

Review article

**Metabolic side effects of antipsychotics and mood stabilizers**

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## INTRODUCTION

Psychopharmacotherapy, which was developed in the 1950's, has represented a true revolution in care to those who suffer from mental disorders. Several psychotic patients, who were condemned to spend the rest of their lives as beggars or in asylums, have been sent back to their families. After the synthesis of chlorpromazine by Delay & Deniker in 1952, imipramine was synthesized by Kuhn in 1957. Efficacy of lithium for the treatment of mania was demonstrated in 1954 by Schou, in the first double-blind study performed with psychiatric medication.<sup>1</sup> Some years later, in the 1970's, the first reports of the efficacy of carbamazepine in patients with bipolar disorder (BD) were published in Japan.<sup>2</sup>

Such advances had their costs. At a first moment, extrapyramidal adverse effects of antipsychotics were the first obstacle to their use, causing great difficulties to treatment tolerance and adherence. Meanwhile, still in the 1960's, there was an increase in cases of diabetes mellitus (DM) in patients taking antipsychotics.<sup>3</sup> Tricyclic antidepressants, monoamine oxidase inhibitors and lithium have also shown major metabolic side effects related to weight gain.<sup>4</sup>

New advances that occurred in the late 1980's eliminated only part of this problem. With regard to antidepressants, the synthesis of selective serotonin and/or noradrenaline reuptake inhibitors, with low potential for weight gain, can be considered a victory.<sup>5</sup> Nevertheless, rehabilitation of clozapine and synthesis of other atypical antipsychotics have once again brought about the metabolic side effects of this drug class. In 2004, the Food and Drug Administration (FDA), an agency responsible for regulating drugs in the United States, determined that every patient taking atypical antipsychotics should be monitored in this respect.<sup>6</sup>

This study aims at reviewing the medical literature about metabolic side effects, i.e., obesity, DM and dyslipidemias, associated with the use of antipsychotics and mood stabilizers.

## METHOD

A search at MEDLINE and LILACS databases was performed, considering articles written in English, Portuguese and Spanish. For MEDLINE, the following expressions were used: *diabetes, dyslipidemia, metabolic syndrome and weight gain*, associated with *antipsychotics, mood stabilizers, mental illness, mental disorder, psychiatric illness, psychiatric disorder, schizophrenia, bipolar disorder and mood disorder*. For LILACS, the following descriptors were used: *diabetes, dyslipidemia, weight gain, syndrome X metabolic*, associated with *antipsychotics, lithium, valproic acid, carbamazepine, schizophrenia and bipolar disorder*. Based on the results obtained, articles that concerned the theme under investigation were selected. Other relevant studies were also included based on the references of selected articles.

## RESULTS

### *Weight gain*

Several studies have assessed weight gain in patients taking psychotropics. Obesity is a frequent side effect in patients taking low-potency conventional antipsychotics, some atypical antipsychotics and the main mood stabilizers.<sup>4,7-9</sup>

The impact of this side effect should not be disregarded. Fontaine et al.<sup>10</sup> have estimated that, despite the fact that clozapine significantly reduces suicidal behavior in schizophrenic patients, consequent reduction in mortality would be in great part avoided due to increase in deaths secondary to diseases caused by weight gain. A 10-year follow-up of a cohort composed of 96 patients taking clozapine has verified high mortality rates due to cardiovascular causes, which serves as corroboration to that hypothesis.<sup>11</sup> However, there are also important data that contradict it, since a recent analysis of epidemiological studies carried out in the USA over the past 3 decades did not confirm the hypothesis that weight gain would necessarily lead to increased mortality.<sup>12</sup>

## Etiologic factors

Weight gain induced by antipsychotics and mood stabilizers has multifactorial etiology.

