Schizophrenia and increased risks of cardiovascular disease

Charles H. Hennekens, MD,[a,b,c] Alissa R. Hennekens, MSW,[d] Danielle Hollar, PhD,[a,b] and Daniel E. Casey, MD[e]
Boca Raton, FL; Boston, MA; and Portand, OR

Objective The aim of the study is to review the absolute and relative impacts of the major causes for premature mortality among patients with schizophrenia.

Data sources We reviewed published articles on causes of mortality in the general population as well as among patients with schizophrenia.

Study selection We selected articles which published total and cause-specific mortality rates.

Data extraction We reviewed the causes of mortality and their risk factors.

Data synthesis The average life expectancy of the general population is 76 years (72 years in men, 80 years in women), whereas the corresponding figure is 61 years (57 years in men, 65 years in women) among patients with schizophrenia. Thus, patients with schizophrenia have approximately a 20% reduced life expectancy compared with the general population. Although patients with schizophrenia are 10 to 20 times more likely than the general population to commit suicide, more than two thirds of patients with schizophrenia, compared with approximately one-half in the general population, die of coronary heart disease (CHD). The chief risk factors for this excess risk of death are cigarette smoking, obesity leading to dyslipidemia, insulin resistance and diabetes, and hypertension.

Conclusions The chief cause of excess premature mortality among patients with schizophrenia is CHD, caused mainly by their adverse risk factor profile. Because patients with schizophrenia have less access to medical care, consume less medical care, and are less compliant with their regimens, the choice of antipsychotic drug regimens that do not further adversely affect their risk factor for CHD is a major clinical and public health challenge among patients with schizophrenia. (Am Heart J 2005;150:1115-21.)

Coronary heart disease (CHD) is far and away the leading cause of mortality in most developed countries, accounting for >1 in 3 total deaths. During the 21st century, CHD will remain the leading cause of death in developed countries, will become the leading cause of death in developing countries, and therefore, will emerge as the leading cause of death in the world. In the general US population, there are numerous large prospective cohort studies which quantitate the relationship of various major risk factors with subsequent incidence of and mortality from CHD.[1,2]

Schizophrenia occurs in approximately 1% of the world's population, including approximately 3 million in the US. Despite the relatively high and uniform prevalence of schizophrenia, prospective data are sparse regarding the relationship of various major risk factors with subsequent incidence of and mortality from CHD. For these and other reasons, little attention has been given to the high frequency of CHD in patients with schizophrenia by generalists, specialists in other fields, or cardiovascular specialists. In this article, we describe the rates of death from CHD in the general population, as well as their major risk factors, to inform generalists as well as specialists in other fields of their relative and absolute importance. We also examine the high rates of death from CHD and their major risk factors among patients with schizophrenia for the cardiovascular specialist. Finally, for all health care providers, we emphasize the crucial importance for patients with

From the [a]Department of Biomedical Science, Center of Excellence in Biomedical and Marine Biotechnology, Florida Atlantic University, Departments of [b]Medicine, and [c]Epidemiology and Public Health, University of Miami School of Medicine, [d]Boston University School of Social Work, and [e]Departments of Psychiatry and Neurology, Oregon Health and Science University.
This work was supported by research funds from the Agatston Research Institute (ARI), the Oregon Health and Science University, and the Danicas Foundation.
Submitted May 25, 2004; accepted February 7, 2005.
Reprint requests: Charles H. Hennekens, MD, 2800 S. Ocean Blvd, PH-A, Boca Raton, FL 33432.
E-mail: profchhmd@prodigy.net
0002-8703/$ - see front matter

doi:10.1016/j.ahj.2005.02.007

Table I. Life expectancy and absolute risks of death in the general population and among patients with schizophrenia

	General population	Patients with schizophrenia
Life expectancy (y)	76 (72 men and 80 women)	61 (57 men and 65 women)
Absolute risks of death		
Suicide (%)	1	10
CHD (%)	33	50-75

schizophrenia of particular antipsychotic drug regimens that do not adversely affect their already high prevalence of major risk factors for CHD.

