CME QUESTIONS

(A) Weight gain is a vexing problem with many psychotropic drugs, especially atypical antipsychotics such as clozapine and olanzapine. With this background, mark True or False against each of the following statements:
1. Reboxetine attenuates weight gain in patients who begin treatment with olanzapine.
2. Metformin prevents weight gain in patients who begin treatment with olanzapine.
3. Metformin promotes weight loss in patients who gain weight with olanzapine.
4. Rimonabant promotes weight loss in patients who gain weight with olanzapine.

(B) There are several reasons why psychiatrists often see diabetic patients: diabetes is associated with an increased risk of depression; psychiatric disorders may be associated with hypercortisolism and other neurohormonal changes that can worsen diabetes; and many medications used in psychiatry may precipitate or worsen diabetes.

The glycated hemoglobin level is a useful measure of blood sugar control during the past 1-3 months; normal levels lie in the 4-6% range. Intensive diabetic control seeks to keep the glycated hemoglobin level within the normal range or, at any rate, below 6.5% With this background, mark True or False against each of the following statements:
1. Intensive diabetic control is associated with a lower risk of ischemic cardiovascular or cerebrovascular events.
2. Intensive diabetic control is associated with a lower risk of mortality.
3. Intensive diabetic control is associated with a lower risk of nephropathy.
4. Intensive diabetic control is associated with a higher risk of hypoglycemic events.

(C) In 2005, the Food and Drug Administration (FDA) in the United States issued an alert that, among elderly patients with dementia, the treatment of behavioral disorders with atypical antipsychotic drugs is associated with a higher mortality rate. With this background, mark True or False against each of the following statements:
1. Recent epidemiological studies suggest that the FDA alert was unjustified.
2. Atypical antipsychotic drugs increase the mortality risk in elderly subjects with dementia.
3. Elderly subjects with dementia who require antipsychotic drugs have a form of illness that is associated with a worse prognosis, including a higher mortality risk.
4. Relative to the atypical drugs, typical antipsychotics carries a lower mortality risk in elderly subjects with dementia.

Answers on page numbers 136-137.
CME ANSWERS

(A) Weight gain with olanzapine
Answers: 1. True; 2. False; 3. True; 4. False.

DISCUSSION

At least two studies[1-2] have shown that reboxetine (4 mg/day), but not fluoxetine[3] attenuates (but does not prevent) weight gain in schizophrenic patients who begin treatment with olanzapine. In other words, patients prescribed olanzapine do gain weight despite reboxetine, but not as much weight had they not taken reboxetine.

Sibutramine, orlistat, and rimonabant are approved treatments for promoting weight loss; of these, only sibutramine (10-15 mg/day) has been studied, with positive results, in patients who gained weight with olanzapine.[4] There are no studies examining the use of rimonabant in the context of weight gain in schizophrenia. Other treatments which promote weight loss in those who gain weight with olanzapine include topiramate[5] and amantadine.[6]

Several studies have shown that, in children and adolescents as well as in adults who receive olanzapine or other psychotropic drugs, metformin (750-1500 mg/day) attenuates (but does not prevent) weight gain and promotes weight loss. The drug is effective and well tolerated in studies that extend for up to 16 weeks[7-12] though, found no benefit with metformin.

Would the discontinuation of the effective medications result in a loss of the accrued benefits? What is the long-term safety and efficacy of drugs prescribed for weight loss in psychiatric patients? Both questions require research. It should be kept in mind that B12 and folate deficiency may develop in chronic users of metformin, and that metformin may also result in fatal lactic acidosis in patients with certain medical disorders.[13]

(B) Intensive control of blood sugar
Answers: 1. False; 2. False; 3. True; 4. True.

DISCUSSION

Outcomes with intensive blood sugar control were investigated in the ACCORD (n = 10,251) and ADVANCE (n = 11,140) randomized controlled trials. These studies found that, in patients with type 2 diabetes mellitus, a glycated hemoglobin target of <6.5% reduced the risk of nephropathy but not the risk of adverse cardiovascular and cerebrovascular events, nor the risk of retinopathy. Alarming, intensive blood sugar control increased the risk of hypoglycemic events and, in the ACCORD study, also increased the risk of mortality.

These studies differed much in their methods, as a result of which the interpretation of results is a complex matter. Nonetheless, neither study clearly encourages the use of intensive treatment regimens for diabetic patients. Interested readers are referred to the excellent commentaries on these two trials.[14,15]

(C) Risks with antipsychotic medications in dementia
Answers: 1. False; 2. True; 3. True; 4. False.

DISCUSSION

Two large epidemiological studies examined the risk of serious adverse events and death associated with atypical antipsychotic prescriptions in elderly subjects with dementia. In a retrospective study of 10,615 elderly patients with dementia, Kales et al.[16] observed that patients started on conventional, atypical, or both categories of antipsychotic medications had a 23-29% one-year mortality rate whereas those started on other psychiatric medications had only a 15% one-year mortality rate. The mortality risk with typical antipsychotics was similar to that with the atypical drugs. Interestingly, the higher mortality rates in patients taking antipsychotic medications appeared to be due to dementia-related causes; this implies that dementia necessitating antipsychotic treatment may be intrinsically associated with a worse prognosis.

