Psychiatria Danubina, 2009; Vol. 21, No. 3, pp 361–367 *Conference paper*

PSYCHOTIC DISORDERS AND COMORBIDITY: SOMATIC ILLNESS VS. SIDE EFFECT

Oliver Kozumplik[1], Suzana Uzun[1] & Miro Jakovljević[2,3]

[1]*University Department of Psychiatry, Psychiatric Hospital Vrapče, Bolnička cesta 32, Zagreb, Croatia*
[2]*University Psychiatric Clinic Rebro, Clinical Hospital Zagreb, Kišpatićeva 12, Zagreb, Croatia*
[3]*School of Medicine, University of Zagreb, Šalata 3b, Zagreb, Croatia*

SUMMARY

Background: *Schizophrenia often co-occurs with chronic medical illnesses. Beside comorbid somatic illness, somatic symptoms appear as a result of side effects of antipsychotics during treatment of psychotic disorders, which may lead to certain diagnostic problems in deciding regarding the origin of such symptoms (somatic illness vs. side effects). The aim of this article is to review literature regarding comorbidity of psychotic disorders and somatic disorders and to point at possible diagnostic problems in differentiating comorbid somatic illness from side effects of antipsychotics.*

Content analysis of literature: *Literature research included structured searches of Medline and other publications on the subject of comorbidity of psychotic disorders and somatic disorders and possible diagnostic problems in differentiating comorbid somatic illnesses from side effects of antipsychotics.*

Conclusion: *Co-occurrence of schizophrenia and somatic illnesses is frequent. Genetic factors, sedentary life style, poor diet, risk behaviors and smoking are some important factors that contribute to such comorbidity. Side effects of antipsychotics may cause diagnostic problems in deciding regarding the origin of such symptoms (somatic illness vs. side effects) during treatment of psychotic disorders. Bearing in mind frequent comorbidity between of psychotic and somatic disorders, early recognition of such comorbidity is important, as well as the selection of antipsychotics. It is important to recognize psychotic symptoms in patients with somatic illnesses, as well as somatic illness in patients primarily treated because of psychotic disorder.*

Key words: *psychotic disorder – somatic illness – side effects - antipsychotics*

* * * * *

INTRODUCTION

Patients with schizophrenia have a higher mortality rate from accidents and natural causes than the general population. Several studies have shown that up to 80% of all patients with schizophrenia have significant concurrent medical illnesses and that up to 50% of these conditions may be undiagnosed (Sadock & Sadock 2008). Severe mental disorders such as bipolar disorder and schizophrenia often co-occur with chronic medical illnesses, especially cardiovascular disease and diabetes. These comorbidities are associated with a more severe course of mental illness, reduced quality of life, and premature mortality (Fagiolini & Goracci 2009). Schizophrenia is often associated with severe loss of functioning and shortened life expectancy. Suicides and accidents are well-known causes of the excess mortality, but patients with schizophrenia have also been reported to be three times as likely to experience sudden unexpected death as individuals from the general population (Koponen et al. 2008). Schizophrenia has been described as a "life-shortening disease", and physical comorbidity accounts for 60% of premature deaths not related to suicide. Patients with schizophrenia and other mental illnesses have a higher rate of preventable risk factors such as smoking, high alcohol consumption, poor diet, and lack of exercise (Lambert et al. 2003). According to results of a previous investigation, morbidity and mortality from general medical conditions are elevated among patients with schizophrenia compared with the general U.S. population. More than 50% of patients with schizophrenia have one or more

comorbid psychiatric or general medical conditions (Weber et al. 2009). Patients with severe mental disorders have increased mortality rates compared with the general population. The leading cause of death for individuals with psychotic illnesses or bipolar disorder is cardiovascular disease (CVD), which is often the result of patients' health problems associated with their psychiatric disorders, including, but not limited to, obesity, metabolic syndrome, and diabetes. Such problems appear more often and have worse outcomes in patients with serious mental illness than the general population because of a combination of factors such as inadequate access to quality care, poor lifestyle choices, and the association between some antipsychotic medications and weight gain (McIntyre 2009). Another problem is time of diagnosing somatic illnesses in patients with schizophrenia and other psychotic disorders. Patients with schizophrenia are at risk of undetected somatic comorbidity. They present physical complaints at a late, more serious stage (Oud & Meyboom 2009). Beside comorbid somatic illnesses, somatic symptoms appear as a result of side effects of antipsychotics during treatment of psychotic disorders, which may lead to certain diagnostic problems in deciding regarding the origin of such symptoms (somatic illness vs. side effects). In the investigation that reviewed therapeutic ways of management of antipsychotics side effects, according to modern guidelines, it was concluded that the guidelines recommend that side effects should be monitored regularly, and the side effect profile of the prescribed antipsychotic should be considered (Kozumplik & Uzun 2009). In this way, by bearing in mind side effect profile of particular antipsychotic from the very beginning of the treatment, and by monitoring the side effects regularly, clearer diagnostic distinction between somatic illness and side effects is enabled.