Mortality among patients with schizophrenia

Whereas the average life expectancy in the general population of the United States is approximately 76 years (72 years in men and 80 years in women),[1] that among patients with schizophrenia is approximately 20% shorter or 61 years (57 years in men and 65 years in women).[3,4] This significantly lower life expectancy for patients with schizophrenia is caused primarily by CHD and also by other etiologies, principally suicide.[5] With respect to suicide, approximately 50% of patients with schizophrenia attempt take their own lives and approximately 10% succeed—a 10-fold higher relative risk than in the general population.[6] In contrast, the relative risk of CHD among patients with schizophrenia is perhaps 2-fold higher than the general population. Nonetheless, because suicides occur in approximately 10% and CHD among perhaps 50% to 75% of patients with schizophrenia, there are more deaths attributable to CHD than suicide. This situation is analogous to cigarette smoking and lung cancer where the relative risk is 20, and smoking and CHD where the relative risk is 2. Because there are so many more deaths in the general population attributable to CHD than lung cancer, if smoking were abolished, there would be more CHD deaths than lung cancer deaths prevented.[7]

In a meta-analysis based on data since 1990, death rates from CHD were 90% higher in patients with schizophrenia than among the general population.[4] In another recent analysis,[8] patients with schizophrenia were twice as likely to die of CHD than the general population. Furthermore, when patients with schizophrenia have major CHD events such as acute myocardial infarction, they are significantly less likely to receive the standard of care received by the general population.[9,10] Table I summarizes the mortality data just reviewed.

Typical antipsychotic drugs, in particular haloperidol, are effective but cause a high frequency of troublesome and even embarrassing side effects to patients with schizophrenia. These side effects are principally extrapyramidal symptoms and tardive dyskinesias. The advent of atypical antipsychotic drugs was a major advance in patients with schizophrenia, in part, because of their far lower risks for extrapyramidal symptoms and tardive dyskinesias. With respect to the Positive And Negative Syndrome Scale, the atypicals have superior efficacy in treating negative symptoms, improving mood and cognition, as well as preventing relapse. These include thioridazine, olanzapine, quetiapine, risperidone, as well as ziprasidone and, most recently, aripiprazole. Some but not all atypical antipsychotic drugs also cause adverse effects on risk factors for CHD including weight gain and a wide range of metabolic abnormalities.[11] These side effects should be particularly worrisome to health care providers because patients with schizophrenia already have far higher risks of CHD than the general population.

Major risk factors for CHD in the general population and among patients with schizophrenia

Major risk factors for CHD, including cigarette smoking, blood cholesterol, hypertension, obesity, and diabetes mellitus, are more common among patients with schizophrenia than in the general population. In the general population, patients often prefer prescription of pills to proscription of harmful lifestyles. Among patients with schizophrenia, compliance with pill taking is difficult to achieve, including their antipsychotic drug regimen. Thus, emphasis on the prescription of antipsychotic drugs of proven benefit which do not adversely affect the major risk factors for CHD assumes great clinical and public health importance.

Cigarette smoking

In the general US population, cigarette smoking is the leading avoidable cause of all premature death,[11] as well as mortality from cancer. In the general population of the United States, approximately 25% are current cigarette smokers compared with approximately 75% among patients with schizophrenia. Furthermore, patients with schizophrenia have great difficulty with smoking cessation in the short term and with smoking avoidance in the long term.[12] In addition, patients with schizophrenia tend to smoke more cigarettes daily than smokers in the general population. Thus, patients with schizophrenia are at markedly increased risk because amount currently smoked is the major risk factor for CHD.

Blood cholesterol

In most general populations in developed countries, elevated blood cholesterol is the leading avoidable cause

Table II. Changes in fasting lipids in a randomized trial

Lipids (mg/dL)	Ziprasidone	Risperidone	Olanzapine	Quetiapine	Thioridazine	Haloperidol
Total cholesterol						
N	34	28	27	29	31	29
Median baseline	197.5	204.0	201.0	196.0	186.0	193.0
Median change	−14.5*	−3.0	4.0	5.0	21.0*	−22.0*
Median % change	−7.5†	−1.6	2.1	2.4	13.7†	−11.5*
LDL cholesterol						
N	33	25	26	28	29	29
Median baseline	122.0	125.0	128.0	117.0	121.0	121.0
Median change	−11.0	9.0	1.5	−0.5	20.0*	−14.0*
Median % change	−8.5	6.5	1.1	−0.3	18.6*	−10.5*
HDL cholesterol						
N	34	27	27	29	30	29
Median baseline	43.5	41.0	44.0	45.0	41.0	43.0
Median change	0.0	−2.0	−2.0	−3.0	1.5	−3.0†
Median % change	0	−4.9	−4.6	−8.6	3.0	−6.0‡
Triglycerides						
N	34	28	27	29	31	29
Median baseline	141.0	158.0	148.0	124.0	120.0	118.0
Median change	−37.0*	−17.0	43.0*	25.0*	9.0	−18.0†
Median % change	−28.0*	−6.7	31.0*	18.3*	7.9	−18.0†
Total cholesterol/HDL ratio						
N	34	27	27	29	30	29
Median baseline	4.31	5.43	5.14	4.42	4.61	4.26
Median change	−0.33†	0.31	0.28	0.48†	0.41†	−0.22‡
Median % change	−7.5†	5.9‡	5.4‡	10.8†	12.4*	−7.0‡

