J Exp Clin Med 2012;4(2):103–107

Contents lists available at SciVerse ScienceDirect

Journal of Experimental and Clinical Medicine

journal homepage: http://www.jecm-online.com

REVIEW ARTICLE

Metabolic and Cardiovascular Adverse Effects Associated with Treatment with Antipsychotic Drugs

Shen-Chieh Chang [1], Mong-Liang Lu [1,2]*

[1] Department of Psychiatry, Taipei Medical University-Wan Fang Medical Center, Taipei, Taiwan
[2] Department of Psychiatry, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan

ARTICLE INFO

Article history:
Received: Jan 9, 2012
Accepted: Jan 19, 2012

KEY WORDS:
adverse effect;
antipsychotic drugs;
cardiovascular disease;
metabolic syndrome;
obesity

Metabolic disturbances and cardiovascular disease are important causes of morbidity and mortality in patients with severe mental illnesses. Antipsychotic medications are the drug of the choice for patients with schizophrenia. However, some antipsychotic drugs have a high tendency to cause weight gain and metabolic abnormalities, therefore increasing the risk of obesity, metabolic syndrome, type 2 diabetes mellitus, and cardiovascular disease. These findings have led to an increased interest in looking into the relationships between schizophrenia, antipsychotic drugs, metabolic dysregulation, and cardiovascular disease. Although some neurotransmitter receptor-binding affinities are correlated with specific metabolic abnormalities, the exact mechanisms underlying antipsychotic-induced adverse metabolic effects are still unclear. The receptor affinity of antipsychotic drugs for histamine H_1, serotonin 5-HT_{2C} and 5-HT_{1A}, muscarinic M_3, dopamine D_2, and adrenergic receptors might be involved in causing metabolic dysregulation. Low-potency first-generation antipsychotic drugs are associated with a higher potential to cause weight gain and metabolic disturbance than are high-potency first-generation antipsychotics. Second-generation antipsychotic drugs carry different risks of causing weight gain and metabolic dysregulation: clozapine and olanzapine have the highest risk; quetiapine and risperidone a moderate risk; and aripiprazole, amisulpride, and ziprasidone the lowest risk. The psychiatric literature has recommended follow-up for metabolic and cardiovascular risk factors, but many antipsychotic-treated patients have not received the recommended regular monitoring for these risk factors. Psychiatrists need to educate and motivate this group of patients to make healthy lifestyle changes. If these lifestyle changes fail, these patients need to receive drug interventions. Adding medications (such as metformin, topiramate, and amantadine) or switching to another antipsychotic drug should be considered to decrease the risk of antipsychotic-induced weight gain and metabolic abnormalities. In conclusion, this review is intended to describe the adverse metabolic and cardiovascular effects related to antipsychotic medications, to explore their possible underlying mechanisms, and to recommend how to monitor and manage those iatrogenic side effects.

1. Introduction

The introduction of chlorpromazine in 1952 heralded a great advance in psychiatric care, dramatically improving the treatment outcome of schizophrenic patients.[1] Antipsychotic drugs are now the drug of choice for treating patients with schizophrenia. Although their primary indication is schizophrenia, several antipsychotic drugs are now used to treat a broad range of psychiatric disorders, including bipolar disorder, treatment-resistant major depressive disorder, and the aggression or irritability of autistic disorder.

Antipsychotic drugs are divided into first generation and second-generation agents. The first-generation antipsychotics (FGAs) are still widely available and are effective in treating the positive symptoms of schizophrenia, such as hallucinations and delusion. FGAs do not, however, adequately improve other salient aspects of psychotic illness, such as negative symptoms (e.g., social withdrawal, apathy, poverty of speech, and anhedonia), cognitive impairment, and mood symptoms. In addition, FGAs can produce extrapyramidal symptoms (such as dystonia, parkinsonism, akathisia, and tardive dyskinesia) at clinically therapeutic doses. These extrapyramidal side effects can be intolerable to patients and lead to subjective distress, function impairment, stigma, and poor medication adherence.