Several of these drugs stimulate appetite and preference for sweet or fat foods, which presupposes a direct action on metabolic systems and nervous centers associated with satiety control and weight.<sup>7</sup> Other factors, such as reduction in physical activity (secondary to sedation caused by some of those drugs), increased thirst, leading to excessive consumption of sweet beverages, and recovery of weight loss caused by the mental disorder should also be considered.<sup>4,7,13-16</sup>

Several studies about antipsychotic-induced weight gain have focused on brain neurotransmitter systems. Transmission mediated by  $\alpha$ -adrenergic receptors seems to stimulate appetite, whereas transmission mediated by  $\beta$ -adrenergic, histaminergic and dopaminergic receptors causes satiety. Relationship with serotonergic receptors is more complex, and stimulation of some subtypes leads to satiety and weight loss.<sup>7</sup>

Blockade of H1 receptors is involved in increased appetite and consequent weight gain. Several antipsychotics block histamine receptors, and there seems to be a logarithmic relationship between affinity with these receptors and weight gain; olanzapine is the drug with the highest affinity.<sup>9,15</sup> Dopaminergic blockade caused by antipsychotics causes side effects related to appetite stimulation,<sup>16,17</sup> whether by direct action on nervous centers associated with appetite, whether by secondary hyperprolactinemia.<sup>9</sup> Blockade of serotonergic 5HT<sub>2C</sub> receptors also leads to increased appetite. Researches suggest that patients who present changes in genes that codify this receptor are more susceptible to weight gain induced by those drugs.<sup>9</sup> However, ziprasidone, a powerful blocker of that receptor, has no association with major weight gain. This paradox can be explained by the compensatory anorectic action caused by noradrenaline reuptake inhibition.<sup>9</sup> Finally, it is known that weight gain caused by antipsychotics, lithium and valproic acid occurs even in the presence of high leptin levels, which is a hormone associated with feeling of satiety; it has been suggested that such drugs could reduce hypothalamus sensitivity to the action of this hormone.<sup>7,9,16,18,19</sup>

With regard to mood stabilizers, additional factors could be involved. An insulin-like action cause by lithium at the treatment initial stage could increase fat deposition. In addition, edema secondary to sodium retention and subclinical hypothyroidism also contribute to weight gain.<sup>4</sup> The mechanism by which the valproic acid causes weight gain is still little known; an action in the sense of inhibiting oxidation of fatty acids might be involved.<sup>20</sup>

### Antipsychotics and weight gain

Clozapine and olanzapine are the antipsychotics that cause more weight gain. A meta-analysis carried out by Allison et al.<sup>21</sup> has estimated mean change in weight secondary to antipsychotics after 10 weeks. In decreasing order: clozapine (+3.99 kg), olanzapine (+3.51 kg), thioridazine (+3.49 kg), chlorpromazine (+2.10 kg), risperidone (+2.0 kg) and haloperidol (+0.48). Fluphenazine (+0.43 kg) and ziprasidone (+0.04 kg) are not associated with statistically significant weight gain. Molindone was associated with slight weight loss (-0.81 kg). Pimozide apparently does not cause weight gain, but data found did not allow adequate analysis. It is worth stressing that weight gain may continue for a much longer period than what was demonstrated in another study, reaching up to 46 weeks in patients taking clozapine.<sup>22</sup>

Other studies have presented similar findings. Czobor et al.<sup>23</sup> analyzed a double-blind trial comparing efficacy of haloperidol (n = 36), clozapine (n = 38), olanzapine (n = 38) and risperidone (n = 39) after 14 weeks and verified that only haloperidol did not cause significant weight gain. In that study, the authors have found strong association between weight gain and therapeutic response to clozapine and olanzapine, but not for haloperidol and risperidone. Simpson et al.,<sup>24</sup> in a double-blind study, compared efficacy and tolerability of ziprasidone (n = 136) *versus* olanzapine (n = 133) in patients with acute schizophrenia or schizoaffective disorder. After 6 weeks, they verified significantly increased weight and body mass index (BMI) in the olanzapine group. Finally, recent data have been presented by the study Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE).<sup>25</sup> CATIE, an independent clinical trial funded by the National Institute of Mental Health