Wilcoxon signed rank test on change from baseline values versus 0 and percent change from baseline values versus 0.
Reprinted from: http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3619b1a.pdf (accessed on August 25, 2004).
*$P < .001$.
†$P < .01$.
‡$P < .05$.

of premature death from CHD.[1,2] The United States National Cholesterol Education Program (NCEP-III)[13] Adult Treatment Panel recommends statins as the drug of choice in the treatment and prevention of CHD because of their statistically significant and clinically important beneficial effects on myocardial infarction, stroke, and cardiovascular death.[14] Despite a large and persuasive totality of evidence, it has been estimated that the NCEP-III guidelines are being achieved by 18% of patients in secondary prevention and approximately 37% in primary prevention.[15]

Patients with schizophrenia are likely to have higher levels and receive less treatment for elevated blood cholesterol. Specifically, patients with schizophrenia and elevated blood cholesterol levels are prescribed statins at approximately 25% of the rate in the general population.[16] Furthermore, some but not all atypical antipsychotic drugs increase total and low-density lipoprotein (LDL) cholesterol as well as triglycerides and decrease high-density lipoprotein (HDL) cholesterol,[17,18] all of which increase risks of CHD.[1,2] For example, patients treated with certain atypical antipsychotic drugs experience increases in cholesterol of approximately 20 mg/dL[13] which are even greater in certain subgroups.[17] Table II shows changes in fasting lipids from a randomized trial of 6 antipsychotic drugs (5 atypicals and 1 typical) over a 1-year follow-up.

Hypertension

In the United States and most developed countries, hypertension affects approximately 15% of the general population[1,2] and perhaps 19% of patients with schizophrenia,[19] in large measure because of obesity.[20] Meta-analyses of randomized trials of drug therapies for hypertension[21,22] have demonstrated statistically significant and clinically important reductions of 42% in stroke and 16% in CHD. Patients with schizophrenia tend to be more obese than the general population, a condition exacerbated by the excessive weight gain that accompanies treatment with certain atypical antipsychotic drugs.[23] In addition, among patients with schizophrenia, their high rates of noncompliance with antipsychotic medications imply similar poor compliance with drugs of proven benefit for the treatment of hypertension, hence making it difficult for their health care providers to achieve the Joint National Commission VII guidelines for treatment of hypertension.[24]

Obesity

Obesity is a leading avoidable cause of all cancer and CHD deaths and also causes metabolic syndrome, a

constellation which includes hypertension, dyslipidemia, and insulin resistance, leading to diabetes.[1,2] In a large prospective study of US female nurses, after controlling for confounding by cigarette smoking, there was a linear relationship between obesity and death from CHD[25] for those with a body mass index (BMI = weight in kilograms divided by height squared in meters) from approximately 19 to 26. For those with a BMI of ≥27, the linear relationship was even more steep.[26]

In the United States, 27% of the general population and 42% of patients with schizophrenia have a BMI of ≥27.[27] The higher prevalence of obesity in patients with schizophrenia can be attributed in part to the disease, and also to the weight gain resulting from atypical antipsychotic drugs.[23,28-31] Based on projections from the Framingham Heart Study data, some atypical antipsychotic drugs could, in theory, result in an additional 416 deaths per 100 000 over 10 years[27] for those with baseline BMIs of ≥27 who also gain an additional 10 kg (22 lb). Table III shows the average weight gain associated with antipsychotic drugs (5 atypical and 1 typical) based on a review of published articles by Lean and Pajonk.[31] The largest increases of almost 7 kg (approximately 15 lb) are for clozapine and olanzapine which are with lesser increases for risperidone and quetiapine. In these data, ziprasidone was weight-neutral, and haloperidol, a typical antipsychotic, caused a weight gain of almost 4 kg (8 lb).

