Quetiapine Leads to Hyperosmolar Hyperglycemic State in a Nonagenarian

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Abstract: Behavioral and psychological symptoms of dementia (BPSD) are present in the vast majority of patients with dementia. Quetiapine, a second-generation antipsychotic used off-label for BPSD, has been associated with adverse metabolic effects in older adults. Despite this, there are no specific guidelines on monitoring serum glucose or lipids after initiation of antipsychotics. We describe a case of hyperosmolar hyperglycemic state (HHS) likely precipitated by quetiapine in an older adult with BPSD. In this patient without a prior history of diabetes, quetiapine likely led to increased insulin resistance and subsequent HHS. Infection and acute ischemia, which commonly precipitate HHS, were absent. This patient had risk factors for diabetes, including a previously elevated random blood glucose level and obesity. Review of encounters preceding hospitalization revealed no symptoms to suggest poorly controlled diabetes. Quetiapine and other antipsychotics associated with metabolic syndrome should be used cautiously in older adults. Routine glucose monitoring is important.

Key words: antipsychotic, behavioral and psychological symptoms of dementia, homeostenosis, hyperosmolar hyperglycemic state, quetiapine
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Neuropsychiatric symptoms are present in up to 90% of patients with dementia.[1] Behavioral and psychological symptoms of dementia (BPSD) are associated with significant cognitive and functional impairment and are a strong predictor of institutionalization and mortality.[1,2] Problematic behaviors, rather than cognitive decline itself, are often the reason for transitioning patients with dementia to long-term care (LTC) facilities and are a significant source of caregiver stress.[3,4] Few recommendations exist regarding treatment of BPSD, except that nonpharmacologic interventions should be used initially. Medications such as antipsychotics, antidepressants, antiepileptics, benzodiazepines, and cholinesterase inhibitors are often used off-label as second-line treatments.[5]

In general, medications should be used at the lowest effective dose for the shortest duration possible. Careful review of side effects and limitations with the patient and the health care surrogate is essential both before initiation and during treatment with these medications. Considering the high prevalence of BPSD and the frequent need for pharmacologic therapy, it is important to establish guidelines that promote safe medication use. The following case report focuses on hyperosmolar hyperglycemic state (HHS) as a potential side effect of off-label quetiapine use in an older adults with BPSD.

Case Presentation

A 96-year-old woman with advanced Alzheimer dementia presented to the

emergency department (ED) via ambulance with generalized weakness and altered mental status. The patient lived at home in an older adult community with a paid 24-hour private duty caregiver. At baseline, the patient was oriented to person only and had a history of physical aggression and agitation attributed to her underlying Alzheimer dementia.

Over several months, she had been experiencing increased frequency of agitation and aggression toward caregivers, including hitting and kicking, and resisting diaper changes and bathing. Consequently, the primary care physician initiated an evening dose of quetiapine 12.5 mg 2 weeks prior to her presentation in the ED. Behavior initially improved; however, a few days prior to presentation, the patient developed lethargy, polydipsia, and decreased appetite, and caregivers noticed that she had a dry mouth despite drinking more fluids. The family initially attributed these symptoms to the new medication. The patient was incontinent of urine at baseline; therefore, it was difficult to assess if polyuria was present. Further review of systems was negative for recent sick contacts, fever, chills, cough, nausea, vomiting, abdominal pain, or diarrhea.

On arrival to the ED, the patient was afebrile, tachycardic (heart rate of 110 beats per minute), tachypneic (respiratory rate of 24 breaths per minute), and normotensive, with oxygen saturation of 95% on 3L of oxygen via nasal cannula. The patient was alert but agitated and disoriented to person, place, and time. Physical exam was significant for dry mucous membranes, poor skin turgor, and decreased breath sounds at bilateral lung bases. There was no abdominal or suprapubic tenderness and no focal motor deficits noted. Labs were concerning for blood glucose of 772 mg/dL and elevated serum osmolality of 375 mOsm/kg. Urinalysis showed 4+ glucose and was negative for ketones, nitrites, and leukocyte esterase. Serum troponin and acetone were unremarkable. A venous blood gas was consistent with respiratory alkalosis and an elevated lactic acid level of 3.4 mmol/L. A respiratory polymerase chain reaction panel and rapid screen for influenza A/B were negative. Chest x-ray showed minor left basilar atelectasis. A computed tomography (CT) scan of the head showed no acute intracranial processes, and a CT scan of the abdomen showed diverticulosis without acute diverticulitis. Electrocardiogram demonstrated sinus tachycardia with normal QTc and otherwise had not significantly changed from tracing 1 year prior.

