mhc
MENTAL HEALTH CLINICIAN

CASE REPORT Open Access

Desvenlafaxine-associated hyperglycemia: A case report and literature review

Andrea D. Mekonnen, PharmD, BCACP[1]; Aubrey A. Mills, PharmD[2]; Andrea L. Wilhite, PharmD[3]; Theresa K. Hoffman, DO, FAWM[4]

How to cite: Mekonnen AD, Mills AA, Wilhite AL, Hoffman TK. Desvenlafaxine-associated hyperglycemia: A case report and literature review. Ment Health Clin [Internet]. 2020;10(3):85-9. DOI: 10.9740/mhc.2020.05.085.

Abstract

Desvenlafaxine is a potent selective serotonin and norepinephrine reuptake inhibitor used to treat depression and anxiety. Several antidepressants have been associated with drug-induced hyperglycemia, but currently there are no reports for desvenlafaxine. A case of suspected desvenlafaxine-induced hyperglycemia is presented involving a 59-year-old female with type 2 diabetes whose average blood glucose increased by 30 mg/dL for fasting blood glucose and 75 mg/dL for postprandial blood glucose 1 month after switching from venlafaxine to desvenlafaxine. Prior to starting desvenlafaxine, she was stable on metformin 1000 mg twice daily, insulin glargine 8 units daily, and dulaglutide 1.5 mg once weekly. Over the course of 3 months after desvenlafaxine initiation, insulin glargine was increased and insulin lispro was initiated as the patient refused alternative antidepressant therapy due to favorable improvements in anxiety and depression. No other cause for elevated blood glucose could be elucidated. The Naranjo scale resulted in a score of 3, indicating a possible cause for the adverse drug reaction. Antidepressants have been associated with glucose dysregulation. However, literature also demonstrates improved glycemic control in treated versus untreated depression. If altered glucose levels are noted, all potential causative factors should be evaluated and risks and benefits weighed to guide therapy.

Keywords: desvenlafaxine succinate, antidepressive agents, hyperglycemia, diabetes mellitus, drug-related side effects and adverse reactions

[1] (Corresponding author) Assistant Professor of Pharmacy Practice, Manchester University College of Pharmacy, Natural and Health Sciences, Fort Wayne, Indiana; Clinical Pharmacist, Lutheran Health Physicians, Fort Wayne, Indiana, amekonnen@manchester.edu, ORCID: https://orcid.org/0000-0002-4976-3821; [2] Pharmacy Practice Resident, Lutheran Health Network, Fort Wayne, Indiana, ORCID: https://orcid.org/0000-0003-2744-3664; [3] Associate Professor of Pharmacy Practice, Manchester University College of Pharmacy, Natural and Health Sciences, Fort Wayne, Indiana; Clinical Pharmacist, Lutheran Health Physicians, Fort Wayne, Indiana, ORCID: https://orcid.org/0000-0003-0318-7934; [4] Family Practice Physician, Lutheran Health Physicians, Fort Wayne, Indiana, ORCID: https://orcid.org/0000-0003-4147-618X

Disclosures: The authors have declared no conflicts of interest for this article.

Introduction

Diabetes mellitus affects approximately 30.3 million individuals in the United States, and 20% have a comorbidity of depression.[1,2] Individuals diagnosed with diabetes and depression have been identified as having overall worse glycemic control.[3] Antidepressant-induced hyperglycemia is an important adverse effect that may impact patients with diabetes and depression. If not appropriately identified, this may result in worsening glycemic control and ultimately microvascular and macrovascular complications.