Table III. Weight gain in kilograms for various antipsychotic drugs

	Clozapine	**Olanzapine**
Wirshing et al[44]*	6.9 ± 0.8†	6.8 ± 1.0
Meyer[30]‡	5.3-6.3	6.8-11.8
Czobor et al[29]§	4.2 ± 4.7‖¶	5.4 ± 4.6*†
	Risperidone	**Quetiapine**
Wirshing et al[44]*	5.0 ± 0.6	–
Meyer[30]‡	2.0-2.3	2.77-5.6
Czobor et al[29]§	2.3 ± 2.8‖#	–
	Ziprasidone	**Haloperidol**
Wirshing et al[44]*	–	3.7 ± 0.6
Meyer[30]‡	0.23	–
Czobor et al[29]§	–	0.2 ± 0.2

Reprinted from Lean et al.[31]
*Maximal weight gain ± SE. Maximal weight gains were adjusted by controlling for age, treatment duration, and initial body weight. These weight gains occurred over treatment periods of 24 to 73 months, and the corrected values are adjusted for duration of treatment. The expected weight gain for the normal population not receiving antipsychotic drugs over this period would be approximately 2 to 3 kg. For clozapine, weight gain ceased at 25 months, compared with 21 months for olanzapine, 15 months for risperidone, and 18 months for haloperidol. Patients in this study were counseled about diet and exercise and were referred to a clinical nutritionist if their weights increased by >4.5 kg.
†$P \leq .01$ vs haloperidol (pairwise comparison, controlled for age, treatment duration, and initial weight).
‡Range of weight gain over 1 year (6 months for ziprasidone).
§Mean weight gain ± SD after 14 weeks' treatment.
‖ $P < .05$ vs baseline.
¶$P < .05$ vs haloperidol.
#No significant difference from haloperidol.

Diabetes mellitus

Diabetes increases the risk of CHD by 2- to 3-fold in men and 3- to 6-fold in women.[1,2] In the general population, as well as among patients with schizophrenia, most of diabetes cases are caused by obesity, which is also associated with dyslipidemia and hypertension. The diabetic patient requires strict management of both dyslipidemia using NCEP-III guidelines[32] and hypertension using Joint National Commission VII guidelines.[24] In addition, the recently published American Diabetes Association guidelines for management of adult-onset diabetes recommend drug therapy and/or therapeutic lifestyle changes and encourage regular physical activity. Finally, it is increasingly recognized that managing diabetic patients requires strict attention to all of their risk factors for CHD.[33]

Among patients with schizophrenia, diabetes is estimated to be 1.5 to 2-fold greater than the general population.[34] These data reflect rates in the early 1990s, so the current figures are likely to be even higher. Furthermore, most but not all atypical antipsychotic drugs are associated with weight gain, increased insulin levels,[13,23,35] and insulin resistance,[13,36] and some directly increase the risk of diabetes. In a recent study, olanzapine was associated with a significant 5.8 times higher risk of diabetes compared with those not taking antipsychotics and a 4.2 times higher risk compared with patients taking typical antipsychotic drugs.[37] The relationship of the various atypical antipsychotic drugs with diabetes, as complied by Lean and Pajonk,[31] is shown in Table IV.

Discussion

Among patients with schizophrenia, there is an enormous clinical and public health burden of CHD which is chiefly responsible for their reduced life expectancy. Although greater emphasis on treatment including favorable modification of risk factors is important, efforts aimed at the primary prevention of unfavorable risk factors assume even greater importance in patients with schizophrenia. The treatment and prevention strategies should include encouraging healthy lifestyles, smoking cessation, appropriate diets and levels of activity, and integrating medical services, as well as screening and treatment.[38] In the general population, individuals tend to prefer prescription of pills to proscription of harmful lifestyles. For example, the NCEP Adult Treatment Panel III guidelines suggest that theoretically, 35% reductions in LDL cholesterol are attainable with therapeutic lifestyle changes, but in practice, only approximately 5% are achieved. Despite

Table IV. Atypical antipsychotic drugs and diabetes

	Date introduced	Reports of diabetes (by January 2002)	Reported cases of ketoacidosis	Diabetes resolved when drug stopped or switch	Diabetes improved when drug stopped or switched*
Clozapine	1989†	26	10	81*	10 (5)
Risperidone	1994	3	1‡	3	–
Olanzapine	1996	21	8	10	7 (3)
Quetiapine	1998	2	1	1	1
Ziprasidone	2001	0	0	–	–