The patient received intravenous insulin and aggressive intravenous fluid hydration and was transferred to the critical care unit. Quetiapine was discontinued, and serum osmolality, glucose, and lactate gradually improved. Overnight, the patient was weaned from the insulin drip and transitioned to subcutaneous insulin. The following day, she was transferred to a general medical ward. With the exception of one dose of haloperidol in the ED, the patient did not require any medications or physical restraints for agitation throughout her stay. Nonpharmacologic interventions including frequent reorienting and promotion of sleep-wake cycle were provided. The patient spent 4 days on the general medical ward, during which her insulin regimen was adjusted. She was discharged on a basal-bolus regimen of insulin and, at the family's request, with a continuous glucose monitor. On follow-up approximately 1 week after hospital discharge, the patient's family reported better blood glucose control; however, she did not tolerate frequent insulin administration. Therefore, an oral hypoglycemic was added in an attempt to decrease the frequency of injections. Approximately 1 month later, sertraline was initiated due to another episode of physical aggression toward a caregiver (the patient hit the caregiver, bruising her own hand in the process). The patient continues to be followed by her primary care provider and neurologist.

Discussion

In this patient with no known history of diabetes, we believe quetiapine led to increasing insulin resistance, resulting in the acute presentation of HHS. The most common precipitating events for HHS, including infection, dehydration, myocardial infarction, and stroke, were quickly ruled out. Family history was negative for diabetes; however, the patient did have risk factors for developing diabetes, including borderline obesity (body mass index of 29) and an elevated random glucose level of 220 mg/dL approximately 1 year prior. No record of fasting glucose was found on review of the patient's medical records, and further work-up for diabetes had not been completed due to the patient's aversion to blood draws. Three primary care visits occurred prior to admission and revealed no evidence of symptoms or signs of diabetes.

Loss of homeostatic reserve (so-called homeostenosis) occurs with aging and is affected by genetic, epigenetic, and environmental factors.[6] Age-related changes in the endocrine system result in increased insulin resistance as well as impaired pancreatic beta cell function and regeneration.[7,8] Important changes in body composition, especially increased deposition of visceral fat and an associated rise in proinflammatory cytokines, also contribute to increased insulin resistance and development of type 2 diabetes seen with increasing age.[9,10] Antipsychotic use, too, is associated with impaired glucose regulation through multiple mechanisms, including inhibition of the insulin signaling pathway, increased weight gain and dyslipidemia, and direct insults to pancreatic beta cells leading to apoptosis and dysfunction.[11,12]

Quetiapine is a second-generation antipsychotic (SGA) commonly used off-label for BPSD.[13] In a systematic review, El-Saifi et al found multiple studies that demonstrated an association between quetiapine use and metabolic side effects in older adults, such as hyperglycemia, new-onset type 2 diabetes, weight change, and lipid abnormalities.[13] Multiple cases of serious and potentially fatal complications of glucose dysregulation, such as HHS and diabetic ketoacidosis,

