Second-Generation Antipsychotic–Associated Diabetes Mellitus and Diabetic Ketoacidosis: Mechanisms, Predictors, and Screening Need

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Antipsychotic medications, as well as schizophrenia, have been associated with an increased risk for diabetes.[1] However, the relative contributions of the underlying illness, unhealthy lifestyle behaviors, and medications used to treat schizophrenia are still unclear. Although first- and second-generation antipsychotics have been contrasted broadly in the literature regarding their risks for glucoregulatory abnormalities, there is now sufficient evidence to suggest that the risk for diabetes is not uniform within each antipsychotic class.[2,3] For example, cases of diabetic ketoacidosis (DKA) have been reported with chlorpromazine, but no such cases have been reported for other first-generation antipsychotics.[4,5] On the other hand, case reports of DKA have been very limited with newer second-generation antipsychotics.

Recently, however, 5 aripiprazole-associated cases of severe glucose dysregulation (DKA,[6–8] hyperglycemic hyperosmolar nonketotic coma,[9] and diabetic ketoacidotic coma[10]) were published. Four of the cases occurred in previously nondiabetic patients, highlighting the fact that this potentially life-threatening complication can occur during treatment with any antipsychotic, even those typically regarded as having a low metabolic risk burden.[1] Risk factors, identified in an analysis[11] of 73 case reports of hyperglycemia associated with clozapine, olanzapine, risperidone, or quetiapine, 4 other atypical antipsychotics that have been associated with high or moderate metabolic risk, were all also highly prevalent in the 5 aripiprazole-treated cases. Of 5 cases, all 5 were aged under 50 years, 4 were obese or overweight, 3 of 4 with available information had an onset of hyperglycemia within 6 weeks of starting aripiprazole treatment, and 3 were of African descent. Four patients did not have preexisting diabetes, and diabetes was reversible in 2 of the 4 cases with available information. These cases suggest that disturbed glucose homeostasis, although not a common phenomenon, can be severe—when it occurs, sometimes leading to life-threatening coma—and can be irreversible, persisting as diabetes mellitus.

However, the questions of causality and mechanisms deserve a more detailed examination. It might be argued that the relationship between diabetes or DKA is not causal but coincidental. The presence of 2 well-established risk factors for diabetes, i.e., African descent and increased body weight, suggests that patients who have DKA during antipsychotic therapy may have developed diabetes independently of their antipsychotic treatment. This argument is strengthened by findings from a chart review study[12] of 11 patients who presented with DKA during antipsychotic therapy. In this study, the mean hemoglobin A_{1c} level at admission was 13.3% ± 1.9% (range, 10.4%–16.9%), which was indistinguishable from that of patients with preexisting diabetes, indicating that the glucose dysregulation was a longer-standing problem.

A second line of reasoning, that schizophrenia is endogenously associated with disturbed glucose homeostasis, is supported by impaired glucose tolerance in antipsychotic-naive patients with schizophrenia or first-degree relatives,[13] albeit this finding has not always been confirmed.[14] An alternative explanation emphasizes the finding that patients with an acute psychotic episode are more likely to have elevated cortisol levels, which can temporarily worsen insulin sensitivity.[15]

A third argument, that publication bias overemphasizes features related to causality, suggests an alternative explanation of the findings: anecdotal case reports, drawn from millions of medication exposures every year, are much more likely to be written and published if there is a close temporal relationship to the initiation of the possibly offending medication and if the condition reverses after its discontinuation. The same is also true with regard to the younger age of the patients, as in older patients medication-independent development of diabetes is a relatively more probable event. The fact that large-scale, randomized trials of the available antipsychotics, with various lengths of follow-up and from which patients with abnormal glucose levels at baseline were excluded, have reported very few, if any, cases of DKA further strengthens all of these arguments.