* Corresponding author. Mong-Liang Lu, Department of Psychiatry, Taipei Medical University-Wan Fang Hospital, No. 111, Section 3, Hsin Long Road, Taipei 116, Taiwan.
E-mail: Mong-Liang Lu <mongliang@hotmail.com>

1878-3317/$ – see front matter
doi:10.1016/j.jecm.2012.01.007

Second-generation antipsychotics (SGAs) have fewer extrapyramidal symptoms at clinically effective doses. Many SGAs are also more effective than FGAs at treating the negative, cognitive, and mood symptoms of schizophrenia, resulting in better treatment compliance and prevention of psychotic relapse.[2]

Schizophrenia and other severe mental illnesses are linked with increased mortality and decreased life expectancy.[3,4] Apart from unnatural causes of death (e.g., suicide and accidents), cardiovascular disease is the leading cause of death among these patients.[5] The increased risk of cardiovascular disease in patients with severe mental illness is due to an unhealthy lifestyle (including poor diet, smoking, and physical inactivity), delayed diagnosis, poor treatment adherence in relation to co-morbid diseases (including hypertension, hyperlipidemia, and diabetes), inherent biological risks associated with mental illness, and pharmacological treatment.[6]

It is difficult to determine whether the prevalence of these metabolic disorders is increased in these psychiatric populations independent of drug treatment, but schizophrenia was shown to be associated with diabetes and abnormal glucose metabolism before the advent of antipsychotic drugs.[7] An increased risk of diabetes or impaired glucose tolerance in the first-degree relatives of schizophrenic patients suggests a role for genetics in the relationship between schizophrenia and metabolic abnormalities.[8,9] Several studies have also shown abnormal glucose homeostasis among treatment-naive subjects with first-episode psychosis.[8,10]

Although antipsychotic drugs are the cornerstones of treatment for several psychiatric diseases, these medications are significantly associated with increased obesity and cardiovascular risk factors.[11,12] Some antipsychotic drugs, especially SGAs, have a high tendency to increase body weight as well as cardiovascular and metabolic abnormalities. In recent years, weight gain and SGA-induced metabolic changes have been extensively studied. The findings have led to an increased interest among psychiatrists and internists in the relationships between schizophrenia, antipsychotic drugs, metabolic abnormalities, and cardiovascular disease. This review is intended to focus on the metabolic and cardiovascular adverse effects associated with antipsychotic medications.

2. Metabolic and cardiovascular risks

2.1. Weight gain

Several,[6,13] but not all of,[14,15] studies have shown that patients with drug-naive schizophrenia have an increased risk of overweight. Several studies have reported the rates of obesity (body mass index [BMI] $\geq$ 30 kg/m^2) in schizophrenic patients to be 42–60%.[16,17] In addition, weight gain is a well-established adverse effect of antipsychotic medication in schizophrenic patients, affecting 15–72% of individuals.[6]

Various antipsychotic drugs are associated with different potentials for weight gain. The low-potency FGAs, such as chlorpromazine and thioridazine, are associated with a higher potential for weight gain than are the high-potency FGAs, such as haloperidol and fluphenazine.[18] SGAs carry different risks of causing weight gain and metabolic dysregulation: clozapine and olanzapine have the highest risk; quetiapine and risperidone a moderate risk; and aripiprazole, amisulpride, and ziprasidone the lowest risks.[18–20] Of note, the greatest amount of weight gain associated with antipsychotic medication in drug-naive schizophrenic patients occurs in the first few months of medication use.