The aim of this article is to review literature regarding comorbidity of psychotic disorders and somatic disorders and to point at possible diagnostic problems in differentiating comorbid somatic illness from side effects of antipsychotics.

CONTENT ANALYSIS OF GUIDELINES AND LITERATURE

Literature research included structured searches of Medline and other publications on the subject of comorbidity of psychotic disorders and somatic disorders and possible diagnostic problems in differentiating comorbid somatic illnesses from side effects of antipsychotics.

Obesity and metabolic disorders

Severe mental illness and obesity are each serious public health problems that overlap to a clinically significant extent (McElroy 2009). Obesity is one of the most common physical health problems among patients with severe and persistent mental illnesses, such as schizophrenia. Multifactorial in origin, obesity can be attributed to an unhealthy lifestyle as well as the effects of psychotropic medications such as second-generation antipsychotics. Excess body weight increases the risk for many medical problems, including type 2 diabetes mellitus, coronary heart disease, osteoarthritis, hypertension, and gallbladder disease (Citrome & Vreeland 2008). Patients with schizophrenia appear to be more obese, with higher body mass indexes (BMIs) than age- and gender-matched cohorts in the general population (Sadock & Sadock 2008). Although the prevalence of obesity and other risk factors such as hyperglycemia are increasing in the general population, patients with major mental illnesses have an increased prevalence of overweight and obesity, hyperglycemia, dyslipidemia, hypertension, and smoking, and substantially greater mortality, compared with the general population (Newcomer 2007). Recent evidence indicates that schizophrenia increases predisposition towards metabolic dysfunction independent of environmental exposure (Meyer & Stahl 2009). Patients with mental illnesses such as schizophrenia and bipolar disorder have an increased prevalence of metabolic syndrome and its components, risk factors for cardiovascular disease and type 2 diabetes (Newcomer 2007). Furthermore, the importance of cholesterol for physical and psychological well-being has been recognized for several decades. Changes in serum cholesterol levels may have a direct impact on mental performance, behavior, treatment response, survival and expected lifetime duration. Hypercholesterolemia has been reported in patients with schizophrenia, obsessive-compulsive disorders, panic disorder, generalized anxiety disorder, PTSD. No definite or reliable insight into a pathophysiological link between cholesterol levels and mental disorders, treatment response and mortality rate is available. The lipoprotein profile, rather than total cholesterol

levels, seems to be important (Jakovljević et al. 2007a). In part, the cardio-metabolic risk factors in patients with schizophrenia are attributable to unhealthy lifestyle, including poor diet and sedentary behavior (de Hert et al. 2009). Factors affecting management of weight gain are negative symptoms, cognitive impairment, low income level, preference of highcalorie food, impaired satiety, level of sedation and reduced ability to handle daily hassles (e.g., shopping and cooking) (Sharpe & Hills 2003).