Antidepressant medications are the cornerstone for treatment of depression with each class having a diverse adverse-effect profile. Some evidence supports the theory that antidepressants with serotonergic effects tend to lower blood glucose and those with noradrenergic effects increase blood glucose; however, the published literature is inconsistent.[4-6] One study[4] reviewed 17 case reports of glucose dysregulation associated with antidepressants

from 1970 to 2010. This study[4] found that 9 out of 17 cases (53%) reported hyperglycemia with clomipramine, fluvoxamine, imipramine, mirtazapine, paroxetine, and sertraline, and 8 out of 17 cases (47%) reported hypoglycemia with doxepin, fluoxetine, imipramine, nefazodone, nortriptyline, maprotiline, and sertraline. Onset of glucose dysregulation usually occurs within 1 month of antidepressant initiation (range: 4 days to 5 months) and was dose dependent.[4,7] Furthermore, glucose dysregulation has not been consistent in all literature with selective norepinephrine reuptake inhibitors (SNRIs)[4,7]; 1 meta-analysis[8] on duloxetine compared to placebo found no change in fasting blood glucose (FBG) or hemoglobin A1c (HbA1c) over a 9- to 27-week time period. In general, antidepressant-associated hyperglycemia is controversial and may be variable between individuals and medications.[4,7] Despite possible glucose dysregulation with antidepressants, studies have shown that patients treated for depression are twice as likely to achieve glycemic control than those not adequately treated (odds ratio = 1.95; 95% confidence interval: 1.02-3.71).[3] The exact mechanism for antidepressant-induced hyperglycemia has not been identified; however, 1 proposed mechanism is development of insulin resistance through weight gain.[9]

Desvenlafaxine is an SNRI that was approved in February 2008 for the treatment of major depression.[10] The most commonly reported adverse effects include nausea, dry mouth, hyperhidrosis, dizziness, headache, and insomnia.[11,12] Desvenlafaxine has warnings and precautions for patients who have hypertension, dyslipidemia, and cardiovascular or cerebrovascular disease due to potential increases in blood pressure, total cholesterol, and low-density lipoprotein.[11,12]

Currently, there are limited published studies documenting hyperglycemia following desvenlafaxine initiation. The following case describes an incidence of desvenlafaxine-induced hyperglycemia 1 month after initiation.

Patient Case

The patient is a 59-year-old female, who has been followed by the pharmacy team for management of her type 2 diabetes mellitus for 5 years. Her past medical history is significant for generalized anxiety disorder (GAD), major depressive disorder (MDD), hypertension, hyperlipidemia, heart murmur, degenerative arthritis of the knee, esophageal reflux disease, iron deficiency anemia, insomnia, and vitamin D deficiency. Her pertinent social history includes tobacco use (5 cigarettes per day) and reports of not being ready to quit. She denies alcohol and illicit drug use. The patient's medications included insulin glargine 8 units subcutaneously daily, metformin extended release (ER) 2000 mg daily, dulaglutide 1.5 mg subcutaneously once weekly, and venlafaxine ER 225 mg daily. She was also taking the following chronic medications: aspirin, losartan, ezetimibe, polysaccharide iron complex, multivitamin, and omeprazole-sodium bicarbonate.

The patient had been on venlafaxine for the previous 4 years with dose titration from venlafaxine ER 75 mg daily up to 225 mg daily. The dose was increased due to reports of continued anxiousness, sadness, and insomnia. She had a previous 2-year trial of desvenlafaxine prior to venlafaxine and was switched due to insurance coverage. She self-reported improved outcomes in regards to GAD and MDD, but there were no screening questionnaires available to confirm this reported improvement.

Three months prior to initiating desvenlafaxine, her HbA1c was 7.5%, and average self-monitoring FBG and bedtime blood glucose were 96 mg/dL (range: 71 to 119) and 175 mg/dL (range: 140 to 256), respectively. She was titrated to dulaglutide 1.5 mg 2 weeks prior to these HbA1c and blood glucose readings. During these 3 months, she maintained all medications listed above and made significant improvements to diet, including reducing snacks prior to bedtime and initiating carbohydrate counting with approximately 45 g per dinner and 15 g per snack. One month prior to switching antidepressants, her FBG and 2-hour postprandial blood glucose (PPBG) were 88 mg/dL (range: 62 to 109) and 165 mg/dL (range: 111 to 205), respectively.