Several predictors of antipsychotic-related weight gain have been identified. Factors related to antipsychotic-induced weight gain include demographic variables (e.g., age and gender), disease characteristics, past and current medications (antipsychotic drugs and other medications), the dose and treatment duration of antipsychotic drugs, and the treatment response, as well as diet and activity levels.[21]

2.2. Metabolic abnormalities

Metabolic syndrome and its major components, including central obesity, glucose intolerance, dyslipidemia, and hypertension, are highly prevalent in schizophrenic patients. The prevalence of metabolic syndrome in schizophrenic patients in Taiwan is 34.9%, with figures of 38.9% for female and 31.5% for male patients.[22] The metabolic syndrome can carry an increased risk of type 2 diabetes mellitus and mortality from cardiovascular disease.[23] Individual antipsychotic drugs differ significantly in their effects on metabolic risk factors.[24] As stated previously, the order of developing metabolic risk is clozapine and olanzapine, then quetiapine and risperidone, followed by aripiprazole, amisulpride and ziprasidone.[25]

3. Mechanisms

Weight gain and changes in glucose and lipid metabolism from antipsychotic drugs are thought to be co-occurring phenomena rather than the results of a single pathophysiology. Metabolic changes in serum glucose and lipid associated with antipsychotic agents occur even before the onset of weight gain, and are probably independent of the amount of weight gain.[26,27]

The proposed mechanisms underlying antipsychotic-induced weight gain include a blockade of central 5-HT$_{2C}$ and histamine H$_1$ receptors.[28,29] Increasing 5-HT transmission in the central nervous system (CNS) can lower food intake and feeding behavior. Antagonism of CNS 5-HT$_{2C}$ receptors by antipsychotic drugs can increase food intake, resulting in weight gain.[30] Consistent evidence supports the role of CNS histamine in food intake and energy metabolism. Antagonism of CNS H$_1$ receptors can have the same orexigenic actions in antipsychotic drugs, leading to increased appetite; this effect can be reversed by the anorexigenic action of leptin.[31]

The affinity of antipsychotic drugs for muscarinic M$_3$, 5-HT$_{1A}$, dopamine D$_2$, and adrenergic receptors may also be related to these metabolic side effects. In addition, antipsychotic drugs may alter glucose homeostasis by increasing peripheral insulin resistance and decreasing insulin secretion.[26,32] Several studies have identified the role of genetic polymorphisms (e.g., in 5-HT$_{2C}$, H$_1$, leptin, and dopamine D$_2$ receptors) in weight gain and metabolic dysregulations related to antipsychotic drugs.[33,34]

Few studies have assessed the characteristics of individual patients that may predispose to antipsychotic-induced weight gain. Possible risk factors include younger age (children and adolescents being at great risk), female gender, first-time use of antipsychotic medication, longer duration of antipsychotic treatment, good clinical response, high parental BMI, and high BMI before the first antipsychotic treatment.[35] Lan et al.[36] applied neuro-fuzzy modeling to physical factors (weight, height as well as waist and hip circumferences), psychiatric factors (severity of psychopathology), lifestyle factors (tobacco use, dietary patterns, and exercise levels), and genetic factors to predict the weight changes of chronic schizophrenic patients receiving antipsychotic drugs. These findings may help to identify patients who are prone to developing metabolic adverse effects.

4. Recommendations for metabolic monitoring

Despite a warning on the diabetic risk of antipsychotic agents that was issued by the US Food and Drug Administration and the consensus statement from the American Diabetes Association,

American Psychiatric Association, and other societies on antipsychotic-induced obesity and diabetes, published in 2004,[18,37] studies have shown that the rate of metabolic screening tests for patients receiving antipsychotics remains low.[38,39] The European Psychiatric Association also published recommendations on the monitoring and management of cardiovascular and diabetic risk factors in psychiatric patients in 2009.[40]

The assessment of metabolic risk factors associated with antipsychotic medications should include the personal and family history of obesity, diabetes, dyslipidemia, hypertension, and cardiovascular disease, smoking behavior, dietary status, and physical activity levels. The individual components of the metabolic syndrome should be assessed at baseline and then monitored at regular intervals. The frequency of monitoring will depend on the patient's medical history and the status of the baseline risk factors.