Reprinted from Lean et al.[31] Data were compiled from surveys[45-48] plus other case reports found in Medline using the search terms "diabetes" and "antipsychotic," "clozapine," "olanzapine," "quetiapine," "risperidone," or "ziprasidone" published between January 1999 and January 2002.[49-58] Data in parentheses indicate cases where the dose of antipsychotic was reduced and/or diabetes was controlled with drugs and/or diet.
*In one of these patients, diabetes resolved completely but recurred when clozapine was restarted and did not resolve when clozapine was subsequently stopped.
†Reintroduced with safeguards to detect potential agranulocytosis.
‡Patient was HIV-positive and taking a protease inhibitor concomitantly with risperidone; protease inhibitors are known to cause diabetes.

the theoretical benefits of such lifestyle modifications, there are few, if any, strategies that have been effective for modification of cardiovascular risk in patients with schizophrenia. Specifically, although the cigarette smoking rates in the general population have decreased from >50% to <25%, the corresponding figure among patients with schizophrenia is >70%. These considerations emphasize the importance of choosing antipsychotic drug regimens that do not adversely affect cardiovascular risk. Furthermore, many drugs prescribed for patients with schizophrenia also are prescribed for patients with other mental disorders. All health care providers who prescribe these drugs need to understand both the benefits and risks of particular antipsychotic drugs. These difficult circumstances also emphasize the crucial importance of the role of the cardiologist in collaboration with both the mental health professional and the primary health care provider in the care of the patient with schizophrenia. As with the general population, minimizing troubling side effects and educating patients with schizophrenia about the role of the medications prescribed,[39] as well as encouraging frequent reassurances and involvement of family members or friends, may help facilitate the goals of the health care team.

In descriptive and analytical epidemiological studies[40] as well as in a large-scale randomized trial of secondary prevention,[41] omega-3 fatty acids were shown to reduce risks of CHD. Interestingly, patients with schizophrenia have lower-than-average levels of omega-3 fatty acids.[42] Further research is necessary to define the potential clinical relevance of this finding to their increased risks of CHD.

In conclusion, lifestyle modifications are crucial to reduce risk factors for CHD in the general population as well as among patients with schizophrenia who are at even higher risks. This situation is exacerbated by a number of barriers such as lack of compliance with their antipsychotic drug regimens, which occurs in ≥50% patients with schizophrenia at some time during their illness.[39] Additional barriers include lack of seeking medical care, even during acute cardiovascular syndromes, and receiving suboptimal cardiovascular care as patients with schizophrenia tend to be offered less cardiovascular procedures and also tend to attend health care facilities that may not offer such modalities.

All of the above considerations lead to unsuccessful modification of cardiovascular risk factors including cigarette smoking, obesity, lipids, and diabetes. Some effective atypical antipsychotic drugs such as olanzapine, clozapine, quetiapine, and risperidone cause significant weight gain in contrast to ziprasidone. In addition, dyslipidemia and insulin resistance, leading to diabetes, have been reported. Furthermore, patients with schizophrenia switched from olanzapine to ziprasidone experience significant weight loss.[43] Consequently, what is paramount for health care providers treating patients with schizophrenia is the prescription of antipsychotic drug regimens that are less likely to adversely affect major risk factors for CHD such as ziprasidone.[38]

References

1. Hennekens CH. Increasing burden of cardiovascular disease: current knowledge and future directions for research on risk factors. Circulation 1998;97:1095-102.
2. Hennekens CH. Clinical and research challenges in risk factors for cardiovascular diseases. Eur Heart J 2000;21:1917-21.
3. Newman SC, Bland RC. Mortality in a cohort of patients with schizophrenia: a record linkage study. Can J Psychiatry 1991;36:239-45.
4. Harris EC, Barraclough B. Excess mortality of mental disorder. Br J Psychiatry 1998;173:11-53.
5. Casey DE, Hansen TE. Excessive morbidity and mortality in schizophrenia. In: Meyer JM, Nasrallah HA, editors. Medical illness and schizophrenia. Washington (DC): American Psychiatric Publishing; 2003. p.13-34.
6. Meltzer HY. Suicide in schizophrenia: risk factors and clozapine treatment. J Clin Psychiatry 1998;59:15-20.