These arguments point against a causal relationship between antipsychotic treatment and diabetes. However, there is another side to the coin. There is ample evidence that most,[16] if not all, antipsychotics cause weight gain, which can indirectly worsen insulin sensitivity, with the potential for diabetes in vulnerable subjects. Although some antipsychotics have been described as "weight neutral,"[1] some caveats apply. First, studies of longer duration suggest that short-term studies underestimate weight gain due to antipsychotic treatment. Second, as studies in first-episode patients report major weight gain for all antipsychotic drugs, switch studies in patients with long treatment duration tend to underestimate the degree of weight gain for all antipsychotics, although the differential weight gain risks among the agents are nevertheless maintained.[17,18]

Aside from weight gain, perhaps the strongest argument for a causal relationship between diabetes and antipsychotic treatment stems from animal and human studies that have shown an almost immediate, weight-independent, deleterious effect of antipsychotic drugs on insulin sensitivity after short-term or even single-dose exposure to clozapine and olanzapine.[2,19–21] However, data are still lacking regarding the degree to which these effects generalize from an individual patient to patient groups and from an individual antipsychotic to other antipsychotics and, if so, to what degree and in which patient groups.

A third and final major argument for a causal relationship between diabetes and antipsychotic treatment is derived from incidence data of DKA, which is increased in those with schizophrenia, varying from 0.3 (risperidone) to 3.1 (clozapine) per 1,000 patient years,[12] compared to the general U.S. population, in which rates vary between 2.8 (1980) and 4.0 (2003)[22] per 10,000 population. This nearly 10-fold increase could be due to an underlying vulnerability for disturbed glucose metabolism associated with schizophrenia, to antipsychotic exposure, or to an interaction between these 2 factors. While the incidence of DKA is greater in those with schizophrenia than in the general population, the actual rate is still sufficiently low that acute-phase, controlled trials of a usual size would not have sufficient power to detect an association of antipsychotic medications with DKA.

Thus, these findings suggest that in patients who, for as yet unknown reasons, are particularly vulnerable, all antipsychotics may be involved in worsening glucose homeostasis, either indirectly, via weight gain, or directly, via currently unclear mechanisms. The recent finding in a prospective study of ethnic differences in glucoregulatory responses to antipsychotic therapy

in schizophrenia[23] might contribute to the clarification of the mechanisms involved.

A review of the arguments listed above suggests the following 3 points. First, unless the denominator of medication exposures and of all cases with diabetes and DKA is known, all of the conclusions that can be drawn from these case reports have to be considered as preliminary and hypothesis generating. Second, systematic research to elucidate the biologic mechanisms and predictors of the development of diabetes and DKA during antipsychotic therapy is needed. A related point is that an evidence-based identification of a subset of patients in whom more frequent testing is needed would be welcome. Third, in view of the absence of currently available, valid predictors for the development of diabetes during antipsychotic treatment, routine and proactive monitoring of fasting glucose and lipids must be mandatory during antipsychotic treatment in clinical practice.[24] In contrast to this evident conclusion, recent studies have shown not only a lamentably low rate of baseline cardiometabolic screening—22% to 28% of the patients receiving antipsychotics had their lipids or glucose screened during the year 2005[25]—but also a resistance to change after introduction of the screening guidelines, as a comparison between pre- and post-guideline cohorts showed.[26] These results clearly demonstrate the difficulties of implementing guidelines with mandatory repeated measurements in real-world outpatient clinical practice, as well as the need to identify effective strategies to enhance clinician and patient adherence to professional guidelines.

In conclusion, until reliable and very sensitive predictors for the development of diabetes and DKA are available, clinicians have no other option to improve the physical and psychiatric outcomes of their patients than to strictly follow the guidelines for medical monitoring. Based on the currently most cited guideline,[24] this includes baseline metabolic monitoring repeated after 3 months, with yearly monitoring thereafter in all patients in whom treatment with antipsychotics is started and continued, as well as management of metabolic abnormalities. Recently, more stringent monitoring—obligatory monthly testing during the first 3 months of second-generation antipsychotic treatment—has been proposed for all patients.[27] An intermediate strategy would be to select patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes, history of gestational diabetes, minority ethnicity, or "marked" weight gain [e.g., ≥ 7% or 1 body mass index point]) for monthly screening in the first 3 months of second-generation antipsychotic treatment.[28] Although this Belgian recommendation,[28] appropriately so, did not consider age to be a risk factor for diabetes in the mentally ill, this recommendation does not take into account the differences in metabolic risk within second-generation and first-generation antipsychotics.