In clinical practice, time pressures, availability of equipment, and patients' cooperation limit psychiatrists in evaluating metabolic side effects in antipsychotic-medicated patients. Lin et al.[41] used an artificial neural network to develop an easy method of identifying metabolic syndrome in patients receiving SGAs. They found that metabolic syndrome could be identified by three noninvasive clinical variables: waist circumference, diastolic blood pressure, and BMI.

5. Management of metabolic and cardiovascular adverse effects

Strategies to decrease adverse metabolic and cardiovascular effects induced by antipsychotics include adopting a better, more healthy lifestyle, adding medications that can reverse metabolic abnormalities, and switching to another antipsychotic medication with a relatively lower metabolic risk.[42]

Many antipsychotic-treated patients are unaware of the need to alter an unhealthy lifestyle, or are unable to make the necessary lifestyle changes. The psychiatric multidisciplinary care team should educate these patients and their caregivers about healthy lifestyles. Strategies of behavioral intervention can motivate patients to make the necessary changes, including smoking cessation, the adoption of a healthy diet, and regular exercise.[43] Studies have shown that nonpharmacological interventions for weight management are cost-efficient and beneficial, and therefore should be a priority, particularly during the early stages of antipsychotic treatment.[44,45]

If behavioral interventions fail, additional drug treatment might be indicated. Drug therapies that have been found to have efficacy in lessening weight gain and metabolic changes from antipsychotic medication include metformin,[46–48] topiramate,[49,50] and amantadine.[51,52]

5.1. Metformin

Among these agents, metformin is probably the most promising drug for attenuating antipsychotic-induced metabolic disturbances.[53] Metformin is an oral antihyperglycemic agent used to treat noninsulin-dependent diabetes mellitus. It reduces blood glucose levels, predominantly by improving insulin sensitivity in the hepatic and peripheral tissues without affecting the secretion of insulin.[54] A prospective study showed that metformin can reverse the weight gain and metabolic disturbance induced by olanzapine treatment.[46] The result of a recent meta-analysis has also shown that metformin can manage antipsychotic-associated metabolic dysregulation.[55]

In addition, Wu et al.[56] conducted a randomized controlled study to compare metformin, lifestyle intervention, lifestyle intervention with metformin, and placebo in 128 first-episode psychotic patients who were receiving antipsychotic medication. At the end of the 12-week study, lifestyle intervention, metformin, and the two in combination showed efficacy against antipsychotic-induced weight gain and metabolic dysregulation. The combination of lifestyle intervention and metformin showed the best effect in terms of weight loss. Metformin treatment is more effective for weight loss and for improving insulin sensitivity than is lifestyle intervention.[56]

5.2. Topiramate

Topiramate, a second-generation anticonvulsant with a mixed GABAergic and antiglutamatergic action, is used to treat epilepsy and migraine. In psychiatric practice, topiramate is used off-label to counteract the weight gain associated with psychotropic drugs. The results of recent double-blind, placebo-controlled trials have shown that topiramate can prevent antipsychotic-induced adverse metabolic effects.[49,50]

5.3. Amantadine

Amantadine, a weak antagonist of the NMDA-type glutamate receptor, can increase dopamine release and block dopamine reuptake to reduce the symptoms of Parkinson's disease and drug-induced extrapyramidal symptoms. Recent double-blind, placebo-controlled studies have shown that amantadine can attenuate weight gain or promote weight loss in antipsychotic-treated patients and has no influence on psychopathology.[51,52]

Augmentation with another antipsychotic with a favorable metabolic profile[57,58] or with an antidepressant[59,60] has also been reported to be an alternative strategy to improve antipsychotic-induced metabolic dysregulation. However, care should be taken in relation to the pharmacokinetic and pharmacodynamic interactions between these two agents.[61,62]

Switching to an antipsychotic drug with a more favorable metabolic profile, particularly aripiprazole, amisulpride, or ziprasidone, can be an effective intervention, especially in patients whose weight gain and metabolic abnormalities are attributable to their current antipsychotic treatment.[63–65] Because antipsychotic switching is not always successful, clinicians should monitor patients carefully to avoid any worsening of their schizophrenia.