7. Hennekens CH, Buring J. Epidemiology in medicine. Boston: Little Brown Co; 1987.
8. Brown S, Inskip H, Barraclough B. Causes of excess mortality of schizophrenia. Br J Psychiatry 2000;177:212-7.
9. Druss BG, Bradford DW, Rosenheck RA, et al. Mental disorders and use of cardiovascular procedures after myocardial infarction. JAMA 2000;283:506-11.
10. Young JK, Foster DA. Cardiovascular procedures in patients with mental disorders [letter]. JAMA 2000;283:3198.
11. Doll R, Peto R. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. J Natl Cancer Inst 1981;66:1191-308.
12. George TP, Ziedonis DM, Feingold A, et al. Nicotine transdermal patch and atypical antipsychotic medications for smoking cessation in schizophrenia. Am J Psychiatry 2000;157:1835-42.
13. Glick ID, Fryburg D, O'Sullivan RL, et al. Ziprasidone's benefits versus olanzapine on weight and insulin resistance. Abstracts of the 2001 Annual Meeting of the American Psychiatric Association; May 2001, New Orleans, LA. [Abstract NR261].
14. Hebert PR, Gaziano MJ, Chan KS, et al. Cholesterol lowering with statin drugs, risk of stroke and total mortality. JAMA 1997;278: 313-21.
15. Pearson TA, Laurora J, Chu H, et al. The Lipid Treatment Assessment Project (L-Tap): a multicenter survey to evaluate the percentages of dyslipidemic patients receiving lipid lowering therapy and achieving low density lipoprotein cholesterol goals. Arch Intern Med 2000;160:459-67.
16. Redelmeier DA, Siew HT, Booth GL. The treatment of unrelated disorders in patients with chronic medical diseases. N Engl J Med 1998;338:1516-20.
17. Meyer JM. Novel antipsychotics and severe hyperlipidemia. J Clin Psychopharmacol 2001;21:369-74.
18. Melkersson KI, Hulting A-L, Brismar KE. Elevated levels of insulin, leptin and blood lipids in olanzapine-treated patients with schizophrenia or related psychoses. J Clin Psychiatry 2000; 61:742-9.
19. Dixon L, Postrado L, Delahanty J, et al. The association of medical comorbidity in schizophrenia with poor physical and mental health. J Nerv Ment Dis 1999;187:496-502.
20. Rosner B, Hennekens CH, Kass EH, et al. Age specific correlation analysis of longitudinal blood pressure data. Am J Epidemiol 1977;106:306-13.
21. Hebert PR, Fiebach NH, Eberlein KA, et al. The community-based randomized trials of pharmacologic treatment of mild-to-moderate hypertension. Am J Epidemiol 1988;127:581-90.
22. Collins R, Peto R, MacMahon S, et al. Blood pressure, stroke and coronary heart disease: part 2, short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. Lancet 1990;335:827-38.
23. Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 1999;156:1686-96.
24. Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure the JNC 7 report. JAMA 2003;289:2560-72.
25. Manson JE, Stampfer MJ, Hennekens CH, et al. Body weight and longevity: a reassessment. JAMA 1987;257:353-8.
26. Willett WC, Manson JE, Stampfer MJ, et al. Weight, weight change, and coronary heart disease in women. Risk within the 'normal' weight range. JAMA 1995;273:461-5.
27. Fontaine KR, Heo M, Harrigan EP, et al. Estimating the consequences of antipsychotic induced weight gain on health and mortality rate. Psychiatry Res 2001;101:277-88.
28. Allison DB, Fontaine KR, Heo M, et al. The distribution of body mass index among individuals with and without schizophrenia. J Clin Psychiatry 1999;60:215-20.
29. Czobor P, Volavka J, Sheitman B, et al. Antipsychotic-induced weight gain and therapeutic response: a differential association. J Clin Psychopharmacol 2002;22:244-51.
30. Meyer JM. Effects of atypical antipsychotics on weight gain and serum lipid levels. J Clin Psychiatry 2001;62:27-34.
31. Lean MEJ, Pajonk FG. Patients on atypical antipsychotic drugs: another high-risk group for type 2 diabetes. Diabetes Care 2003;26:1597-605.
32. National Cholesterol Education Program. Executive summary of the third report of The National Cholesterol Education Program Expert Panel on detection, evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 2001;285:2508-9.
33. American Diabetes Association. Hypertension management in adults with diabetes. Diabetes Care 2004;27:S65-7.
34. Mukherjee S, Decina P, Bocola V, et al. Diabetes mellitus in schizophrenic patients. Comp Psychiatry 1996;37:68-73.
35. Melkersson KI, Hulting A-L. Insulin and leptin levels in patients with schizophrenia or related psychoses—a comparison between different antipsychotic agents. Psychopharmacology 2001;154: 205-12.
36. Henderson DC, Cagliero E, Gray C, et al. Clozapine, diabetes mellitus, weight gain and lipid abnormalities: a five-year naturalistic study. Am J Psychiatry 2000;157:975-81.
37. Koro CE, Fedder DO, L'Italien GJ, et al. Assessment of independent effect of olanzapine and risperidone on risk of diabetes among patients with schizophrenia: population based nested case-control study. BMJ 2002;325:243-5.
38. Casey DE, Haupt DW, Newcomer JW, et al. Anti-psychotic drug associated weight gain and metabolic abnormalities: implications for increased mortality from schizophrenia. J Clin Psychiatry 2004;65(Suppl 7):4-18.
39. Marder SR. Overview of partial compliance. J Clin Psychiatry 2003;64(Suppl 16):3-9.
40. Harper CR, Jacobson TA. Beyond the Mediterranean diet: the role of omega-3 fatty acids in the prevention of coronary heart disease. Prev Cardiol 2003;6:136-46.
41. Marchioli R, Barzi F, Bomba E, et al. Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. Circulation 2002;105:1897-903.
42. Richardson AJ, Cyhlarova E, Ross MA. Omega-3 and omega-6 fatty acid concentrations in red blood cell membranes relate to schizotypal traits in healthy adults. Prostaglandins Leukot Essent Fatty Acids 2003;69:461-6.
43. Weiden PJ, Daniel DG, Simpson G, et al. Improvement in indices of health status in outpatients with schizophrenia switched to ziprasidone. J Clin Psychopharmacol 2003;23:595-600.
44. Wirshing DA, Wirshing WC, Kysar L, et al. Novel antipsychotics: comparison of weight gain liabilities. J Clin Psychiatry 1999;60: 358-63.
45. Liebzeit KA, Markowitz JS, Caley CF. New onset diabetes and atypical antipsychotics. Eur Neuropsychopharmacol 2001;11: 25-32.

