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Adverse metabolic effects following the use of atypical antipsychotics

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Abstract

The administration of atypical antipsychotics in patients with psychosis might lead to a marked increase in body weight and metabolic abnormalities (atherogenic dyslipidemia, hyperglycemia, diabetes mellitus). These adverse metabolic effects could result in increased rates of cardiovascular mortality. In chronic schizophrenic patients, obesity could be more pronounced because of illness-related risk factors, such as poor dietary conditions (lack of fruit, vegetables, fibre, an excess of calories and saturated fat), cigarette smoking and a more sedentary lifestyle. Screening and monitoring of cardiovascular and metabolic risk factors is essential and should be pursued throughout the course of antipsychotic treatment. If the patient's body weight increases more than 5% of the initial measure, switching to another antipsychotic agent with a more favourable metabolic profile (ziprasidone or aripiprazole) should be considered. Furthermore, patients should engage in a variety of interventions like wellness programs, CBT, nutritional education and diet, weight management and exercise to improve their physical health.

Keywords: Atypical antipsychotics, psychosis, schizophrenia, metabolic syndrome, weight gain, metabolic abnormalities, dyslipidemia, diabetes mellitus, hypertension, CBT, wellness program, weight management, exercise.

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The beneficial effects of atypical antipsychotics (AP) on positive symptoms, negative symptoms and cognition in schizophrenia, as well as the reduced rate of extrapyramidal effects or tardive dyskinesia have led to the wide use of these drugs in clinical practice (Davis et al., 2003; Lieberman et al., 2005). On the other hand their administration might lead to a marked increase in body weight and metabolic abnormalities (atherogenic dyslipidemia, hyperglycemia, diabetes mellitus) (Allison et al., 1999; ADA, 2004; Casey et al., 2004;Haddad, 2005; McEvoy et al., 2005; Newcomer 2005, 2007; Henderson, 2007; Smyrnis and Theleritis, 2008; Theleritis et al., 2012; Bonaccorso et al., 2015).

These adverse metabolic effects could result in increased rates of cardiovascular mortality (Foley and Morley, 2011). Moreover, in chronic schizophrenic patients, obesity could be more pronounced because of illness-related risk factors, such as poor dietary conditions (lack of fruit, vegetables, fibre, an excess of calories and saturated fat), cigarette smoking and a more sedentary lifestyle (Brown et al., 1999; Bushe et al., 2005; Compton et al., 2006). Among AP, the risk for weight gain, type II diabetes mellitus, and lipid abnormalities appear to be quite high with clozapine and olanzapine, moderate with risperidone and quetiapine, and relatively low with aripiprazole and ziprasidone (Allison et al., 1999; ADA, 2004; Casey et al., 2004). It should be noted that a percentage of patients with schizophrenia experience metabolic abnormalities in the absence of significant increase in weight (Newcomer 2005, 2007).

The metabolic syndrome (MS) (NCEP, 2002), as defined by the NCEP Expert Panel, is a cluster of interrelated cardiovascular disease risk factors (excess total body fat, central fat distribution, and increased visceral fat); atherogenic dyslipidemia (including hypertriglyceridemia, decreased HDL cholesterol, and increased LDL cholesterol); insulin resistance, impaired glucose tolerance, type 2 diabetes mellitus; and hypertension. Nearly half the patients suffering from schizophrenia may be affected from MS (Casey et al., 2004; McEvoy et al., 2005). On the basis of the most recent NCEP ATP III definition, a patient with three or more of the five criteria of Table 1 has MS(NCEP,2002;Grundy et al., 2005).

Given that the management of MS requires treatment of each of the risk factors which might be present in a patient, one should bear in mind that targeting or preventing even one of them might be important for the patient's health (Newcomer 2007).

Screening and monitoring of cardiovascular and metabolic risk factors is essential and should be pursued throughout the course of antipsychotic treatment. A consensus statement by the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists and the North American Association for the Study of Obesity proposes certain screening guidelines for all the patients under treatment with AP that are presented in Table 2 (ADA 2004).

The patient's weight should be assessed at 4, 8 and 12 weeks after the initiation or change of an AP, and quarterly after that (ADA 2004). If the patient's body weight increases more than 5% of the initial measure, switching to another antipsychotic agent with a more favourable metabolic profile (ziprasidone or aripiprazole) should be considered (ADA 2004;Casey et al., 2004; Weiden and Buckley, 2007).