If metabolic or cardiovascular disease is diagnosed, the patient should be referred to a specialist to receive appropriate care. Pharmacological treatments, including antidiabetic drugs, antihypertensive agents, or lipid-lowering medications, might be indicated.

6. Conclusion

Many studies have confirmed the potential of antipsychotic drugs to induce or trigger metabolic dysregulation. The tendencies to induce weight gain and metabolic abnormalities differ markedly between different antipsychotic agents. In general, SGAs are more greatly associated with an increased risk of those adverse effects than are FGAs.

Despite an increased understanding of the biochemical effects of antipsychotic drugs, the pharmacological mechanisms underlying their association with metabolic abnormalities remain unclear. The affinities of antipsychotic drugs for H_1, 5-HT_{2C}, M_3, 5-HT_{1A}, D_2, and adrenergic receptors might be implicated in causing metabolic abnormalities.

Despite existing guidelines and recommendations, baseline and follow-up assessments of metabolic and cardiovascular abnormalities in patients treated with antipsychotic drugs are inadequate. In addition, psychiatrists and multidisciplinary care team members should educate and motivate patients to promote their healthy

lifestyle through behavioral intervention. If lifestyle interventions do not succeed, additional pharmacological treatment might be indicated. Adding another pharmacological treatment or switching to an antipsychotic drug with a more favorable metabolic profile can be an effective intervention option.

Acknowledgments

The authors are grateful for the support of the research grants from the Taipei Medical University-Wan Fang Medical Center (101-wf-eva-13) and the National Science Council, Taiwan (99-2314-B-038-020-MY3). They also report no conflict of interest with relation to any of the medications mentioned in this article. Winston W. Shen reviewed the content of the article and found no conflict of interest.