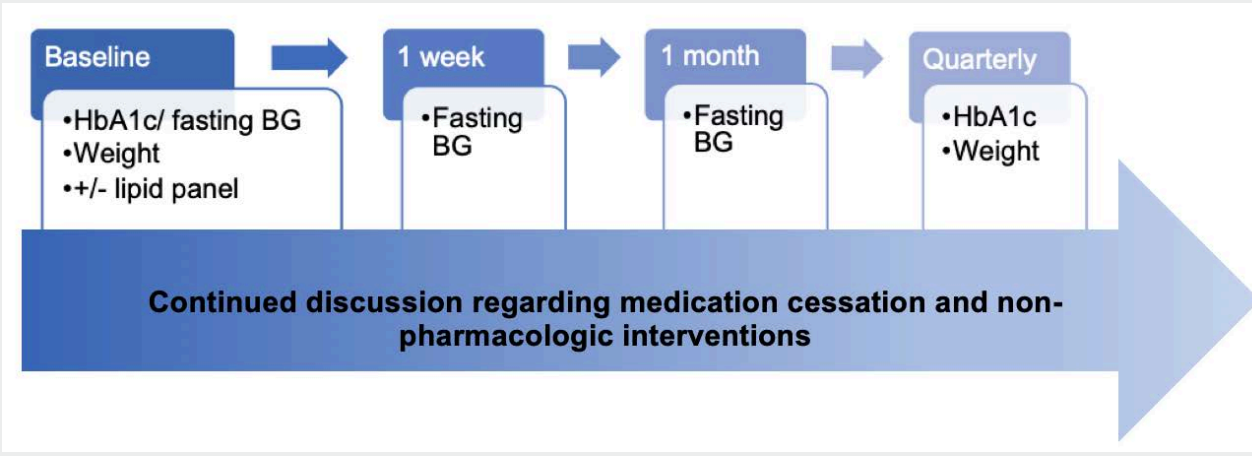

Figure 1. Summary of Screening Recommendations for Use of Atypical Antipsychotics in Older Adults
Abbreviations: BG, blood glucose; HbA_1c, hemoglobin A_1c

associated with quetiapine use have been reported.[14-16] Despite these serious consequences, a significant number of patients prescribed atypical antipsychotics do not undergo routine screening for metabolic syndrome.[17-19] Routine monitoring of blood glucose is an essential part of prescribing antipsychotics. This is particularly important for older patients because age-related changes lead to less effective responses to stress, as well as for patients with dementia whose inability to report symptoms can make monitoring for side effects difficult.

Hyperglycemic emergencies such as HHS are life-threatening. Mortality rates can be as high as 10% to 20% among older adults with HHS. Furthermore, up to 20% of presenting patients do not have an established diagnosis of diabetes.[20] As this case report illustrates, in older adults, especially the old-old (age 85 years and older) and those with cognitive impairment, signs and symptoms of HHS can be nonspecific. The most common precipitant for HHS is infection; however, use of atypical antipsychotics and other medications account for a significant number of cases.[20] Considering the unprecedented growth in the proportion of Americans over age 65 years and the high prevalence of dementia and BPSD, we anticipate the occurrence of neuroleptic-induced metabolic decompensation will only increase if these medications continue to be used without close monitoring and a deeper understanding of their effects on older adults.

In 2004, the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity released a consensus statement regarding the use of SGAs. In addition to screening for family and personal history of cardiovascular disease, hypertension, diabetes, obesity, and dyslipidemia, baseline measurements of weight, height, waist circumference, blood pressure, fasting plasma glucose, and lipid profile are recommended before antipsychotics are initiated. Follow-up monitoring of weight is recommended at 4, 8, and 12 weeks after beginning the medication, and quarterly thereafter. Measurements of fasting glucose, lipids, and blood pressure are recommended at 3 months after initiation, then at least annually.[21]

In an attempt to identify if this consensus statement led to significant change in metabolic screening rates among patients prescribed SGAs, Morrato et al analyzed the frequency of metabolic screening in adults aged 20 to 88 years prescribed SGAs between 2001 and 2006. They concluded that there was a gradual increase in screening rates over the 6-year period, however, these changes were not temporally related to the release of the statement. Despite the increase in testing, approximately 75% of adults had not received baseline glucose testing, and 90% did not have baseline lipid testing in late 2005.[22] Data on consensus statement compliance from the past 15 years is limited. Morrato et al analyzed Missouri Medicaid data from January 2010 through December 2012 and found a significant increase in annual testing rates for glucose (79.6%) and lipids (41.2%) among adults aged 18 to 64 years receiving antipsychotic medications.[23] Importantly, this data did not include information for adults aged 65 years and older, whom, we argue, are more sensitive to these medications.

While the 2004 consensus statement recommendations are reasonable for the general population, they may not be applicable for older adults, given reduced life expectancy and risks associated with aggressive treatment (including increased risk of hypoglycemia). Overall goals of care must be taken into account, as strict control of blood glucose and lipids may not be appropriate in certain populations. There is little benefit in aggressively treating diabetes in patients with limited life spans, yet severe hyperglycemia should certainly be avoided

given the significant morbidity and mortality associated with hyperglycemic emergencies. This is even more important in older adults with dementia who have baseline deficits and may not be able to communicate symptoms.

