminobutyric acid (GABA)-ergic neurotransmitter systems.[1] Depression in these patients not only impinges upon quality of life, but may also adversely impact the overall prognosis of migraine treatment.[1]

Flunarizine, is a calcium-channel antagonist used for acute and prophylactic treatment of migraine headaches.[1] Flunarizine is a di-fluorinated derivative of cinnarizine, being 2.5 to 15 times more potent than cinnarizine.[7] Flunarizine acts as a selective calcium entry channel blocker and is also neuroleptic-simile, and has antihistaminic, anti-serotonergic, and antidopaminergic activity.[7]

A study done by Fabiani *et al.*[7] which assessed for chronic use of cinnarizine and flunarizine subsequently causing movement disorders and other side effects, wherein out of 26 outpatients, nine patients met the DSM-IV diagnostic criteria for major depression as well as diagnostic criteria for parkinsonism: one patient reported bucco-linguo masticatory syndrome (BLMS) plus parkinsonism, one reported BLMS plus parkinsonism and akathisia, one reported BLMS only, and one reported dystonia. Capellà *et al.*[8] in Spain reporting adverse drug reactions secondary to calcium channel blocker use, found 86 reports which refer to cinnarizine as the suspected drug, 25 to flunarizine, and five to both drugs taken simultaneously. Of these 116 reports, 87 described extrapyramidal symptoms, or depression, or both; cinnarizine had been taken in 70 cases, flunarizine in 13, and both drugs in four.[8]

In a randomised, double-blind, prospective study of migraine prophylaxis, eight per cent of flunarizine-treated

**Table 1:** Evidence for drug-induced depression associated with drug groups[9]

Drug class/drug	Level of evidence	Available literature	Comments
Beta blockers	Limited evidence	Case reports, randomised clinical trials, large scale meta-analyses	Evidence is conflicting: propranolol may have the strongest association with symptoms after starting or increasing dose
Calcium channel blockers	Limited evidence	Case reports, case series, cohort study examining suicide rates	Results are conflicting: newer agents have fewer reports
Angiotensin-converting enzyme inhibitors	Limited evidence	Prescription symmetry analysis	Some reports have found antidepressant effects
Angiotensin II receptor blockers	Limited evidence	Case reports	Preliminary data suggest some angiotensin II receptor blockers may have antidepressant effects
Isotretinoin	Very strong evidence	Over 400 case reports, prescription symmetry analysis, case-crossover study	No comment
Corticosteroids	Strong evidence	Case-control study, cross-sectional analysis	Results of trials are suggestive of drug-induced depression, especially in patients aged >65 years; but, not conclusive

patients developed depressive symptoms that led to treatment discontinuation.[1] Commonly, onset of depressive symptoms varies from three months to 20 months after initiating flunarizine. Exact mechanism of flunarizine-induced depression is not understood, may be due to the antiserotonergic and antidopaminergic properties of the drug. Possible mechanism for calcium channel blocker-induced depression may be due to blockage of slow influx of calcium into the cell, inhibiting calcium-dependent neurotransmitter release and reducing neurotransmitter amplification through the second-messenger system.[9] It has been identified that more than a dozen classes of medications have putative depressive effects.[9] Some have provoked official alerts from the US Food and Drug Administration (FDA), whereas others have elicited isolated case reports of drug-induced depression.[9] A list of the agents is presented in Table 1, where the level of evidence associated with each class is indicated.[9]

The limitations are that the scientific evidence associating specific drugs with depression is not extensive, and some information presented in reference sources may consequently be poorly supported by research. Further research is required on clinical and scientific grounds.

## Conclusion

Flunarizine is prone to induce depression in susceptible patients and the same must be looked for whenever patient is on long-term treatment with flunarizine. The ability of a drug to cause depression (or other toxicity) is only one of several considerations in deciding whether to discontinue the use of the drug.[10] These decisions should be made on an individual basis, weighing the clinical benefits of continuing the drug against the potential risks. Awareness regarding

possible risks when extensive long-term use of medications without medical follow-ups occurs should also be emphasised during patient psychoeducation.

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