

Blood Sugar Blues:

Hypoglycemia and Antidepressants

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Venlafaxine (Effexor™) is a relatively new selective serotonin and norepinephrine reuptake inhibitor (SNRI) antidepressant. It has been available in Canada for less than 10 years. Like other selective serotonin reuptake inhibitors (SSRIs), the safety profile of venlafaxine in overdose is significantly better than the tricyclic antidepressants.¹ However, evidence has accumulated over the last decade suggesting that it may not be as benign as original-

Julia's case

Julia, 28, presented after a generalized seizure at home. Four hours earlier, she had taken an intentional overdose of 60 x 75 mg tablets of venlafaxine. She had consumed several alcoholic drinks eight hours prior to admission, but denied all other ingestions/drug use. She has a history of depression, but no previous suicide attempts. She has been taking venlafaxine, 75 mg orally, three times daily for one year.

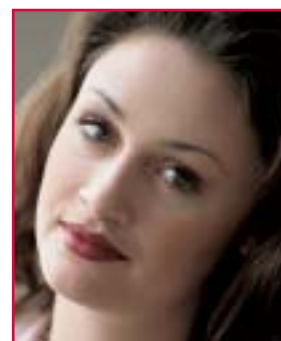


Table 1

Lab exams

- BP: 120/80 mmHg
- HR: 164 bpm
- Temperature: 37.8 C
- Myoclonic jerking
- Marked physiologic nystagmus
- Normal, symmetric reflexes
- Liver not palpable
- Normal span on percussion
- Remainder of exam unremarkable

BP: Blood pressure
HR: Heart rate
bpm: Beats per minute

The post-seizure blood glucometer reading was below the glucometer's lower limit of detection and the patient was able to take a 30 g glucose load orally. On admission to the emergency department (ED), just after the oral glucose load, Julia's blood sugar was reported by the lab as 4.5 mmol/L. She had a second seizure in the ED that was treated with intravenous (IV) lorazepam. Her blood sugar was not checked again for 20 hours (Table 1).

Julia remained obtunded during her first day in hospital, and was maintained on IV dextrose, 5%, at 100 cc/hour. Despite this, when a repeat glucometer reading was taken, it was found to be 1.8 mmol/L. The lab measured her glucose as 2.9 mmol/L on a sample drawn a few minutes later, as an IV bolus of 50% glucose solution was given to correct Julia's persistent hypoglycemia. When the IV glucose was discontinued, subsequent glucometer readings remained low, between 2.9 mmol/L and 3.3 mmol/L. Therefore, Julia was given IV dextrose, 5%, until her third day in hospital, when she was able to begin eating normally.

For a followup on Julia, see page 66.

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A followup on Julia

Julia was contacted by telephone approximately 14 months after her overdose. She remains well, is off all antidepressants, and is finishing university. She has had no subsequent problems with blood sugar, symptoms of hypoglycemia, or seizures. She continues to deny any co-ingestions at the time of her overdose, and confirmed the same version of events that she had initially described on her history in the ED.

ly thought. To date, the most commonly reported serious adverse effect of overdose is seizure.

What is the differential diagnosis of hypoglycemia?

A diagnosis of hypoglycemia requires three criteria (Whipple's Triad):

- The serum glucose must be < 2.2 mmol/L in women and < 2.8 mmol/L in men.
- There must be adrenergic or central nervous system symptoms of hypoglycemia.
- There must be improvement in symptoms with administration of glucose.

Hypoglycemia has multiple causes, including hyperinsulinism, glucose overutilization, and glucose underproduction (Table 2).

In Julia's case, she fulfilled the clinical criteria for hypoglycemia, but did not appear to fit into any of the above diagnostic categories. Her lowest glucometer reading was 1.8 mmol/L. A serum sample, taken while her blood sugar was

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Table 2

Glucose production

Glucose overutilization/hyperinsulinism

- Drugs (sulfonylureas, ethanol, salicylates, quinine, haloperidol)
- Factitious (exogenous insulin)
- Insulinoma
- Insulin receptor antibodies

Glucose underproduction

- Liver disease or dysfunction (impaired hepatic gluconeogenesis)
- Malnutrition
- Hormone deficiency
- Toxic or septic shock
- Congenital metabolic disorders
- Congenital enzyme deficiency

2.9 mmol/L, was tested for first- and second-generation sulfonylureas. She had no detectable sulfonylurea level.

Hyperinsulinism (exogenous insulin or insulinoma) was also considered in the differential diagnosis. Insulin levels in normal subjects should be suppressed in the presence of hypoglycemia. Julia's insulin level, drawn when the measured glucose was 2.7 mmol/L, was relatively low at 14 pmol/L. The standard method of determining whether the degree of insulin suppression is appropriate for the severity of the hypoglycemia is to calculate the ratio of the serum insulin to glucose levels (IRI/G). Julia's IRI/G ratio was 0.04 (the normal range is 0.03 to 0.30). Her C-peptide level was also in the low to normal range, at 232 pmol/L, which rules out any insulinoma.

Julia's undetectable sulfonylurea level and appropriately suppressed insulin levels supported her claim that she had not taken any other prescription drugs.

Hypoglycemia and Antidepressants

What is the normal response?