In a retrospective study of 41,241 elderly patients with dementia, Rochon et al.[17] observed that the 1-month risk of a serious adverse event or death was two to three times higher in patients receiving antipsychotic medication relative to those not prescribed antipsychotic medication. The risk with conventional antipsychotics was slightly higher than that with the atypical drugs.

Studies such as these cannot attribute risk causality to antipsychotic medication. Causality was shown by a meta-analysis of 15 randomized, placebo-controlled trials[18] that mortality was significantly higher in dementia patients who received antipsychotic medication than in those who received placebo (3.5% vs. 2.3% respectively).

REFERENCES

1. Poyurovsky M, Isaacs I, Fuchs C, Schneiderman M, Faragian S, Weizman R, et al. Attenuation of olanzapine-induced weight gain with reboxetine in patients with schizophrenia: A double-blind, placebo-controlled study. Am J Psychiatry 2003;160:297-302.
2. Poyurovsky M, Fuchs C, Pashianian A, Levi A, Faragian S, Maayan R, et al. Attenuating effect of reboxetine on appetite and weight gain in olanzapine-treated schizophrenia patients: A double-blind placebo-controlled study. Psychopharmacology (Berl) 2007;192:441-8.
3. Poyurovsky M, Pashianian A, Gill-Ad I, Maayan R, Schneiderman M, Fuchs C, et al. Olanzapine-induced weight gain in patients with first-episode schizophrenia: A double-blind, placebo-controlled study of fluoxetine addition. Am J Psychiatry 2002;159:1088-90.
4. Henderson DC, Copeland PM, Daley TB, Borba CP, Cather C, Nguyen DD, et al. A double-blind, placebo-controlled trial of sibutramine for olanzapine-associated weight gain. Am J Psychiatry 2005;162:954-62.
5. Nickel MK, Nickel C, Muehlbacher M, Leiberich PK, Kaplan P, Lahmann C, et al. Influence of topiramate on olanzapine-related adiposity in women: A random, double-blind, placebo-controlled study. J Clin Psychopharmacol 2005;25:211-7.

6. Graham KA, Gu H, Lieberman JA, Harp JB, Perkins DO. Double-blind, placebo-controlled investigation of amantadine for weight loss in subjects who gained weight with olanzapine. Am J Psychiatry 2005;162:1744-6.

7. Morrison JA, Cottingham EM, Barton BA. Metformin for weight loss in pediatric patients taking psychotropic drugs. Am J Psychiatry 2002;159:655-7.

8. Klein DJ, Cottingham EM, Sorter M, Barton BA, Morrison JA. A randomized, double-blind, placebo-controlled trial of metformin treatment of weight gain associated with initiation of atypical antipsychotic therapy in children and adolescents. Am J Psychiatry 2006;163:2072-9.

9. Baptista T, Rangel N, Fernandez V, Carrizo E, El Fakih Y, Uzcategui E, et al. Metformin as an adjunctive treatment to control body weight and metabolic dysfunction during olanzapine administration: A multicentric, double-blind, placebo-controlled trial. Schizophr Res 2007;93:99-108.

10. Chen CH, Chiu CC, Huang MC, Wu TH, Liu HC, Lu ML. Metformin for metabolic dysregulation in schizophrenic patients treated with olanzapine. Prog Neuropsychopharmacol Biol Psychiatry 2008;32:925-31.

11. Wu RR, Zhao JP, Guo XF, He YQ, Fang MS, Guo WB, et al. Metformin addition attenuates olanzapine-induced weight gain in drug-naive first-episode schizophrenia patients: A double-blind, placebo-controlled study. Am J Psychiatry 2008;165:352-8.

12. Baptista T, Martinez J, Lacruz A, Rangel N, Beaulieu S, Serrano A, et al. Metformin for prevention of weight gain and insulin resistance with olanzapine: A double-blind placebo-controlled trial. Can J Psychiatry 2006;51:192-6.

13. Towbin KE. Gaining: Pediatric patients and use of atypical antipsychotics. Am J Psychiatry 2006;163:2034-8.

14. Cefalu WT. Glycemic targets and cardiovascular disease. N Engl J Med 2008;358:2633-5.

15. Dluhy RG, McMahon GT. Intensive glycemic control in the ACCORD and ADVANCE trials. N Engl J Med 2008;358:2630-3.

16. Kales HC, Valenstein M, Kim HM, McCarthy JF, Ganoczy D, Cunningham F, et al. Mortality risk in patients with dementia treated with antipsychotics versus other psychiatric medications. Am J Psychiatry 2007;164:1568-76.

17. Rochon PA, Normand SL, Gomes T, Gill SS, Anderson GM, Melo M, et al. Antipsychotic therapy and short-term serious events in older adults with dementia. Arch Intern Med 2008;168:1090-6.

18. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: Meta-analysis of randomized placebo-controlled trials. JAMA 2005;294:1934-43.

Source of Support: Nil, Conflict of Interest: None declared