Although lifestyle and genetics may contribute independent risks of cardiometabolic dysfunction in schizophrenia and other serious mental illness, antipsychotic treatment also represents an important contributor to risk of cardiometabolic dysfunction, particularly for certain drugs and for vulnerable patients (Stahl et al. 2009). In general, the rank order of risk observed for the second-generation antipsychotic medications suggests that the differing weight gain liability of atypical agents contributes to the differing relative risk of insulin resistance, dyslipidaemia and hyperglycaemia. From this perspective, a possible increase in risk would be predicted to appear in association with any treatment that produces increases in weight and adiposity. However, case reports tentatively suggest that substantial weight gain or obesity may not be a factor in up to one-quarter of cases of new-onset diabetes that appear during treatment (Newcomer 2005). Weight gain is associated with the use of many psychotropic medications, including antidepressants, mood stabilizers, antipsychotics, and may have serious long term consequences: it can increase health risks, specifically from overweight (BMI=25-29.9 kg/m2) to obesity (BMI> or =30 kg/m2), according to BMI, and the morbidity associated therewith in a substantial part of patients (hypertension, coronary heart disease, ischemic stroke, impaired glucose tolerance, diabetes mellitus, dyslipidemia, respiratory problems, osteoarthritis, cancer) (Ruetsch et al. 2005). Up to 40% of patients treated with first generation antipsychotics gain weight, with the greatest risk associated with the low-potency antipsychotics (Kane & Lieberman 1992). Antipsychotics, typical or atypical, are known to induce in patients with schizophrenia weight gain and abnormalities in glucose and lipid metabolisms. These modifications, in addition to metabolic risk factors, intrinsic to the psychiatric illness (physical inactivity, smoking, diabetes), increase the risk of cardiovascular complications (Chabroux et al. 2009). In the study that examined the main metabolic side effects induced by antipsychotic treatment in a cohort of first-episode drug-naive subjects, drug-naive patients experienced an extraordinary weight gain with first- and second-generation antipsychotics after the first 12 weeks of treatment. It was concluded that weight gain and metabolic disturbances induced by antipsychotics may increase the risk of developing cardiovascular disease (Perez-Iglesias et al. 2007). Metabolic syndrome can contribute to significant morbidity and premature mortality and should be accounted for in the treatment of mental disorders (Jakovljević et al. 2007b). Some antipsychotics are associated with a higher risk of metabolic disorders. Before starting such a medication, all risk factors must be taken into account. In case of even effectiveness, one should consider the risk of inducing metabolic disorders, as well as the intrinsic risk factors of the patient, in order to prescribe the medication associated with the lower metabolic risk (Chabroux et al. 2009). First-line medication choices for patients with severe mental illness and obesity should be effective for treating the mental disorder, safe, well-tolerated, and, if possible, weight-neutral or associated with weight loss. If drugs with weight-inducing effects must be used, emerging data indicate that behavioral weight management, if not already in place, should be implemented and that adjunctive pharmacotherapeutic strategies should be considered. Severe mental illness with obesity must be viewed as 2 chronic illnesses that each require long-term management (McElroy 2009).

Diabetes

Patients with schizophrenia are at increased risk of developing diabetes mellitus (Blonde et al. 2008). An increased prevalence of type 2 diabetes in schizophrenia patients has been observed (Irvin et al. 2009). There is evidence that schizophrenia itself is an independent risk factor for impaired glucose tolerance, which is a known risk factor for developing type 2 diabetes, regardless of whether patients receive antipsychotic medication (Ryan et al. 2003; Bushe & Holt 2004). The analysis of the scientific literature indicates that an increase of diabetes prevalence in schizophrenic populations was already described before the introduction of neuroleptics. Then, after the introduction of the first neuroleptics in the 1950s, an increase of diabetes prevalence was reported among treated patients and the same alarms appeared in the 1990s

after the introduction of second-generation antipsychotics (Gury 2004). The association of schizophrenia with an increased risk of type 2 diabetes mellitus, probably due, in part, to association with obesity (Sadock & Sadock 2008). Furthermore, exposure to antipsychotics has been shown to induce metabolic dysregulation in some patients but not all treated patients (Irvin et al. 2009). Recent epidemiological studies have confirmed the increase prevalence of diabetes in patients with schizophrenia, particularly in patients with schizophrenia before any antipsychotic treatment. Among the suggested mechanisms, there are sedentary life (due to hospitalisation and sedative effects of neuroleptics), food imbalance, as well as shared genetic factors for diabetes and schizophrenia (Gury 2004).

