



Letter to the Editor

Possible desvenlafaxine associated hypoglycemia in an adult woman with major depressive disorder



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1. Introduction

Both selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors (SNRIs) have been implicated in rare cases of hypoglycaemia through potential mechanisms involving enhanced insulin sensitivity, increased peripheral glucose uptake, altered insulin secretion, and reduced hepatic gluconeogenesis (Derijks et al., 2008). Among SNRIs, hypoglycemia has been reported most frequently with venlafaxine, predominantly following overdose, although rare cases have also been described at therapeutic doses (Francino et al., 2012; Özdemir, 2022).

Desvenlafaxine, the principal active metabolite of venlafaxine, shares similar pharmacological properties; yet, there are no available reports of hypoglycaemia associated with its therapeutic use. We describe what we believe to be the first such report, involving a medically healthy adult woman who developed recurrent symptomatic hypoglycaemia while receiving concomitant fluoxetine and desvenlafaxine. Although an additive serotonergic effect cannot be excluded, the temporal relationship with the onset of hypoglycemia and sustained resolution following desvenlafaxine withdrawal suggests a possible causal role for desvenlafaxine.

2. Case report

Mrs. T, a 38-year-old married woman, presented with a five-month history of major depressive disorder with prominent obsessive symptoms. She had no personal history of diabetes mellitus, endocrine illness, hepatic disease, renal disease, or any other significant medical disorder. She had a positive family history of depression in her father.

She was initially treated elsewhere with escitalopram 10 mg/day and olanzapine 5 mg/day for approximately three months without meaningful clinical improvement. Following evaluation at our center, both medications were discontinued, and fluoxetine was gradually titrated to 60 mg/day over three weeks. She remained on fluoxetine 60 mg/day for a further four weeks without developing hypoglycemia or any other significant adverse effects. As her clinical improvement remained

suboptimal, desvenlafaxine was added and gradually titrated to 100 mg/day. Clonazepam 0.5 mg/day was also prescribed to manage her anxiety symptoms.

The patient showed significant improvement and remained stable on the combination of fluoxetine 60 mg/day, desvenlafaxine 100 mg/day, and clonazepam 0.5 mg/day for approximately four months. During the fifth month of combination treatment, she presented to the emergency department with sudden onset of sweating, palpitations, tremulousness, giddiness, and marked fatigue. She reported having consumed her usual meals and denied any dietary modifications, fasting, or increased physical activity. She also confirmed that there had not been any change in the brand of any of the prescribed medications.

Physical examination was unremarkable. Her plasma blood glucose was 56 mg/dL, and the corresponding serum insulin level was 50 μ U/mL. Glycated haemoglobin (HbA1c) was 5.6%. Further investigations, including complete blood count, serum electrolytes, liver, renal, and thyroid function tests, serum cortisol, and electrocardiogram were within normal limits.

She improved following intravenous dextrose administration and was discharged. However, she returned the following day with identical symptoms occurring at approximately the same time. This time, her blood glucose was 40 mg/dL, and serum insulin level was 100 μ U/mL. The symptoms again resolved promptly following intravenous glucose administration. In view of the recurrent episodes of hypoglycemia, desvenlafaxine was discontinued. Fluoxetine 60 mg/day and clonazepam 0.5 mg/day were continued unchanged. No other therapeutic modifications were made.

Following discontinuation of desvenlafaxine, she experienced no further hypoglycemic episodes. One week later, fasting blood glucose was 120 mg/dL with a corresponding serum insulin level of 20 μ U/mL. A repeat test, 3 weeks later, showed a blood glucose of 130 mg/dL and a serum insulin level of 15 μ U/mL. Her depressive symptoms remained well controlled while continuing fluoxetine therapy. She has remained under regular psychiatric follow-up for six months after discontinuation of desvenlafaxine, without any recurrence of hypoglycemia.

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patient.