Even in patients with first episode psychosis (FEP), weight gain seems to be associated with the use of antipsychotics (Theleritis et al., 2006; Papadimitriou et al., 2006; Verma et al., 2009; Diaz et al., 2011; Foley and Morley, 2011; Mitchell et al., 2013). Sedative effects could lead to less activity and less energy expenditure, thus promoting body weight gain (Baptista 2002). Patients should engage in a variety of interventions like wellness programs, CBT, nutritional education and diet, weight management and exercise to improve physical health or health perception (Faukner et al., 2007; Smith et al., 2007; Theleritis et al., 2007; Alvarez Jiménez et al.,2008;Lindenmayer et al., 2009; Papanastasiou 2012)

A recent meta-analysis by Bonfioli et al. (2012) has demonstrated that when compared to treatment as usual, lifestyle interventions including diet and physical activity reduce weight in patients with psychosis by −0.98 BMI points. Unfortunately, despite the introduction of guidelines for metabolic screening in schizophrenia, metabolic monitoring in routine clinical practice is still unusual (Mitchell et al., 2012).

Fasting glucose plasma level, lipid levels and blood pressure should be assessed early in treatment for high risk patients or when rapid increase in weight occurs and at least three months after the initiation of AP treatment for all patients with schizophrenia. It should be underlined that the postload oral glucose tolerance test could be an earlier and more credible indicator of failing glucose levels along with other earlier signs of insulin resistance like elevating plasma triglyceride levels (Newcomer 2007). In fact, the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III has identified LDL cholesterol as the primary target for reducing risk for cardiovascular disease (NCEP, 2002; Casey et al., 2004).

It is proposed that people with schizophrenia might benefit by participating in lifestyle management programs early in the course of the illness (NCEP, 2002; Haddad, 2005; Bushe et al., 2005; Compton et al., 2006; Newcomer 2007; Henderson, 2007). In primary care settings, interventions that address weight gain and other risk factors for cardiovascular disease, such as cigarette smoking have been proven helpful. Furthermore, counseling, and cognitive behavioral techniques aimed at improving diet and increasing physical activity in people with impaired glucose tolerance have been shown to ameliorate abnormalities related to the MS, thereby reducing the risk for type 2 diabetes mellitus and cardiovascular disease (Tuomilehto et al., 2001; Casey et al., 2004; Newcomer 2007; Henderson, 2007). However, one should always bear in mind that people with schizophrenia might exhibit a variety of neurocognitive deficits along with lack of motivation and other negative symptoms and as a result a poor adherence to therapeutic treatment and healthy lifestyle instructions (Nasrallah et al., 2006; Theleritis et al., 2007).

In addition to medication type and age, other factors can influence antipsychotic-induced weight gain, such as lower BMI and extended duration of treatment (Allison et al., 1999; Asher-Svanum et al., 2005; Gentile, 2006; Safer, 2004; Basson et al., 2001; Lane et al., 2003). Studies of olanzapine, risperidone, and quetiapine have clearly documented that adults whose pretreatment BMI is less than 23 have substantially more drug-induced weight gain than those whose baseline BMI exceeds 27 (Safer 2004). Recovery from depression and from psychotic symptoms is often associated with improved appetite and better social functioning, which could lead to greater food intake and potential weight gain (Michelson et al., 1999; Asher-Svanum et al., 2005; Theleritis et al., 2006; Lane et al., 2003).The mechanisms responsible for weight gain in schizophrenic patients are not fully understood. Weight gain is due to either increased energy intake, decreased energy expenditure or both, and may also depend on complex interactions between various drugs (Haddad, 2005). Moreover, factors affecting the decision to eat are complex and involve environmental, cognitive, emotional and behavioral elements (Tighe and Dinan, 2005). In conclusion, the collaboration of all parties involved with patients' care (physicians, mental health professionals, caregivers, family members, and the patients themselves) (Theleritis et al., 2007) is needed for the prevention of the adverse metabolic reactions in psychiatric patients treated with AP.

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Tables

Table 1. Criteria for the metabolic syndrome.

1. Abdominal obesity, defined as a waist circumference of > 40 in for men or > 35 in for women
2. Triglycerides ≥ 150 mg/dL
3. HDL-cholesterol < 40 mg/dL in men or < 50 mg/dL in women
4. Blood pressure ≥ 135/80 mm Hg
5. Fasting glucose > 100 mg/dL

Table 2. Screening guidelines when treating with atypical antipyschotics.

1. Personal and family history of obesity, diabetes, dyslipidemia, hypertension, or cardiovascular disease
2. Body mass index (BMI)
3. Waist circumference at the level of the umbilicus
4. Blood pressure
5. Fasting plasma glucose
6. Fasting lipid profile