At a pharmacy and physician follow-up appointment, her diabetes continued to improve. Her HbA1c decreased to 7.2% and average FBG remained steady at 106 mg/dL (range: 79 to 135), but her PPBG decreased to 129 mg/dL (range: 89 to 180) with 60% of her PPBG in range (less than 140 mg/dL). At this visit, the patient asked to change from venlafaxine to desvenlafaxine due to self-reported better control in GAD symptoms and no longer having a cost barrier. At this visit, venlafaxine was discontinued, and desvenlafaxine ER 50 mg daily was initiated. Her baseline patient health questionnaire-9 score was 8, but no GAD scores were available.

One month after switching to desvenlafaxine, she followed up with the pharmacy team for diabetes management. Her average blood glucose increased with an FBG of 136 mg/dL (range: 107 to 184) and PPBG of 207 mg/dL (range: 168 to 257). She self-reported no changes to diet or exercise over the previous month. Insulin glargine was increased from 8 to 10 units daily at this visit.

Two months after switching to desvenlafaxine, her blood glucose had improved but still was not at goal. Her average FBG was 129 mg/dL (range: 107 to 150) and PPBG 192 mg/dL (range: 166 to 257). Insulin glargine was

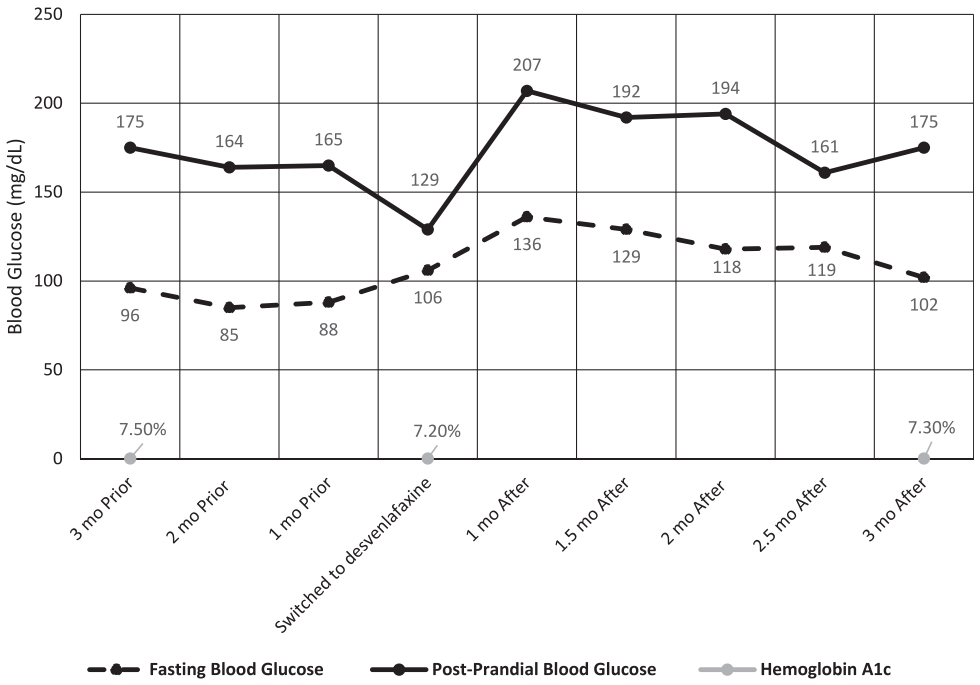

FIGURE: Fasting and postprandial blood glucose trends before and after desvenlafaxine initiation

titrated to 12 units daily. Ten days later, the FBG and PPBG averages were 118 mg/dL (range: 104 to 128) and 194 mg/dL (range: 156 to 262), respectively. Due to not reaching blood glucose goals, insulin lispro 2 units before dinner was initiated.