(NIMH), has assessed, in its first stage, effectiveness of antipsychotics by independently comparing four atypical antipsychotics (olanzapine, quetiapine, risperidone and ziprasidone) and one traditional antipsychotic (perphenazine). In that study, the number of patients taking olanzapine who presented weight gain higher than 7% was significantly higher than those taking quetiapine, risperidone, perphenazine and ziprasidone (30 versus 16, 14, 12 and 7%, respectively). Mean weight gain per month of treatment was 0.9 kg for olanzapine, 0.2 kg for quetiapine, 0.2 kg for risperidone, -0.1 kg for perphenazine and -0.1 kg for ziprasidone.<sup>25</sup>

Aripiprazole, which was not included in the CATIE study neither in the meta-analysis described above, is probably not associated with significant weight gain. McQuade et al.<sup>26</sup> have assessed participants of a controlled double-blind study comparing aripiprazole and olanzapine in the treatment of acute schizophrenia. The aripiprazole group presented mean weight loss of 1.37 kg at week 26, whereas the olanzapine group had weight gain of 4.23 kg. Fourteen per cent of patients in the aripiprazole group presented weight gain  $\geq 7\%$  initial weight, *versus* 37% of patients in the olanzapine group. Another open study with a small number of patients has suggested that aripiprazole may reverse weight gain in patients who have previously taken other antipsychotics.<sup>27</sup>

Weight gain also occurs with some depot antipsychotics. Silverstone et al.<sup>28</sup> have assessed 226 patients taking fluphenazine decanoate or flupentixol decanoate and found prevalence of obesity four-fold higher than the general population.

#### Mood stabilizers and weight gain

Weight gain is a major side effect of the main mood stabilizers. Chronic treatment with lithium is associated with increased weight, reaching more than 10 kg in 20% of patients.<sup>4</sup> Valproic acid also leads to unequivocal weight gain. McIntyre et al.,<sup>29</sup> in an open cross-sectional study of 38 women with BD, have concluded that weight gain caused by valproic acid is similar to weight gain caused by lithium. Weight gain, however, seems to be lower with carbamazepine. A retrospective study carried out by Corman et al.<sup>30</sup> has verified weight gain higher than 5% in 71% of patients

taking valproic acid (n = 70), *versus* 43% of patients taking carbamazepine (n = 20). Lamotrigine, another anticonvulsant that acts as a mood stabilizer, is not associated with significant weight gain.<sup>7</sup>

### *Hyperglycemia and diabetes*

Several studies have demonstrated that increased glucose levels or development of type II DM may be secondary to the use of psychotropics.<sup>8</sup> Although most cases of hyperglycemia and DM associated with atypical antipsychotics are associated with major weight gain, a significant number of cases occurs in non-obese patients. Clozapine and olanzapine are the main drugs associated with these side effects. On the other hand, disorders in glucose metabolism caused by the main mood stabilizers (lithium and valproic acid) are probably secondary to weight gain.

Pretreatment obesity, hypertension, previous history of disorder in glucose regulation and family history of DM are risk factors for development of antipsychotic-induced type II DM. In the USA, individuals belonging to Hispanic or African ethnic groups also present higher risk. Probability of developing type II DM would also be higher in patients diagnosed with schizophrenia.<sup>14,16,31</sup> Nevertheless, this has not been confirmed by a controlled study by Arranz et al.,<sup>19</sup> who demonstrated that reduced sensitivity to insulin and hyperinsulinemia found in schizophrenic patients are related not to the diagnosis itself, but to previous use of antipsychotics. Hyperglycemia associated with antipsychotics does not seem to be dose-dependent; it is reversible upon treatment cessation and tends to be recurrent when administration of the drug is resumed.<sup>14</sup>

### Etiologic factors

Reduction in insulin sensitivity resulting from increase in visceral adiposity is the main mechanism by which weight excess leads to disorders in glucose metabolism. Sowell et al.<sup>32</sup> have assessed insulin sensitivity in healthy individuals taking olanzapine (n = 17), risperidone (n = 13) or placebo (n = 18) using the clamp method for over 2 weeks. In that study, higher resistance to insulin was correlated with increased BMI. Similarly, Newcomer et al.<sup>33</sup> have compared insulin sensitivity

in patients taking antipsychotics and in controls. They verified that increase in insulin resistance was strongly associated with increased adiposity.