References

1. Shen WW. A history of antipsychotic drug development. *Compr Psychiatry* 1999;**40**:407–14.
2. Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet* 2009;**373**:31–41.
3. Chen YH, Lee HC, Lin HC. Mortality among psychiatric patients in Taiwan – results from a universal National Health Insurance programme. *Psychiatry Res* 2010;**178**:160–5.
4. Chang CK, Hayes RD, Broadbent M, Fernandes AC, Lee W, Hotopf M, Stewart R. All-cause mortality among people with serious mental illness (SMI), substance use disorders, and depressive disorders in southeast London: a cohort study. *BMC Psychiatry* 2010;**10**:77.
5. Brown S. Excess mortality of schizophrenia. A meta-analysis. *Br J Psychiatry* 1997;**171**:502–8.
6. De Hert M, Correll CU, Bobes J, Cetkovich-Bakmas M, Cohen D, Asai I, Detraux J, et al. Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. *World Psychiatry* 2011;**10**: 52–77.
7. Kohen D. Diabetes mellitus and schizophrenia: historical perspective. *Br J Psychiatry Suppl* 2004;**47**:S64–6.
8. Spelman LM, Walsh PI, Sharifi N, Collins P, Thakore JH. Impaired glucose tolerance in first-episode drug-naive patients with schizophrenia. *Diabet Med* 2007;**24**:481–5.
9. Fernandez-Egea E, Bernardo M, Parellada E, Justicia A, Garcia-Rizo C, Esmatjes E, Conget I, et al. Glucose abnormalities in the siblings of people with schizophrenia. *Schizophr Res* 2008;**103**:110–3.
10. Ryan MC, Collins P, Thakore JH. Impaired fasting glucose tolerance in first-episode, drug-naive patients with schizophrenia. *Am J Psychiatry* 2003; **160**:284–9.
11. Casey DE, Haupt DW, Newcomer JW, Henderson DC, Sernyak MJ, Davidson M, Lindenmayer JP, et al. Antipsychotic-induced weight gain and metabolic abnormalities: implications for increased mortality in patients with schizophrenia. *J Clin Psychiatry* 2004;**65**(Suppl. 7):4–18. quiz 19–20.
12. De Hert M, Detraux J, van Winkel R, Yu W, Correll CU. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. *Nat Rev Endocrinol* 2011;**8**:114–26.
13. Thakore JH, Mann JN, Vlahos I, Martin A, Reznek R. Increased visceral fat distribution in drug-naive and drug-free patients with schizophrenia. *Int J Obes Relat Metab Disord* 2002;**26**:137–41.
14. Foley DL, Morley KI. Systematic review of early cardiometabolic outcomes of the first treated episode of psychosis. *Arch Gen Psychiatry* 2011;**68**:609–16.
15. Dasgupta A, Singh OP, Rout JK, Saha T, Mandal S. Insulin resistance and metabolic profile in antipsychotic naive schizophrenia patients. *Prog Neuropsychopharmacol Biol Psychiatry* 2010;**34**:1202–7.
16. Coodin S. Body mass index in persons with schizophrenia. *Can J Psychiatry* 2001;**46**:549–55.
17. Strassnig M, Brar JS, Ganguli R. Body mass index and quality of life in community-dwelling patients with schizophrenia. *Schizophr Res* 2003;**62**: 73–6.
18. 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. *J Clin Psychiatry* 2004;**65**:267–72.
19. Allison DB, Mentore JL, Heo M, Chandler LP, Cappelleri JC, Infante MC, Weiden PJ. Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry* 1999;**156**:1686–96.
20. Rummel-Kluge C, Komossa K, Schwarz S, Hunger H, Schmid F, Lobos CA, Kissling W, et al. Head-to-head comparisons of metabolic side effects of second generation antipsychotics in the treatment of schizophrenia: a systematic review and meta-analysis. *Schizophr Res* 2010;**123**:225–33.
21. Correll CU, Lencz T, Malhotra AK. Antipsychotic drugs and obesity. *Trends Mol Med* 2011;**17**:97–107.
22. Huang MC, Lu ML, Tsai CJ, Chen PY, Chiu CC, Jian DL, Lin KM, et al. Prevalence of metabolic syndrome among patients with schizophrenia or schizoaffective disorder in Taiwan. *Acta Psychiatr Scand* 2009;**120**:274–80.
23. Mottillo S, Filion KB, Genest J, Joseph L, Pilote L, Poirier P, Rinfret S, et al. The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. *J Am Coll Cardiol* 2010;**56**:1113–32.
24. Newcomer JW. Antipsychotic medications: metabolic and cardiovascular risk. *J Clin Psychiatry* 2007;**68**(Suppl. 4):8–13.
25. Pramyothin P, Khaodhiar L. Metabolic syndrome with the atypical antipsychotics. *Curr Opin Endocrinol Diabetes Obes* 2010;**17**:460–6.