Over the next month, the patient had 2 follow-up appointments with pharmacy for insulin lispro titration. By the end of the third month, the patient was increased to 8 units prior to dinner. At this visit, the patient's average FBG and PPBG were 106 mg/dL (range: 81 to 130) and 146 mg/dL (range: 115 to 198), respectively, and her HbA1c was 7.3%. After further diabetes medication adjustments, her next 3-month follow-up HbA1c was 6.9%. The Figure demonstrates increases in FBG, PPBG, and HbA1c in relation to initiation of desvenlafaxine. Subsequent decline in FBG and PPBG is attributed to adjustment of diabetes medications in response to uncontrolled blood glucose.

Throughout this 3-month period, the patient reported being adherent to medications and keeping a consistent diet and exercise routine. She kept a food diary for carbohydrate counting, maintaining approximately 45 g for her dinner and 15 g with snacks. Her weight remained stable between 62.7 to 63.6 kg. Six months after initiating desvenlafaxine, her patient health questionnaire-9 score remained unchanged at 8, and no GAD score was available. The only known change during this timeline was changing venlafaxine to desvenlafaxine. The patient was not interested in trialing a discontinuation of desvenlafaxine due to improvement in self-reported anxiety in social situations and overall energy level.

Discussion

A Pubmed literature search was performed using MeSH (medical subject headings) and nonMeSH terms *antidepressant associated hyperglycemia*, *desvenlafaxine associated hyperglycemia*, *pristiq associated hyperglycemia*, and *desvenlafaxine AND hyperglycemia*. Additionally, the Food and Drug Administration Safety Information and Adverse Event Reporting Program MedWatch was searched using the phrases *pristiq* and *desvenlafaxine*. Both searches resulted in no published reports of desvenlafaxine causing hyperglycemia. However, one 10-month, open-label study[13] found a potentially clinically important elevated blood glucose in 1 participant out of 1195 who were using desvenlafaxine for MDD. It should be noted that doses of 200 to 400 mg/d were being used, which is above typical doses for treatment of MDD. No details were provided on this elevated blood glucose case.

This case study is believed to be the first to describe hyperglycemia associated with desvenlafaxine. The month following desvenlafaxine initiation, despite no other reported changes, there was an increase in both average FBG and PPBG of 30 mg/dL and 75 mg/dL, respectively. The blood glucose elevation is clinically important as it could result in 1% to 1.5% increase in HbA1c because there is a 0.5% increase in HbA1c for approximately every 15 mg/dL increase in average blood glucose.[14]

The Naranjo scale was used to estimate the probability of adverse drug reactions, and it resulted in a score of 3, indicating a possible cause for the adverse drug reaction. The score of 3 comes from a positive response to the following questions: Did the adverse event appear after the suspected drug was given (*yes*, +2 points), and was the adverse event confirmed by any objective evidence (*yes*, +1 point)?[15] A score of 5 (probable cause) could be reasonable for a response to the following question: Are there alternative causes that could have caused the reaction (*no*, +2 points)? However, due to potential for elevation in blood glucose being correlated with diabetes progression and reported information coming from the patient, it was deemed there might be alternative causes for the blood glucose elevation in this case. To the best of the authors' knowledge, all likely causes for her hyperglycemia were ruled out. To further support desvenlafaxine as the culprit for blood glucose elevation, it would have been preferred to do a discontinuation of desvenlafaxine to assess if hyperglycemia resolved. However, the patient refused to discontinue desvenlafaxine due to self-reported improvement in her MDD and anxiety.