The major counter-regulatory hormones involved in blood glucose control are (in order of importance): glucagon, epinephrine, cortisol, and growth

hormone. These hormones stimulate the glycogenolysis and gluconeogenesis in the liver.² Julia did not have features on history or physical exam to suggest a deficiency of the above hormones.

Table 3

Side-effects of venlafaxine

Clinical and post-marketing

- Nausea
- Asthenia
- Constipation
- Somnolence
- Dry mouth
- Dizziness
- Nervousness
- Tremor
- Blurred vision
- Abnormal orgasm/ejaculation
- Dose-dependent increases in blood pressure (3% of patients)
- Increases in mean serum cholesterol (8%)
- Hyperglycemia and hypoglycemia are rare

Venlafaxine overdose effects reported in the literature

- Seizure
- Cardiac dysrhythmia (both fatal and non-fatal)
- Serotonin syndrome
- Hepatitis/liver enzyme elevation
- Death

Additional suspected effects (reported to Health Canada's Adverse Drug Reaction Monitoring Program [CADRMP]* between 1995 and 2003)

- Hyponatremia
- Hypokalemia
- Rhabdomyolysis
- Glucose disturbance

*CADRMP reports are considered to be suspicions, as a definite causal association often cannot be determined. In some cases, the reported clinical data may be incomplete, or the given reaction may be due to the underlying disease or to another coincidental factor.

Do antidepressants affect glucose homeostasis?

Monoamine oxidase (MAO) inhibitor antidepressants have a hypoglycemic effect that potentiates insulin-induced hypoglycemia.³ In contrast, both serotonin (5-HT) and its precursor, 5-hydroxytryptophan (5-HTP) are well-known to cause hypoglycemia in experimental animals, which is independent of insulin levels.



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Hypoglycemia and Antidepressants

Frequently Asked Questions

1. What are some of the metabolic effects of antidepressants?

- Tricyclic antidepressants may cause weight gain and carbohydrate cravings.
- SSRI and SNRI antidepressants and venlafaxine may result in decreased insulin requirements in people with diabetes, as well as hypoglycemia and hypoglycemia unawareness.
- Venlafaxine is associated with an increase in serum cholesterol in about 8% of patients.

2. What are the common side-effects of therapy and risks with overdose of venlafaxine?

Common side-effects of venlafaxine therapy are nausea, asthenia, constipation, somnolence, dry mouth, dizziness, nervousness, tremor, blurred vision, and abnormal orgasm/ejaculation. The most common effect reported in venlafaxine overdose is seizure.

There are several published case reports of the effects of other SSRI antidepressants (fluoxetine, sertraline) on glucose homeostasis in the literature, but none concerning venlafaxine. The effect of antidepressants on glucose control in patients with diabetes was thoroughly reviewed by Goodnick in 1995.⁴

Deeg described a male patient with diabetes taking glyburide, who became recurrently hypoglycemic after initiation of fluoxetine,⁵ and Takhar described similar effect of sertraline in a man with diabetes also taking glyburide.⁶

Katz reported two cases: improved glucose control in a man with diabetes started on fluoxetine, and hyperglycemia upon withdrawal of fluoxetine in another patient with diabetes.⁷

Sawka and colleagues published two cases of hypoglycemia in young women with Type 1 diabetes which was more frequent and severe while they were taking sertraline and paroxetine, respectively. Each patient returned to her baseline glucose control upon stopping the SSRI medication.⁸

Potter van Loon studied the glycemic effects of fluoxetine in humans and found that it reduced hepatic glucose production and increased insulin-mediated cellular glucose reuptake.⁹

What does the literature say about venlafaxine?

Venlafaxine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake, and a weak inhibitor of dopamine reuptake. It is chemically unrelated to other available antidepressants and anxiolytic agents. Venlafaxine is well-absorbed orally, and peak concentrations of the drug and its major metabolite are reached in two to four hours after oral dosing.

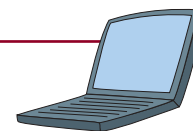
Venlafaxine has been shown to have few side-effects (Table 3).

An unusual case

Julia's case represents an unusual manifestation of venlafaxine toxicity—hypoglycemia—which has not previously been reported in the literature. Some evidence exists linking other SSRI antidepressants

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Health Canada Adverse Drug Reaction Information:
www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/index_adverse_e.html



Hypoglycemia and Antidepressants




Take-home message

How can the risk for hypoglycemia be reduced?

- Monitor the blood glucose of patients presenting with venlafaxine overdose.
- People with diabetes should also be monitored carefully for changes in blood sugar when venlafaxine or other SSRI medications are initiated or discontinued.

to disturbances of glucose homeostasis, both in humans and in animal models. While the exact mechanism of Julia's hypoglycemia is unclear, venlafaxine's effects on neurotransmitter chemistry are similar to these other medications, providing a possible explanation for the effect observed.

This case suggests that patients presenting with significant venlafaxine overdose should have baseline and periodic glucose measurements while in hospital. Patients with intrinsically abnormal glucose metabolism (*i.e.*, patients with diabetes) should be monitored carefully for changes in blood sugar venlafaxine or SSRI antidepressant medications are initiated or discontinued. 

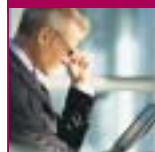
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