26. Chiu CC, Chen KP, Liu HC, Lu ML. The early effect of olanzapine and risperidone on insulin secretion in atypical-naive schizophrenic patients. *J Clin Psychopharmacol* 2006;**26**:504–7.
27. Lean ME, Pajonk FG. Patients on atypical antipsychotic drugs: another high-risk group for type 2 diabetes. *Diabetes Care* 2003;**26**:1597–605.
28. Roerig JL, Steffen KJ, Mitchell JE. Atypical antipsychotic-induced weight gain: insights into mechanisms of action. *CNS Drugs* 2011;**25**:1035–59.
29. Stahl SM, Mignon L, Meyer JM. Which comes first: atypical antipsychotic treatment or cardiometabolic risk? *Acta Psychiatr Scand* 2009;**119**:171–9.
30. Reynolds GP, Hill MJ, Kirk SL. The 5-HT2C receptor and antipsychotic-induced weight gain – mechanisms and genetics. *J Psychopharmacol* 2006;**20**:15–8.
31. Kim SF, Huang AS, Snowman AM, Teuscher C, Snyder SH. From the Cover: antipsychotic drug-induced weight gain mediated by histamine H1 receptor-linked activation of hypothalamic AMP-kinase. *Proc Natl Acad Sci U S A* 2007;**104**:3456–9.
32. Chiu CC, Chen CH, Chen BY, Yu SH, Lu ML. The time-dependent change of insulin secretion in schizophrenic patients treated with olanzapine. *Prog Neuropsychopharmacol Biol Psychiatry* 2010;**34**:866–70.
33. Correll CU, Malhotra AK. Pharmacogenetics of antipsychotic-induced weight gain. *Psychopharmacology (Berl)* 2004;**174**:477–89.
34. Kuo PH, Kao CF, Chen PY, Chen CH, Tsai YS, Lu ML, Huang MC. Polymorphisms of INSIG2, MC4R, and LEP are associated with obesity- and metabolic-related traits in schizophrenic patients. *J Clin Psychopharmacol* 2011;**31**:705–11.
35. Gebhardt S, Haberhausen M, Heinzel-Gutenbrunner M, Gebhardt N, Remschmidt H, Krieg JC, Hebebrand J, et al. Antipsychotic-induced body weight gain: predictors and a systematic categorization of the long-term weight course. *J Psychiatr Res* 2009;**43**:620–6.
36. Lan TH, Loh EW, Wu MS, Hu TM, Chou P, Lan TY, Chiu HJ. Performance of a neuro-fuzzy model in predicting weight changes of chronic schizophrenic patients exposed to antipsychotics. *Mol Psychiatry* 2008;**13**:1129–37.
37. 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**:596–601.
38. 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**:1037–42.
39. Morrato EH, Druss B, Hartung DM, Valuck RJ, Allen R, Campagna E, Newcomer JW. Metabolic testing rates in 3 state Medicaid programs after FDA warnings and ADA/APA recommendations for second-generation antipsychotic drugs. *Arch Gen Psychiatry* 2010;**67**:17–24.
40. De Hert M, Dekker JM, Wood D, Kahl KG, Holt RI, Moller HJ. Cardiovascular disease and diabetes in people with severe mental illness position statement from the European Psychiatric Association (EPA), supported by the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC). *Eur Psychiatry* 2009;**24**:412–24.
41. Lin CC, Bai YM, Chen JY, Hwang TJ, Chen TT, Chiu HW, Li YC. Easy and low-cost identification of metabolic syndrome in patients treated with second-generation antipsychotics: artificial neural network and logistic regression models. *J Clin Psychiatry* 2010;**71**:225–34.
42. Maayan L, Vakhrusheva J, Correll CU. Effectiveness of medications used to attenuate antipsychotic-related weight gain and metabolic abnormalities: a systematic review and meta-analysis. *Neuropsychopharmacology* 2010;**35**: 1520–30.
43. Alvarez-Jimenez M, Hetrick SE, Gonzalez-Blanch C, Gleeson JF, McGorry PD. Non-pharmacological management of antipsychotic-induced weight gain: systematic review and meta-analysis of randomised controlled trials. *Br J Psychiatry* 2008;**193**:101–7.
44. Chen CK, Chen YC, Huang YS. Effects of a 10-week weight control program on obese patients with schizophrenia or schizoaffective disorder: a 12-month follow up. *Psychiatry Clin Neurosci* 2009;**63**:17–22.
45. Menza M, Vreeland B, Minsky S, Gara M, Radler DR, Sakowitz M. Managing atypical antipsychotic-associated weight gain: 12-month data on a multimodal weight control program. *J Clin Psychiatry* 2004;**65**:471–7.
46. 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.
47. Wu RR, Zhao JP, Guo XF, He YQ, Fang MS, Guo WB, Chen JD, 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.
48. Baptista T, Martinez J, Lacruz A, Rangel N, Beaulieu S, Serrano A, Arape Y, 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.