46. Mir S, Taylor D. Atypical antipsychotics and hyperglycaemia. Int Clin Psychopharmacol 2001;16:63-74.
47. Muensch J, Carey M. Diabetes mellitus associated with atypical antipsychotic medications: new case report and review of the literature. J Am Board Pam Pract 2001;14:278-82.
48. Wirshing DA, Spellberg BJ, Erhart SM, et al. Novel antipsychotics and new onset diabetes. Biol Psychiatry 1998;44:778-83.
49. Bonanno DG, Davydov L, Batts SR. Olanzapine-induced diabetes mellitus. Ann Pharmacother 2001;35:563-5.
50. Brugman NJ, Cohen D, De Vries RH. Diabetes mellitus onstaan na behandeling met clozapine. Ned Tijdsehr Geneeskd 2000;144:437-9.
51. Croarkin PE, Jacobs KM, Bain BK. Diabetic ketoacidosis associated with risperidone treatment? Psychosomatics 2000;41: 369-370.
52. Procyshyn RM, Pande S, Tse G. New-onset diabetes mellitus associated with quetiapine. Can J Psychiatry 2000;45:668-9.
53. Rigalleau V, Gatta B, Bonnaud S, et al. Diabetes as a result of atypical antipsychotic drugs: a report of three cases. Diabet Med 2000;17:484-6.
54. Roefaro J, Mukherjee SM. Olanzapine-induced hyperglycaemic nonketoic coma. Ann Pharmacother 2001;35:300-2.
55. Selva KA, Scott SM. Diabetic ketoacidosis associated with olanzapine in an adolescent patient. J Pediatr 2001;138:936-8.
56. Smith H, Kenney-Hebert J, Knowles L. Clozapine-induced diabetic ketoacidosis. Aust N Z J Psychiatry 1999;33:120-1.
57. Wirshing DA, Pierre JM, Eyeler J, et al. Risperidone-associated new-onset diabetes. Biol Psychiatry 2001;50:148-9.
58. Wu G, Dias F, Wu C. Hyperglycemia, hyperlipidaemia and periodic paralysis: a case report of new side effects of clozapine. Prog Neuropsychopharmacol Biol Psychiatry 2000;24: 1395-400.