However, side effects on glucose metabolism cannot be completely explained by weight gain. According to FDA data, 25% of patients taking antipsychotics who developed DM did not present obesity or significant weight gain.<sup>14,34</sup> Howes et al.,<sup>35</sup> in a 2.5-month follow-up of 20 schizophrenic patients taking clozapine, found significant increase in fasting glucose and glucose tolerance post-test, which were not correlated with increased BMI. Henderson et al.<sup>36</sup> assessed 36 schizophrenic patients taking atypical antipsychotics, demonstrating that olanzapine and clozapine cause resistance to insulin significantly higher than risperidone, despite absence of obese individuals in their sample.

Other mechanisms should be implied in antipsychotic-induced metabolic disorders. Ardizzone et al.<sup>37</sup> have demonstrated that clozapine, risperidone, fluphenazine, loxapine and amoxapine inhibit glucose transport in PC12 cells and in rat muscle cells in a dose-dependent fashion. Blockade of 5HT<sub>1A</sub> receptors in pancreatic islet  $\beta$  cells and inhibition of insulin release by  $\alpha_2$ -adrenergic receptors have also been pointed as possible causes in this respect.<sup>15,17</sup>

The hypothesis of an action on neurochemical or neurohormonal mechanisms that regulate glucose homeostasis has not been corroborated by recent studies. Howes et al.<sup>38</sup> demonstrated that clozapine does not change serum levels of growth hormone (GH), insulin-like growth factor-1 (IGF-1) or insulin-like growth factor binding protein-1 (IGFBP-1), which are all substances that affect glucose regulation. Blockade of hypothalamic dopaminergic receptors might be involved, since it has been demonstrated that bromocriptine, a dopaminergic agonist, reduces glucose levels in non-diabetic obese women.<sup>15</sup> However, haloperidol, a potent D<sub>2</sub> antagonist, does not induce significant hyperglycemia in rats, opposed to what occurs with clozapine, quetiapine and chlorpromazine.<sup>39</sup>

Mood stabilizers are not likely to have any direct effects on glucose metabolism; in case there are such effects, they would be secondary to weight gain.<sup>4,20,40</sup>



## Antipsychotics, hyperglycemia and diabetes

Regarding atypical antipsychotics, clozapine and olanzapine are those that have the strongest association with this side effect, although there are some reports involving quetiapine and risperidone as well.<sup>8,14,15,34</sup> Among conventional antipsychotics, chlorpromazine and thioridazine are those most associated with DM.<sup>14</sup> According to FDA data, most new cases of DM occur during the first 6 months of treatment.<sup>34</sup> Literature reviews in MEDLINE, EMBASE and Current Contents databases have found 20 case reports of hyperglycemia or DM associated with clozapine, 15 reports associated with olanzapine, four reports associated with quetiapine and two reports associated with risperidone. In some cases, initial presentation occurred as diabetic ketoacidosis.<sup>14,41,42</sup> Risk seems to be even lower with haloperidol. FDA MedWatch data have revealed 131 cases of hyperglycemia associated with risperidone *versus* only 13 cases of hyperglycemia associated with haloperidol.<sup>43</sup> Mackin et al.<sup>44</sup> did not find correlation between insulin sensitivity and type of antipsychotic; however, there was higher prevalence of fasting hyperglycemia and DM in patients taking atypical antipsychotics. Henderson et al.,<sup>11</sup> in a prospective study with patients taking clozapine, estimated a 43% incidence of new DM cases over a 10-year period.