3. Discussion

This case suggests a probable association between desvenlafaxine therapy and recurrent symptomatic hypoglycemia. While venlafaxine-associated hypoglycemia has been documented previously, to our knowledge, there are no prior reports of desvenlafaxine-associated hypoglycemia. In fact, the only available report of desvenlafaxine effects on glucose homeostasis described a case of treatment-emergent hyperglycemia (Mekonnen et al., 2020).

Several biological mechanisms may account for hypoglycemia with desvenlafaxine, the major active metabolite of venlafaxine. It has been suggested that increased serotonergic tone can enhance insulin sensitivity and increase peripheral glucose utilization (McIntyre et al., 2006). Pre-clinical evidence also suggests a direct effect of serotonin on insulin secretion (Yamada et al., 1990). Venlafaxine has also been suggested to exert μ -opioid receptor-mediated effects that may contribute to hypoglycemia (Brvar et al., 2015).

An important consideration in the present case is the concurrent administration of fluoxetine and desvenlafaxine. SSRIs have also been associated with alterations in glucose homeostasis, and the mechanisms underlying SSRI- and SNRI-associated hypoglycemia overlap substantially (Derijks et al., 2008). Consequently, a synergistic or additive serotonergic effect of both agents cannot be entirely excluded.

Nonetheless, several observations point to desvenlafaxine as the more likely culprit. First, the patient tolerated fluoxetine monotherapy 60 mg/day for four weeks without developing hypoglycemia. Second, recurrent hypoglycemia episodes developed only after desvenlafaxine was added to the treatment regimen. Third, following withdrawal of desvenlafaxine, hypoglycemia resolved completely despite continuation of fluoxetine at the same dose, with no recurrence over 6 months of follow-up. Furthermore, the concomitant elevation of serum insulin during hypoglycemic episodes suggests a drug-related alteration in insulin regulation or sensitivity rather than simple fasting hypoglycemia. Collectively, these findings suggest that desvenlafaxine was the more likely contributor, although a synergistic effect of the two serotonergic antidepressants cannot be excluded.

The Naranjo Adverse Drug Reaction Probability Scale yielded a score of 4, indicating a “possible” adverse drug reaction (Naranjo et al., 1981). The score was based on the temporal relationship between drug exposure and onset of hypoglycemia, objective confirmation of hypoglycemia, and complete resolution following withdrawal. Rechallenge was not attempted for ethical reasons.

Clinicians should remain vigilant of the possibility of hypoglycemia during treatment with serotonergic antidepressants, particularly during combination treatment. Prompt recognition of this uncommon adverse effect may facilitate timely diagnosis, management, and prevent potentially serious complications. In the index patient, no hypoglycemic episodes occurred in the first four months of combination treatment; prior reports have shown variable intervals between onset of treatment and hypoglycemic episodes (Özdemir, 2022; Pollak et al., 2001), and this merits further study.

To our knowledge, this is the first report of recurrent symptomatic hypoglycemia temporally associated with desvenlafaxine therapy. Although an additive serotonergic effect cannot be completely excluded, the temporal sequence, positive dechallenge, normalization of blood glucose and serum insulin levels following desvenlafaxine withdrawal, and absence of recurrence during six months of follow-up support a possible causal association with desvenlafaxine. Additional pharmacovigilance reports and observational evidence are needed to better characterize the relationship between desvenlafaxine and disturbances in glucose homeostasis.

CRedit authorship contribution statement

Pattath Narayanan Suresh Kumar: Writing – original draft, Resources, Methodology, Investigation, Conceptualization. **Rohith Suresh:** Writing – review & editing, Methodology, Investigation. **Vikas Menon:** Writing – review & editing, Project administration, Conceptualization.

Ethics declaration

This is a case report of a single case and hence, ethics committee approval was not required. Written informed consent from the patient was obtained for publication.

This research follows the CARE guidelines and the CARE checklist.

Informed consent statement

Written informed consent for publication of this report has been obtained from the patient.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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