Cardiovascular comorbidity

Patients with schizophrenia are at increased risk of developing cardiovascular disease (Blonde et al. 2008), and have increased rates of morbidity and mortality compared with the general population, primarily due to cardiovascular disease (Van Gaal 2006). Many antipsychotic medications have direct effects on cardiac electrophysiology. In addition, obesity, increased rates of smoking, diabetes, hyperlipidemia, and a sedentary lifestyle all independently increase the risk of cardiovascular morbidity and mortality (Sadock & Sadock 2008). Though increased risk of sudden death in patients with schizophrenia is well-documented, the mechanisms remain unclear (Jindal et al. 2009). Patients with schizophrenia have been reported to experience sudden cardiac death 3 times more likely than individuals from the general population. One important factor related to an increased risk of cardiac arrhythmias and sudden death is the prolongation of the QTc interval (Bär et al. 2007). According to the results of the study that examined whether acute psychosis might influence the beat-to-beat variability of the QT interval, which reflects effectively cardiac repolarization lability (electrocardiographic (ECG) recordings were performed in unmedicated patients with acute schizophrenia and matched controls), increased QT variability in patients with schizophrenia indicates abnormal cardiac repolarization lability, which can result in serious cardiac arrhythmias. The correlation of positive symptoms with QT variability might indicate high sympathetic cardiac activity in these patients, which might be associated with increased cardiovascular mortality (Bär et al. 2007). Autonomic dysfunction seen as low heart rate variability and decreased baroreflex sensitivity may also contribute via malignant arrhythmias. Due to the complex interaction of various risk factors for sudden death, the patients need a comprehensive follow-up of their physical health (Koponen et al. 2008). The duration of QTc interval is the major determinant of the risk of drug-induced torsades. Congenital long QT syndrome, female gender, hypokalemia and use of sympathomimetics increase the risk of torsades, and potentiate the QT prolonging effects of drugs (Cubeddu LX, 2003). Prolongation of the QT interval can lead to torsades de pointes, arrhythmia, syncope, ventricular fibrillation, and sudden death. Risk seems to be greater with QTc values over 500 ms (Hennessy et al. 2002). A number of antipsychotic and antidepressant drugs are known to increase the risk of ventricular arrhythmias and sudden cardiac death. Based largely on a concern over QT prolongation and the development of life-threatening arrhythmias, a number of antipsychotic drugs have been temporarily or permanently withdrawn from the market or their use restricted (Sidouri & Antzelevitch 2008).

Neurological comorbidity

Psychosis may be seen with movement disorders - Parkinson's disease, dementia with Lewy bodies and Huntington's disease (Chou et al. 2007). Parkinson's disease (PD) is a neurodegenerative disorder causing not only motor dysfunction but also cognitive, psychiatric, autonomic and sensory disturbances. Symptoms of dementia and psychosis are common: longitudinal studies suggest that up to 75% of patients with PD may eventually develop dementia, and the prevalence of hallucinations ranges from 16-17% in population-based surveys to 30-40% in hospital-based series (Wiliams-Gray et al. 2006). Indeed, in PD about 30-40% of the patients suffer fluctuating psychotic symptoms, mainly paranoid delusions and/or visual or acoustic hallucinations, symptoms considered to represent major contributors to patient and caregiver distress and nursing home placement (Wolters 2006). Psychotic symptoms in PD have consistently been shown to be associated with poor outcome. PD psychosis has unique clinical features, namely that it arises within a context of a clear sensorium and retained insight, there is relative prominence of visual hallucinations and

progression appears over time. PD psychosis tends to emerge later in the disease course, and disease duration represents one risk factor for its development. The use of anti-PD medications (particularly dopamine receptor agonists) has been the most widely identified risk factor for PD psychosis (Zahodne & Fernandez 2008). Psychotic symptoms may appear in Huntington's disease, also. Psychotic symptoms are more common in patients with Huntington's disease than in the general population. Previous investigation showed that patients with Huntington's disease and psychotic symptoms may have a familial predisposition to develop psychosis (Tsuang et al. 2000). In Huntington's disease psychiatric manifestations vary and may precede motor and cognitive changes. Paranoid schizophrenia-like symptoms appear in 6% to 25% of cases (Corrêa et al. 2006). Spontaneous movement disorders (SMDs), such as spontaneous dyskinesia and parkinsonism have been described in patients with schizophrenia who have never been treated with antipsychotic medication. Results of investigation that reviewed studies investigating spontaneous abnormal movements elicited on clinical examination in antipsychotic-naive patients with first-episode psychosis supported the notion that spontaneous abnormal movements are part of a neurodysfunction intrinsic to the pathogenesis of schizophrenia (Pappa & Dazzan 2009).