49. Narula PK, Rehan HS, Unni KE, Gupta N. Topiramate for prevention of olanzapine associated weight gain and metabolic dysfunction in schizophrenia: a double-blind, placebo-controlled trial. *Schizophr Res* 2010;**118**: 218–23.
50. Afshar H, Roohafza H, Mousavi G, Golchin S, Toghianifar N, Sadeghi M, Talaei M. Topiramate add-on treatment in schizophrenia: a randomised, double-blind, placebo-controlled clinical trial. *J Psychopharmacol* 2009;**23**:157–62.
51. Deberdt W, Winokur A, Cavazzoni PA, Trzaskoma QN, Carlson CD, Bymaster FP, Wiener K, et al. Amantadine for weight gain associated with olanzapine treatment. *Eur Neuropsychopharmacol* 2005;**15**:13–21.
52. 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.
53. Hasnain M, Vieweg WV, Fredrickson SK. Metformin for atypical antipsychotic-induced weight gain and glucose metabolism dysregulation: review of the literature and clinical suggestions. *CNS Drugs* 2010;**24**:193–206.
54. Dunn CJ, Peters DH. Metformin. A review of its pharmacological properties and therapeutic use in non-insulin-dependent diabetes mellitus. *Drugs* 1995;**49**: 721–49.
55. Hasnain M, Fredrickson SK, Vieweg WV. Metformin for obesity and glucose dysregulation in patients with schizophrenia receiving antipsychotic drugs. *J Psychopharmacol* 2011;**25**:715–21.
56. Wu RR, Zhao JP, Jin H, Shao P, Fang MS, Guo XF, He YQ, et al. Lifestyle intervention and metformin for treatment of antipsychotic-induced weight gain: a randomized controlled trial. *JAMA* 2008;**299**:185–93.
57. Chen CH, Huang MC, Lu ML. Aripiprazole improves metabolic adversity in olanzapine-treated schizophrenic patients. *J Clin Psychopharmacol* 2007;**27**: 516–7.
58. Henderson DC, Fan X, Copeland PM, Sharma B, Borba CP, Boxill R, Freudenreich O, et al. Aripiprazole added to overweight and obese olanzapine-treated schizophrenia patients. *J Clin Psychopharmacol* 2009;**29**:165–9.
59. Lu ML, Lane HY, Lin SK, Chen KP, Chang WH. Adjunctive fluvoxamine inhibits clozapine-related weight gain and metabolic disturbances. *J Clin Psychiatry* 2004;**65**:766–71.
60. Hinze-Selch D, Deuschle M, Weber B, Heuser I, Pollmacher T. Effect of coadministration of clozapine and fluvoxamine versus clozapine monotherapy on blood cell counts, plasma levels of cytokines and body weight. *Psychopharmacology (Berl)* 2000;**149**:163–9.
61. Lu ML, Lane HY, Chen KP, Jann MW, Su MH, Chang WH. Fluvoxamine reduces the clozapine dosage needed in refractory schizophrenic patients. *J Clin Psychiatry* 2000;**61**:594–9.
62. Lu ML, Lane HY, Jann MW, Chang WH. Dosing strategies of clozapine-fluvoxamine cotreatment. *J Clin Psychopharmacol* 2002;**22**:626–8.
63. Stroup TS, McEvoy JP, Ring KD, Hamer RH, LaVange LM, Swartz MS, Rosenheck RA, et al. A randomized trial examining the effectiveness of switching from olanzapine, quetiapine, or risperidone to aripiprazole to reduce metabolic risk: comparison of antipsychotics for metabolic problems (CAMP). *Am J Psychiatry* 2011;**168**:947–56.
64. Lin CC, Bai YM, Wang YC, Chen TT, Lai IC, Chen JY, Chen SY, et al. Improved body weight and metabolic outcomes in overweight or obese psychiatric patients switched to amisulpride from other atypical antipsychotics. *J Clin Psychopharmacol* 2009;**29**:529–36.
65. Alptekin K, Hafez J, Brook S, Akkaya C, Tzebelikos E, Ucok A, El Tallawy H, et al. Efficacy and tolerability of switching to ziprasidone from olanzapine, risperidone or haloperidol: an international, multicenter study. *Int Clin Psychopharmacol* 2009;**24**:229–38.