No specific guidelines exist for the use of antipsychotics in older adults with dementia or patients in LTC, but it seems reasonable to suggest baseline screenings of weight and hemoglobin A_1c (HBA_1c) or fasting glucose before initiating antipsychotic medications. Repeat fasting glucose should be obtained at 1 and 4 weeks after initiation, followed by quarterly measurement of HBA_1c and weight. Obtaining a lipid panel and measuring waist circumference should be considered when consistent with goals of care. As noted earlier, it is unclear to what extent these parameters are currently being monitored in older individuals or in individuals with dementia. Once this is clarified, more tailored guidelines can be developed and, more importantly, implemented. This could involve regulatory or legislative action. Perhaps in the long-term care setting, this could be tracked by the facility with the help of pharmacy. **Figure 1** provides a summary of recommendations.

After discontinuing quetiapine, the patient did not require medications or physical restraints for agitation during hospitalization. This was not unexpected. With nonpharmacologic interventions such as verbal redirection and encouragement of proper sleep-wake cycles (eg, minimizing lab draws, vitals monitoring, and lights, TV, and other stimuli at night), she was able to remain calm.

A recent meta-analysis by Pan et al concluded that antipsychotic discontinuation did not significantly change BPSD severity compared with continued treatment.[24] While some studies suggest a subset of patients with BPSD may worsen with antipsychotic discontinuation, particularly those with more severe neuropsychiatric symptoms, most patients with Alzheimer dementia will not be harmed by medication cessation.[25] Most importantly, the risk of adverse effects from these medications must be seriously considered against potential benefits. As mentioned previously, discussion regarding medication cessation and nonpharmacologic interventions for BPSD should occur often throughout treatment.

Summary

Quetiapine and other SGAs should be used with caution in older adults, especially those at high risk of developing metabolic syndrome. Age-related changes affecting body composition and metabolic function, and pharmacokinetics predispose older adults to adverse drug effects. This loss of physiologic reserve can lead to significant consequences in response to stressors, such as infection, trauma, or initiation of a new medication. Consequently, pharmacologic treatment of BPSD should be avoided whenever possible.

If quetiapine or other medication associated with metabolic decompensation is necessary, we recommend screening fasting glucose or HBA_1c and weight. Follow-up of these measurements should occur regularly, accompanied by discussions on whether to decrease dose, discontinue medication, or supplement with nonpharmacologic interventions. In patients with a predisposition to developing diabetes, agents other than SGAs should be considered. ■