Reviewing the available data, we suggest a risk-based screening that differentiates between characteristics of the prescribed atypical drugs and between patients' characteristics. Obligatory screening would occur at months 1 and 2 in patients who are prescribed certain atypical drugs (clozapine, olanzapine, quetiapine, or risperidone) or in patients with the risk factors listed above who are prescribed other antipsychotic drugs (first-generation antipsychotics, amisulpride, aripiprazole, or ziprasidone). This screening paradigm would have detected 4 of the 5 cases with DKA associated with aripiprazole. It is important to note that the recommended targeted monitoring needs to be discussed and agreed upon by authoritative work groups and/or professional organizations. Clearly, more research is needed in this area in order to arrive at data-driven, targeted, and individualized screening recommendations.

Finally, all patients on antipsychotic treatment should be screened at each visit for symptoms and signs of new-onset diabetes, such as unexplained weight loss, drowsiness, fainting spells, or polydipsia/polyuria, which should prompt immediate blood sugar testing.

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References

1. Newcomer JW. CNS Drugs 2005;19(suppl 1): S1–S93
2. Houseknecht KL, Robertson AS, Zavadoski W, et al. Neuropsychopharmacology 2007;32:289–297
3. Chintoh AF, Mann SW, Lam L, et al. Schizophr Res 2009 Mar; 108(1–3):127–133
4. Paulose KP. J Assoc Phys India 1995;43:146
5. de Boer C, Gaete HP. Br J Psychiatry 1992;161:856–858
6. Church CO, Stevens DL, Fugate SE. Diabet Med 2005;22:1440–1443
7. Logue DD, Gonzalez N, Heligman SD, et al. Am J Psychiatry 2007;164:173
8. Reddymasu S, Bahta E, Levine S, et al. J Pancreas 2006;7:303–305
9. Campanella LM, Lartey R, Shih R. Ann Emerg Med 2009;53:264–266
10. Makhzoumi ZH, McLean LP, Lee, et al. Pharmacotherapy 2008;28: 1198–1202
11. Cohen D. Pharmacopsychiatry 2004;37:1–11
12. Henderson DC, Cagliero E, Copeland PM, et al. J Clin Psychiatry 2007;68(4):533–541
13. Ryan MC, Collins P, Thakore JH. Am J Psychiatry 2003;160:284–289
14. Arranz B, Rosel P, Ramírez N, et al. J Clin Psychiatry 2004;65(10): 1335–1342
15. Shiloah E, Witz S, Abramovitch Y, et al. Diabetes Care 2003;26:1462–1467
16. Allison DB, Mentore JL, Heo M, et al. Am J Psychiatry 1999;156: 1686–1696
17. Meltzer HY, Alphs L, Green AI, et al. Arch Gen Psychiatry 2003;60:82–91
18. Alvarez-Jiménez M, González-Blanch C, Crespo-Facorro B, et al. CNS Drugs 2008;22:547–562
19. Chintoh AF, Mann SW, Lam L, et al. J Clin Psychopharmacol 2008;28: 494–499
20. Henderson DC, Cagliero E, Copeland PM, et al. Arch Gen Psychiatry 2005;62:19–28
21. Kinon BJ, Stauffer VL, Kollack-Walker S, et al. J Clin Psychopharmacol 2008;28:601–607
22. Centers for Disease Control and Prevention Web site. Age-Adjusted Hospital Discharge Rates for Diabetic Ketoacidosis as First-Listed Diagnosis per 10,000 Population, United States, 1980–2005. Available at: http://www.cdc.gov/diabetes/statistics/dkafirst/fig7.htm. Accessed September 22, 2008
23. Ader M, Garvey WT, Phillips LS, et al. J Psychiatr Res 2008;42:1075–1085
24. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity. J Clin Psychiatry 2004;65(2):267–272
25. Barnes TRE, Paton C, Cavanagh M-R, et al. Schizophr Bull 2007;33: 1397–1403
26. Haupt DW, Rosenblatt LC, Kim E, et al. Am J Psychiatry 2009;166(3): 345–353
27. Duiverman ML, Cohen D, van Oven W, et al. Neth J Med 2007;65(9): 346–348
28. De Nayer A, De Hert M, Scheen A, et al. Pharmakon 2006;38:13–23

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