Some studies have searched databases of health or pharmacovigilance systems. Lund et al.<sup>45</sup> analyzed data from the Iowa Medicaid Program and found, considering age group between 20 and 34 years, relative risk (RR) for DM significantly higher for patients taking clozapine, compared with those taking conventional antipsychotics (RR = 2.5; IC95% 1.2-5.4). Nevertheless, the difference found was no longer significant when all age groups were considered. Sernyak et al.<sup>46</sup> analyzed data from over 38,000 schizophrenic patients taking antipsychotics and concluded that atypical antipsychotics have a 9% higher probability of having DM, compared with conventional antipsychotics. Among atypical antipsychotics, prevalence of DM was significantly higher with clozapine, olanzapine and quetiapine; for those aged less than 40 years, prevalence was also significantly increased with risperidone. In general terms, DM prevalence rates in adults aged 40

years or less were significantly higher in patients taking atypical or conventional antipsychotics, compared with the general population. Koro et al.<sup>47</sup> assessed data from over 18,000 schizophrenic patients of the British health system and concluded that those taking olanzapine presented increased risk for DM development, compared with a control group (OR = 5.8; IC95% 2.0-16.7) and with patients taking conventional antipsychotics (OR = 4.2; IC95% 1.5-12.2).

Analyses based on clinical trials have been performed. Meyer<sup>48</sup> compared the metabolic parameters of patients taking olanzapine and risperidone and found increased glucose significantly higher in the olanzapine group. Howes et al.<sup>35</sup> measured glucose levels of 20 schizophrenic patients before and after an average 2.5-month period of treatment with clozapine, and found significant increase in fasting glucose and glucose tolerance post-test. Of the patients who were assessed, one developed DM, eight started to present altered glucose tolerance, and two started to present altered fasting glucose. Lindenmayer et al.<sup>49</sup> analyzed a 14-week double-blind trial, with 101 patients taking clozapine, olanzapine, risperidone and haloperidol, and found that only risperidone was not associated with significant increase in glucose. Of those who participated in the study, six taking clozapine, four taking olanzapine, three taking risperidone and one taking haloperidol presented fasting glucose > 125 mg/dl during the study. In the double-blind study by Simpson et al.,<sup>24</sup> both olanzapine and ziprasidone did not cause significant increase in fasting glucose; however, olanzapine was associated with increased serum insulin, C-peptide and insulin resistance, assessed using the Homeostasis Model Assessment (HOMA). Henderson et al.<sup>36</sup>, assessing non-obese schizophrenic patients, founds that the use of clozapine and olanzapine was associated with higher insulin resistance than use of risperidone. To date, there have been no reports of DM caused by ziprasidone. Incidence of hyperglycemia in clinical trials with this drug is close to the incidence associated with placebo.<sup>34</sup> In the CATIE study, means of increased glucose and percentage of glycated hemoglobin (adjusted for drug exposure time) were 13.7 mg/dl and 0.40% for olanzapine, 7.5 mg/dl and 0.04% for quetiapine, 6.6 mg/dl and 0.07% for risperidone, 5.4 mg/dl and 0.09% for perphenazine and 2.3 mg/dl and 0.11% for ziprasidone. Glycated hemoglobin values for the

olanzapine group was significantly higher than for the others; the same did not occur with means of increased glucose.<sup>25</sup>

Short-term studies have also found incidence of hyperglycemia caused by aripiprazol similar to placebo.<sup>34</sup> Use of aripiprazol could also improve disorders in glucose metabolism induced by other antipsychotics. Littrell et al.<sup>27</sup> assessed 10 schizophrenic patients identified as insulin resistant, whose antipsychotic had been replaced by aripiprazol. After 16 weeks, 70% of the patients presented improved insulin resistance, assessed using the HOMA index ( $p = 0.04$ ).

Some cross-sectional studies do not corroborate some of the findings above. Mukherjee et al.<sup>50</sup> assessed schizophrenic patients admitted to a long-term care facility and found higher prevalence of DM in those who were not taking antipsychotics. Hägg et al.<sup>51</sup> compared the prevalence of DM and altered glucose tolerance in patients taking clozapine and in patients taking depot antipsychotics (haloperidol, zuclopenthixol, fluphenazine, perphenazine or flupenthixol) and found no significant difference (12 and 10% in the clozapine group *versus* 6 and 3% in the depot medication group). However, mean age in the depot medication group was significantly higher.