In the presented case report, the patient self-reported improvement in her GAD and MDD with desvenlafaxine but not venlafaxine, which could be due to pharmacogenetic and binding affinity differences. Venlafaxine is converted into O-desmethylvenlafaxine, also known as desvenlafaxine, by CYP2D6.[12,14] In patients who are taking venlafaxine and are CYP2D6 poor metabolizers, there is potential for reduced conversion to O-desmethylvenlafaxine. This could be 1 contributing factor to this observed difference. It should be noted that no pharmacogenomics testing was completed in this patient. Furthermore, because hyperglycemia is noted with SNRIs and not selective serotonin reuptake inhibitors, it could be theorized that the altered glucose effects may be linked with norepinephrine activity. The binding affinity for venlafaxine for the norepinephrine receptors is lower (ki 1920 $\pm$ 158 nmol/L) compared to desvenlafaxine (ki 558 $\pm$ 121 nmol/L).[17] It should be noted that both are relatively low compared to other available SNRIs: duloxetine (1.17 $\pm$ 0.11 nmol/L), milnacipran (22 $\pm$ 2.58 nmol/L), and levomilnacipran (92.2 nmol/L).[17] Furthermore, the serotonin to norepinephrine selectivity ratio for venlafaxine is 30:1 compared to desvenlafaxine, which is 14:1.[17] These differences in pharmacogenomics, binding affinity, and selectivity to receptors could indicate why differences were observed between these 2 drug compounds. However, because the mechanism of glucose dysregulation has not been elucidated, there could be other causes, especially because no hyperglycemia has been observed with duloxetine, and it has a higher binding affinity to norepinephrine than either venlafaxine and desvenlafaxine.[8,17] Finally, in this patient, the glucose dysregulation could not be due to weight gain, which is 1 theorized cause, as this patients weight remained stable throughout the 6-month evaluation time.

Strengths of this study include frequent follow-ups to assess the changes with home blood glucose monitoring. Monthly follows-ups allowed for determination of no changes in external causes for glucose elevation and quick identification of worsening diabetes control prior to the 3-month follow-up. The Naranjo scale, which is widely used and accepted for adverse drug causation, also supports a possible cause of desvenlafaxine-induced hyperglycemia.

A key limitation is not being able to do a discontinuation trial of desvenlafaxine to determine if glucose results are reproducible. This would provide a more definitive determination of cause and effect. Due to the patient refusing a medication-discontinuation trial, this was unable to be assessed. Furthermore, key information in this case report is reliant on patient reporting, which leads to increased risk for error due to unknown confounding variables. Frequent follow-ups with the patient help mitigate this risk, but there is always potential for inaccurate patient reporting, particularly in relationship to lifestyle changes. One factor that can be evaluated to assess changes to diet and exercise is patient weight. Although only 1 component, it should be noted this patient's weight did not change during the course of antidepressant treatment, indicating potentially no change in diet or exercise.

Conclusion

The findings of this case report and the respective literature support evidence that antidepressants have effects on glucose dysregulation and that desvenlafaxine may cause hyperglycemia. Health care providers should be aware of the potential changes in glucose dysregulation with desvenlafaxine and other antidepressants when initiating treatment for depression.[4-7,12,13] After initiation of any antidepressant, appropriate monitoring of blood glucose in patients with diabetes is vital to assess glucose dysregulation and other potential adverse reactions. However, incidence of glucose dysregulation is low, and research does support that treatment of depression helps improve glycemic control. In cases of drug-induced hyperglycemia, risks and benefits should be weighed in creating an appropriate treatment plan. Switching antidepressants or intensifying therapy for diabetes management may be reasonable options based on the patient's and clinician's mutual decision.