Extrapyramidal symptoms (EPS) as side effects of therapy with antipsychotics are well known side effects emerging as a result of blockade in dopaminergic transmission in nigrostriatal pathway. Results of previous investigations suggested higher incidence of EPS in typical antipsychotics, and modern algorithms agree that atypical antipsychotics (except clozapine) should be first line of treatment during first episode of schizophrenia, because of better tolerability and lower risk for extrapyramidal symptoms (EPS), especially tardive dyskinesia (American Psychiatric Association (APA) 2004; National Institute for Clinical Excellence (NICE) 2002; Royal Australian and New Zealand College of Psychiatrists (RANZCP) 2005) compared to typical antipsychotics. Although modern algorithms point out the advantages of atypical over typical antipsychotics there are other questions seeking to be answered, for instance what atypical antipsychotic to choose for first-episode and multi-episode patients. Diagnostic problems may arise regarding bradykinesia, akinesia or akathisia in patients with schizophrenia treated with antipsychotics. Bradykinesia and akinesia, common in Parkinson's syndrome may be misdiagnosed as part of negative symptoms of schizophrenia. Akathisia in PD and iron deficiency anemia are very similar to akathisia that appears as a side effect of antipsychotics (Uzun et al. 2005).

Other somatic comorbidity

Beside that above described comorbidity between psychosis and somatic illnesses, other comorbid somatic illnesses have been observed in patients with psychotic disorders, also. The results of the study that determined types of comorbid disorders and their prevalence among hospitalized patients with and without schizophrenia (data from the National Hospital Discharge Survey, a nationally representative sample, were analyzed for 1979-2003; the conditions of those with a primary diagnosis of schizophrenia were compared with those with other primary diagnoses) showed that discharge records with a primary diagnosis of schizophrenia showed higher proportions of all comorbid psychiatric conditions examined and of some general medical conditions, including acquired hypothyroidism, contact dermatitis and other eczema, obesity, epilepsy, viral hepatitis, diabetes type II, essential hypertension, and various chronic obstructive pulmonary diseases (Weber et al. 2009). Rates of chronic obstructive pulmonary disease are reportedly increased in patients with schizophrenia compared to the general population. The increased prevalence of smoking is an obvious contributor to this problem and may be the only cause (Sadock & Sadock 2008). Furthermore, patients with schizophrenia appear to have a risk of HIV infection that is 1.5 to 2 times that of the general population. This association is thought to be due to increased risk behaviors, such as unprotected sex, multiple partners, and increased drug use (Sadock & Sadock 2008). Psychiatric and psychological factors play an important role in at least 30% of dermatologic disorders. In many cases the impact of the skin disorder upon the quality of life is a stronger predictor of psychiatric morbidity than the clinical severity of the disorder as per physician ratings. Furthermore, in certain disorders such as acne and psoriasis, the psychiatric comorbidity, which can be associated with psychiatric emergencies such as suicide, is an important measure of the overall disability experienced by the patient (Gupta &

Gupta 2003). En example of co-occurrence between dermatological and psychotic symptoms is neuroborreliosis, a tick-borne infection of the nervous system manifests with various dermatological, cardiac, articular, and neurologic manifestations, but psychiatric disorders such as depression, panic attacks, and schizophrenia-like psychosis can also arise (Bär et al. 2005).

CONCLUSION

Co-occurrence of schizophrenia and somatic illnesses is frequent. Genetic factors, sedentary life style, poor diet, risk behaviors and smoking are some important factors that contribute to such comorbidity. Side effects of antipsychotics may cause diagnostic problems in deciding regarding the origin of such symptoms (somatic illness vs. side effects) during treatment of psychotic disorders. Bearing in mind frequent comorbidity between of psychotic and somatic disorders, early recognition of such comorbidity is important, as well as the selection of antipsychotics. It is important to recognize psychotic symptoms in patients with somatic illnesses, as well as somatic illness in patients primarily treated because of psychotic disorder.