Methodological flaws found in several of the studies mentioned above demand great care in their interpretation. DM is generally underdiagnosed, and database studies cannot solve this problem. Furthermore, it is not possible to control some confounding factors, such as previous use of other drugs.<sup>16,34</sup> Finally, prescription of atypical antipsychotics may reflect the presence of more severe forms of psychosis – which is known to be true for clozapine – or access to better quality health services, in which there is higher possibility of DM diagnosis.<sup>16</sup>

#### Mood stabilizers, hyperglycemia and diabetes

Reduction in glucose tolerance after subchronic treatment with lithium has not been confirmed by Vestergaard & Schou.<sup>40</sup> Those authors followed 460 patients for up to 6 years and did not find significant increase in glucose levels; only one patient developed diabetes. McIntyre et al.,<sup>29</sup> in a cross-sectional study of women with BD taking valproic acid ( $n = 18$ ) or lithium ( $n = 20$ ),

did not find glucose values that were significantly different between themselves or compared with mean normal range.

### *Dyslipidemias*

Most studies on dyslipidemia and psychotropics are related to antipsychotics. Of these, clozapine and olanzapine are once again the drugs with the strongest association, with the highest increases in total cholesterol, LDL-cholesterol (LDL) and triglycerides, and with the highest reduction in HDL-cholesterol (HDL).<sup>8,52</sup> The studies on quetiapine are contradictory, especially concerning increase in triglyceridemia.<sup>52</sup> Deleterious action of risperidone on the lipid metabolism is questionable, and there are data pointing to the opposite direction.<sup>52</sup> Risk of hyperlipidemia with haloperidol is also questionable.<sup>49</sup> Ziprasidone and aripiprazol do not seem to cause deleterious effects on the lipid metabolism.<sup>24,26,52</sup> Studies concerning dyslipidemia caused by mood stabilizers are contradictory; there are some studies that even found beneficial effects in patients taking valproic acid or carbamazepine.

### Etiologic factors

Most dyslipidemias secondary to antipsychotics and mood stabilizers can be explained by weight gain. However, some clinical trials have not found correlation between weight gain and dyslipidemia. These discrepancies can be explained by methodological flaws in those studies, such as short follow-up time and absence of control for initial BMI values or for previous use of other antipsychotics.<sup>52</sup> Existence of other little known mechanisms in the genesis of dyslipidemia associated with psychotropics has been suggested. With regard to antipsychotics, changes in the lipid metabolism may be related to the three-ring structure of dibenzodiazepine derivatives (clozapine, quetiapine and olanzapine), presenting a space configuration similar to the phenothiazine nucleus, which is also involved in side effects on the lipid metabolism.<sup>52</sup>

## Antipsychotics and dyslipidemias

Disorders in the lipid metabolism are associated with use of traditional or atypical antipsychotics, although not all drugs are involved in this association. Among traditional antipsychotics, phenothiazine drugs are those that cause the highest risk of dyslipidemia. Sasaki et al.,<sup>53</sup> in a controlled cross-sectional study, verified that prolonged use of phenothiazine antipsychotics is associated with HDL levels significantly lower ( $p < 0.001$ ) and triglyceride levels significantly higher ( $p < 0.05$ ). The authors have also reported that use of phenothiazine drugs for only 1 week caused a 24% reduction in HDL levels. A data analysis from the Iowa Medicaid Program showed significant increase in incidence rate of dyslipidemias in patients taking clozapine, compared with those taking conventional antipsychotics, but only for age group between 20 and 34 years (RR = 2.4; IC95% 1.1-5.2).<sup>45</sup> In the study by Lindenmayer et al.,<sup>49</sup> both olanzapine and clozapine were associated with increased total cholesterol levels, which did not occur with risperidone and haloperidol. Henderson et al.,<sup>11</sup> in a follow-up of patients taking clozapine for up to 10 years, found significant increase in serum triglycerides, but not in total cholesterol. Koro et al.<sup>54</sup> analyzed databases with more than 18,000 schizophrenic patients and found that use of olanzapine was associated with an almost five-fold increase in incidence of dyslipidemia, compared with the control group (OR = 4.65; IC95% 2.44-8.85), and more than three-fold increase compared with traditional antipsychotics (OR = 3.36; IC95% 1.77-6.39). Use of traditional antipsychotics was also significantly associated with dyslipidemia, which did not occur with use of risperidone. Meyer<sup>48</sup> compared patients taking risperidone and olanzapine after 1 year of treatment and found increased total cholesterol and triglycerides significantly higher with olanzapine. Alméras et al.<sup>55</sup> assessed patients taking olanzapine and risperidone for 6 months. Use of olanzapine was associated with higher triglyceridemia, increased levels of apolipoprotein B, lower HDL levels and smaller LDL particle diameter, compared with use of risperidone or control group. HDL levels were lower with use of risperidone, compared with control groups. However, triglyceride, total cholesterol and LDL levels were also lower than the control group. In the study by Simpson et al.,<sup>24</sup> ziprasidone, as