References

1. Cerejeira J, Lagarto L, Mukaetova-Ladinska EB. Behavioral and psychological symptoms of dementia. *Front Neurol.* 2012;3:73. doi:10.3389/fneur.2012.00073
2. Hersch EC, Falzgraf S. Management of the behavioral and psychological symptoms of dementia. *Clin Interv Aging.* 2007;2(4):611-621. doi:10.2147/cia.s1698
3. Afram B, Stephan A, Verbeek H, et al. Reasons for institutionalization of people with dementia: informal caregiver reports from 8 European countries. *J Am Med Dir Assoc.* 2014;15(2):108-116. doi:10.1016/j.jamda.2013.09.012
4. Azermai M, Petrovic M, Elseviers MM, Bourgeois J, Van Bortel LM, Vander Stichele RH. Systematic appraisal of dementia guidelines for the management of behavioural and psychological symptoms. *Ageing Res Rev.* 2012;11(1):78-86. doi:10.1016/j.arr.2011.07.002
5. Gauthier S, Cummings J, Ballard C, et al. Management of behavioral problems in Alzheimer's disease. *Int Psychogeriatr.* 2010;22(3):346-372. doi:10.1017/S1041610209991505
6. Khan SS, Singer BD, Vaughan DE. Molecular and physiological manifestations and measurement of aging in humans. *Aging Cell.* 2017;16(4):624-633. doi:10.1111/acel.12601
7. Barzilai N, Huffman DM, Muzumdar RH, Bartke A. The critical role of metabolic pathways in aging. *Diabetes.* 2012;61(6):1315-1322. doi:10.2337/db11-1300
8. Kushner JA. The role of aging upon ß cell turnover. *J Clin Invest.* 2013;123(3):990-995. doi:10.1172/JCI64095
9. Kuk JL, Saunders TJ, Davidson LE, Ross R. Age-related changes in total and regional fat distribution. *Ageing Res Rev.* 2009;8(4):339-348. doi: 10.1016/j.arr.2009.06.001
10. Lumeng CN, Liu J, Geletka L, et al. Aging is associated with an increase in T cells and inflammatory macrophages in visceral adipose tissue. *J Immunol.* 2011;187(12):6208-6216. doi:10.4049/jimmunol.1102188
11. Chen J, Huang XF, Shao R, Chen C, Deng C. Molecular mechanisms of antipsychotic drug-induced diabetes. *Front Neurosci.* 2017;11:643. doi:10.3389/fnins.2017.00643
12. Newcomer JW, Haupt DW. The metabolic effects of antipsychotic medications. *Can J Psychiatry.* 2006;51(8):480-491. doi:10.1177/070674370605100803
13. El-Saifi N, Moyle W, Jones C, Tuffaha H. Quetiapine safety in older adults: a systematic literature review. *J Clin Pharm Ther.* 2016;41(1):7-18. doi:10.1111/jcpt.12357
14. Chen WY, Chen CC, Hung GC. Hyperglycemic hyperosmolar state associated with low-dose quetiapine treatment in a patient with bipolar disorder. *Curr Drug Saf.* 2011;6(3):207-208. doi: 10.2174/157488611797579276
15. Ely SF, Neitzel AR, Gill JR. Fatal diabetic ketoacidosis and antipsychotic medication. *J Forensic Sci.* 2013;58(2):398-403.
16. Jalota R, Bond C, José RJ. Quetiapine and the development of the metabolic syndrome. *QJM.* 2015;108(3):245-247. doi:10.1093/qjmed/hcs142
17. Motsinger C, Slack M, Weaver M, Reed M. Physician patterns of metabolic screening for patients taking atypical antipsychotics: a retrospective database study. *Prim Care Companion J Clin Psychiatry.* 2006;8(4):220-223. doi:10.4088/pcc.v08n0405
18. Barnes TR, Bhatti SF, Adroer R, Paton C. Screening for the metabolic side effects of antipsychotic medication: findings of a 6-year quality improvement programme in the UK. *BMJ Open.* 2015;5(10):e007633. doi:10.1136/bmjopen-2015-007633
19. Mackin P, Bishop DR, Watkinson HM. A prospective study of monitoring practices for metabolic disease in antipsychotic-treated community psychiatric patients. *BMC Psychiatry.* 2007;7:28. doi:10.1186/1471-244X-7-28
20. Pasquel FJ, Umpierrez GE. Hyperosmolar hyperglycemic state: a historic review of the clinical presentation, diagnosis, and treatment. *Diabetes Care.* 2014;37(11):3124-3131. doi:10.2337/dc14-0984
21. American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care.* 2004;27(2):596-601. doi:10.2337/diacare.27.2.596
22. Morrato EH, Newcomer JW, Kamat S, Baser O, Harnett J, Cuffel B. Metabolic screening after the American Diabetes Association's consensus statement on antipsychotic drugs and diabetes. *Diabetes Care.* 2009;32(6):1037-1042. doi:10.2337/dc08-1720
23. Morrato EH, Campagna EJ, Brewer SE, et al. Metabolic testing for adults in a state Medicaid program receiving antipsychotics: remaining barriers to achieving population health prevention goals. *JAMA Psychiatry.* 2016;73(7):721-730. doi:10.1001/jamapsychiatry.2016.0538
24. Pan YJ, Wu CS, Gau SS, Chan HY, Banerjee S. Antipsychotic discontinuation in patients with dementia: a systematic review and meta-analysis of published randomized controlled studies. *Dement Geriatr Cogn Disord.* 2014;37(3-4):125-140. doi:10.1159/000355418
25. Ballard C, Lana MM, Theodoulou M, et al. A randomised, blinded, placebo-controlled trial in dementia patients continuing or stopping neuroleptics (the DART-AD trial). *PLoS Med.* 2008;5(4):e76. doi:10.1371/journal.pmed.0050076