REFERENCES

1. *American Psychiatric Association: Practice guideline for the treatment of patients with schizophrenia. 2nd ed. Am J Psychiatry 2004; 161:1-114.*
2. *Bär KJ, Jochum T, Häger F, Meissner W & Sauer H: Painful hallucinations and somatic delusions in a patient with the possible diagnosis of neuroborreliosis. Clin J Pain 2005; 21:362-3.*
3. *Bär KJ, Koschke M, Boettger MK, Berger S, Kabisch A, Sauer H, Voss A & Yeragani VK: Acute psychosis leads to increased QT variability in patients suffering from schizophrenia. Schizophr Res 2007; 95:115-23.*
4. *Blonde L, Kan HJ, Gutterman EM, L'Italien GJ, Kim MS, Hanssens L & McQuade RD: Predicted risk of diabetes and coronary heart disease in patients with schizophrenia: aripiprazole versus standard of care. J Clin Psychiatry 2008; 69:741-8.*
5. *Bushe C & Holt R: Prevalence of diabetes and impaired glucose tolerance in patients with schizophrenia. Br J Psychiatry 2004; 184:S67-71.*
6. *Chabroux S, Haffen E & Penfornis A: (Diabetes and second-generation (atypical) antipsychotics.) Ann Endocrinol (Paris). 2009 Aug 21. (Epub ahead of print)*
7. *Chou KL, Borek LL & Friedman JH: The management of psychosis in movement disorder patients. Expert Opin Pharmacother 2007; 8:935-43.*
8. *Citrome L & Vreeland B: Schizophrenia, obesity, and antipsychotic medications: what can we do? Postgrad Med 2008; 120:18-33.*
9. *Corrêa BB, Xavier M & Guimarães J: Association of Huntington's disease and schizophrenia-like psychosis in a Huntington's disease pedigree. Clin Pract Epidemol Ment Health 2006; 2:1.*
10. *Cubeddu LX: QT prolongation and fatal arrhythmias: a review of clinical implications and effects of drugs. Am J Ther 2003; 10:452-7.*
11. *de Hert M, Schreurs V, Nancampfort D & van Winkel R: Metabolic syndrome in people with schizophrenia: a review. World Psychiatry 2009; 8:15-22.*
12. *Fagiolini A & Goracci A: The effects of undertreated chronic medical illnesses in patients with severe mental disorders. J Clin Psychiatry 2009; 70:22-9.*
13. *Gupta MA & Gupta AK: Psychiatric and psychological co-morbidity in patients with dermatologic disorders: epidemiology and management. Am J Clin Dermatol 2003; 4:833-42.*
14. *Gury C. [Schizophrenia, diabetes mellitus and antipsychotics]. Encephale 2004; 30:382-91.*
15. *Hennessy S, Bilker WB, Knauss JS, Margolis DJ, Kimmel SE, Reynolds RF, Glasser DB, Morrison MF & Strom BL: Cardiac arrest and ventricular arrhythmia in patients taking antipsychotic drugs: cohort study using administrative data. BMJ 2002; 325:1070.*
16. *Irvin MR, Weiner HW, Perry RP, Savage RM & Go RC: Genetic risk factors for type 2 diabetes with pharmacologic intervention in African-American patients with schizophrenia or schizoaffective disorder. Schizophr Res 2009 Jul 28. [Epub ahead of print]*
17. *Jakovljević M, Crncevic Z, Ljubičić Đ, Babić D, Topić R & Šarić M: Mental disorders and metabolic syndrome: a fatamorgana or warning reality? Psychiatr Danub 2007; 19:76-86.*
18. *Jakovljević M, Reiner Z & Miličić D: Mental disorders, treatment response, mortality and serum cholesterol: a new holistic look at old data. Psychiatr Danub 2007; 19:270-81.*
19. *Jindal RD, Keshevan MS, Eklund K, Stevens A, Montrose DM & Yeragani VK: Beat-to-beat heart rate and QT interval variability in first episode neuroleptic-naive psychosis. Schizophr Res 2009; 113:176-80.*
20. *Kane JM & Lieberman JA: Adverse effects of psychotropic drugs. New York: Guilford, 1992.*
21. *Koponen H, Alaräisänen A, Saari K, Pelkonen O, Huikuri H, Raatikainen MJ, Savolainen M &*

Isohanni M: Schizophrenia and sudden cardiac death: a review. Nord J Psychiatry 2008; 62:342-5.