opposed to olanzapine, was not associated with increased total cholesterol, LDL or triglyceride levels, both treatments did not significantly change HDL levels. An analysis of a double-blind randomized trial comparing olanzapine and aripiprazol in schizophrenic patients showed worsening of lipid profile after 26 weeks for the olanzapine group, with significant difference between groups for total cholesterol, HDL and triglyceride levels.<sup>26</sup> In the CATIE study, means of increased total cholesterol and serum triglycerides (adjusted for drug exposure time) were 9.4 mg/dl and 40.5% for olanzapine, 6.6 mg/dl and 21.2% for quetiapine, -1.3 mg/dl and -2.4% for risperidone, 1.5 mg/dl and 9.2% for perphenazine and -8.2 mg/dl and -16.5% for ziprasidone. Difference between drugs was significant for both means; however, which one was responsible for such difference was not informed.<sup>25</sup>

#### Mood stabilizers and dyslipidemias

Studies about mood stabilizers are not in accordance. Beneficial effects have been found by some authors, especially in children with epilepsy. Heldenberg et al.<sup>56</sup> assessed epileptic children (n = 33) taking anticonvulsants (phenobarbital, valproic acid or carbamazepine) and concluded that, compared with healthy controls, they presented higher HDL levels. Children taking valproic acid also presented reduced LDL levels. Another controlled study, also with children undergoing anticonvulsant treatment (n = 208), did not find significant changes in HDL and triglycerides levels associated with use of carbamazepine or valproic acid. Nevertheless, in the group taking carbamazepine, there was significant increase in total cholesterol levels.<sup>57</sup> Calandre et al.<sup>58</sup> assessed 101 patients undergoing anticonvulsant treatment for at least 3 months. Compared with controls paired for gender and age, patients taking valproic acid (n = 48) presented significantly lower total cholesterol and LDL levels; patients taking carbamazepine (n = 34) presented significantly increased HDL and apolipoprotein A levels. McIntyre et al.,<sup>29</sup> in a cross-sectional study of women with BD taking lithium (n = 20) and valproic acid (n = 18), found that total cholesterol, LDL, HDL and triglyceride levels did not significantly differ from mean normal range or between both groups.

In absolute terms, the lipid profile of the group taking valproic acid was worse than the group taking lithium. Casey et al.<sup>59</sup> analyzed a clinical trial to assess efficacy of the association between divalproex and treatment with risperidone or olanzapine in acute schizophrenia and found a protective effect on increased total cholesterol in groups that used combined therapy. However, on the contrary, Isojärvi et al.<sup>20</sup> found high triglyceride levels and low HDL levels in women with epilepsy taking valproic acid, compared with controls. Lamotrigine, in its turn, was not associated with changes in the lipid metabolism.

### *Metabolic syndrome*

Studies about association of psychotropics with metabolic syndrome (MS) are still rare. The few studies available only deal with antipsychotics.