References

1. Centers for Disease Control and Prevention. New CDC report: More than 100 million Americans have diabetes or prediabetes [published 2017 Jul 18; cited 2019 May 22]. Available from:

https://www.cdc.gov/media/releases/2017/p0718-diabetes-report.html
2. Roy T, Lloyd CE. Epidemiology of depression and diabetes: a systematic review. J Affect Disord. 2012;142 Suppl:S8-21. DOI: 10.1016/S0165-0327(12)70004-6. PubMed PMID: 23062861.
3. Brieler JA, Lustman PJ, Scherrer JF, Salas J, Schneider FD. Antidepressant medication use and glycaemic control in co-morbid type 2 diabetes and depression. Fam Pract. 2016;33(1): 30-6. DOI: 10.1093/fampra/cmv100. PubMed PMID: 26743722.
4. Khoza S, Barner JC. Glucose dysregulation associated with antidepressant agents: an analysis of 17 published case reports. Int J Clin Pharm. 2011;33(3):484-92. DOI: 10.1007/s11096-011-9507-0. PubMed PMID: 21487738.
5. McIntyre RS, Soczynska JK, Konarski JZ, Kennedy SH. The effect of antidepressants on glucose homeostasis and insulin sensitivity: synthesis and mechanisms. Expert Opin Drug Saf. 2006;5(1): 157-68. DOI: 10.1517/14740338.5.1.157. PubMed PMID: 16370964.
6. Hennings JM, Schaaf L, Fulda S. Glucose metabolism and antidepressant medication. Curr Pharm Des. 2012;18(36):5900-19. DOI: 10.2174/138161212803523662. PubMed PMID: 22681169.
7. Fathallah N, Slim R, Larif S, Hmouda H, Ben Salem C. Drug-induced hyperglycaemia and diabetes. Drug Saf. 2015;38(12): 1153-68. DOI: 10.1007/s40264-015-0339-z. PubMed PMID: 26370106.
8. Crucitti A, Zhang Q, Nilsson M, Brecht S, Yang CR, Wernicke J. Duloxetine treatment and glycemic controls in patients with diagnoses other than diabetic peripheral neuropathic pain: a meta-analysis. Curr Med Res Opin. 2010;26(11):2579-88. DOI: 10.1185/03007991003769241. PubMed PMID: 20874076.
9. Barnard K, Peveler RC, Holt RIG. Antidepressant medication as a risk factor for type 2 diabetes and impaired glucose regulation: systematic review. Diabetes Care. 2013;36(10):3337-45. DOI: 10.2337/dc13-0560. PubMed PMID: 24065841; PubMed Central PMCID: PMC3781547.
10. Desvenlafaxine. Lexi-Comp Online [cited 2019 Apr 19]. Hudson (OH): Lexi-Comp, Inc. Available from: http://online.lexi.com/crlonline
11. Septien-Velez L, Pitrosky B, Padmanabhan SK, Germain J-M, Tourian KA. A randomized, double-blind, placebo-controlled trial of desvenlafaxine succinate in the treatment of major depressive disorder. Int Clin Psychopharmacol. 2007;22(6):338-47. DOI: 10.1097/YIC.0b013e3281e2c84b. PubMed PMID: 17917552.
12. Pristiq [package insert]. Philadelphia: Pfizer; 2011.
13. Tourian KA, Pitrosky B, Padmanabhan SK, Rosas GR. A 10-month, open-label evaluation of desvenlafaxine in outpatients with major depressive disorder. Prim Care Companion CNS Disord. 2011;13(2):10m00977. DOI: 10.4088/PCC.10m00977. PubMed PMID: 21977353.
14. American Diabetes Association. eAG/A1C Conversion Calculator [cited 2019 Dec 19]. Available from: https://professional.diabetes.org/diapro/glucose_calc
15. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30(2):239-45. DOI: 10.1038/clpt.1981.154. PubMed PMID: 7249508.
16. Shelton RC. Serotonin and norepinephrine reuptake inhibitors. Handb Exp Pharmacol. 2019;250:145-80. DOI: 10.1007/164_2018_164. PubMed PMID: 30838456.
17. Raouf M, Glogowski AJ, Bettinger JJ, Fudin J. Serotonin-norepinephrine reuptake inhibitors and the influence of binding affinity (Ki) on analgesia. J Clin Pharm Ther. 2017;42(4):513-7. DOI: 10.1111/jcpt.12534. PubMed PMID: 28503727.