22. *Kozumplik O & Uzun S: Recommendations from treatment guidelines for schizophrenia regarding monitoring of side effects of antipsychotics: brief review. Psychiatria Danubina 2009; 21:95-8.*
23. *Lambert TJ, Velakoulis D & Pantelis C: Medical comorbidity in schizophrenia. Med J Aust 2003; 178:S67-70.*
24. *McElroy SL: Obesity in patients with severe mental illness: overview and management. J Clin Psychiatry 2009; 70:12-21.*
25. *McIntyre RS: Overview of managing medical comorbidities in patients with severe mental illness. J Clin Psychiatry 2009; 70:e17.*
26. *Meyer JM & Stahl SM: The metabolic syndrome and schizophrenia. Acta Psychiatr Scand 2009; 119:4-14.*
27. *National Institute for Clinical Excellence: Guidance on the Use of Newer (Atypical) Antipsychotic Drugs for the Treatment of Schizophrenia. Technology Appraisal Guidance 43. London: NICE, 2002.*
28. *Newcomer JW: Metabolic syndrome and mental illness. Am J Manag Care 2007; 13: S170-7.*
29. *Newcomer JW: Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. CNS Drugs 2005; 19:1-93.*
30. *Oud MJ & Meyboom-de Jong B: Somatic diseases in patients with schizophrenia in general practice: their prevalence and health care. BMC Fam Pract 2009; 10:32.*
31. *Pappa S & Dazzan P: Spontaneous movement disorders in antipsychotic-naive patients with first-episode psychoses: a systematic review. Psychol Med 2009; 39:1065-76.*
32. *Perez-Iglesias R, Crespo-Faccoro B, Amada JA, Garcia Unzueta MT, Ramirez-Bonilla ML, Gonzales-Blanch C, Martinez-Garcia O & Vazquez-Barquero JL: A 12-week randomized clinical trial to evaluate metabolic changes in drug-naive, first-episode psychosis patients treated with haloperidol, olanzapine, or risperidone. J Clin Psychiatry 2007; 68:1733-40.*
33. *Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for the Treatment of Schizophrenia and Related Disorders: Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of schizophrenia and related disorders. Australian and New Zealand Journal of Psychiatry 2005; 39:1–30.*
34. *Ruetsch O, Viala A, Bardou H, Martin P & Vacheron MN: (Psychotropic drugs induced weight gain: a review of the literature concerning epidemiological data, mechanisms and management). Encephale 2005; 31:507-16.*
35. *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.*
36. *Sadock BJ & Sadock VA: Kaplan & Sadock's Concise Textbook of Clinical Psychiatry. Third Edition. Philadelphia: Lippincott Williams & Wilkins, a Wolters Kluwer business, 2008.*
37. *Sharpe JK & Hills AP: Atypical antipsychotic weight gain: a major clinical challenge. Aust NZ J Psychiatry 2003; 37:705-9.*
38. *Sidouri S & Antzelevitch C: Sudden cardiac death secondary to antidepressant and antipsychotic drugs. Expert Opin Drug Saf 2008; 7:181-94.*
39. *Stahl SM, Mignon L & Meyer JM: Which comes first: atypical antipsychotic treatment or cardiometabolic risk? Acta Psychiatr Scand 2009; 119:171-9.*
40. *Tsuang D, Almqvist EW, Lipe H, Strgar F, DiGiacomo L, Hoff D, Eugenio C, Hayden MR & Bird TD: Familial aggregation of psychotic symptoms in Huntington's disease. Am J Psychiatry 2000; 157:1955-9.*
41. *Uzun S, Kozumplik O, Mimica N & Folnegović-Šmalc V: Nuspojave psihofarmaka. Zagreb: Medicinska naklada, Psihijatrijska bolnica Vrapče, 2005.*
42. *Van Gaal LF. Long-term health considerations in schizophrenia: metabolic effects and the role of abdominal adiposity. Eur Neuropsychopharmacol 2006; 16:S142-8.*
43. *Weber NS, Cowan DN, Millikan AM & Niebuhr DW: Psychiatric and general medical conditions comorbid with schizophrenia in the National Hospital Discharge Survey. Psychiatr Serv 2009; 60:1059-67.*
44. *Williams-Gray CH, Foltynie T, Lewis SJ & Barker RA: Cognitive deficits and psychosis in Parkinson's disease: a review of pathophysiology and therapeutic options. CNS Drugs 2006; 20:477-505.*
45. *Wolters ECh: PD-related psychosis: pathophysiology with therapeutical strategies. J Neural Transm Suppl 2006; (71):31-7.*
46. *Zahodne LB & Fernandez HH: Pathophysiology and treatment of psychosis in Parkinson's disease: a review. Drugs Aging 2008; 25:665-82.*

Correspondence:

Oliver Kozumplik, PhD, MD
Psychiatric Hospital Vrapče
Bolnička cesta 32, 10090 Zagreb, Croatia
E-mail: okozumplik@hotmail.com