Casey et al.<sup>60</sup> compared patients taking aripiprazol (n = 504) and olanzapine (n = 505) to detect the incidence or exacerbation of MS after 16 weeks. Occurrence of such events was 8.5% ( $\pm$  1.7%) for aripiprazol *versus* 14.4% ( $\pm$  1.9%) for olanzapine and, after 1 year, 10% ( $\pm$  1.9) for aripiprazol *versus* 20.05 ( $\pm$  2.3%) for olanzapine (RR = 2.1; IC95% 1.3-3.1). The authors did not describe the criteria used for MS diagnosis. Kato et al.<sup>61</sup> assessed presence of MS in 48 schizophrenic patients. Although having found increased prevalence of MS, they did not find association between MS and use of any specific antipsychotic drug. Half of the patients were taking clozapine, 21% haloperidol, 15% olanzapine and 15% risperidone. Mackin et al.,<sup>44</sup> in a cross-sectional study of 103 outpatients taking antipsychotics, found that eight of them met criteria for MS; all were taking atypical antipsychotics. Blood pressure, one of the criteria for MS diagnosis, was not measured in that study, which makes us suppose that the number of affected patients is higher.

## CONCLUSION

This review allows us to conclude that metabolic side effects are still major challenges to be overcome by psychopharmacology. Occurrence of significant weight gain is frequent in patients taking clozapine, olanzapine and traditional low-potency antipsychotics. The main mood stabilizers are also associated with major weight gain. Other metabolic side effects, such as hyperglycemia, type II DM and dyslipidemias, also occur with previously mentioned antipsychotics, due to weight gain or direct deleterious action on glucose metabolism. Association of mood stabilizers with disorders in glucose metabolism and dyslipidemias is questionable; when it does occur, it seems to be secondary to weight gain.

Despite FDA recommending that every patient taking atypical antipsychotics should be monitored for occurrence of hyperglycemia or type II DM, studies have demonstrated that some of these drugs cause few metabolic side effects. New antipsychotics, such as ziprasidone and aripiprazol, do not seem to present major side effects on weight and on glucose and lipid metabolism. Incidence of type II DM or weight gain with risperidone is small, compared with clozapine or olanzapine. It has even been suggested that risperidone might have some beneficial effect on dyslipidemias. Weight gain in patients taking haloperidol is also lower, and development of DM secondary to this drug is unlikely to occur.

Finally, it is important that psychiatrists, when prescribing such drugs, become aware of their different profiles of side effects, so that they can compare advantages and disadvantages in the use of these drugs for each particular patient. Being aware of these side effects, psychiatrists will also be able to guide their patients preventively with regard to a healthy diet and practice of physical activity.



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#### *ABSTRACT*

*Background: An increase in the incidence of obesity and diabetes mellitus in psychiatric patients using antipsychotic drugs was observed as early as the 1960's. In the 1980's and 1990's, rehabilitation of clozapine, synthesis of other atypical antipsychotics, and spread of the use of lithium and valproic acid once again directed the attention to their metabolic effects. This study aims to review the medical literature with regard to metabolic side effects associated with the use of antipsychotics and mood stabilizers.*

*Method: Research was carried out at MEDLINE and LILACS through October 2005.*

*Conclusion: Metabolic side effects remain a major concern for psychopharmacology. Clinically relevant weight gain occurs frequently in patients taking antipsychotics and mood*

*stabilizers, particularly clozapine, olanzapine, lithium, and valproic acid. Clozapine and olanzapine are also associated with higher incidence of diabetes mellitus and dyslipidemias, either due to weight gain or because of a direct deleterious action on glucose metabolism. Incidence of obesity and other metabolic disorders is lower with risperidone when compared to olanzapine or clozapine. Carbamazepine is associated with lower weight gain when compared to lithium or valproic acid. Drugs such as haloperidol, ziprasidone, aripiprazole and lamotrigine are not associated with significant weight gain or with higher incidence of diabetes mellitus. They are alternatives for patients more likely to develop these adverse effects.*

Keywords: *Antipsychotics, mood stabilizers, metabolic syndrome, diabetes mellitus, dyslipidemia, weight gain.*

Title: *Metabolic side effects of antipsychotics and mood stabilizers*

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