

# Obesity and antipsychotics

## Abstract

The increase in obesity among the Western population is a major health problem, and its management is particularly complex when complicating a serious psychiatric disorder. Antipsychotic drugs are important therapeutic tools for patient with schizophrenia and other forms of psychosis, but weight gain and obesity with different incidence according to the drug considered, remain one of the major side effects related to traditional or atypical antipsychotics. Clozapine and olanzapine tends to be the most dangerous in terms of weight gain, while the risk of weight gain during therapy with risperidone and quetiapine tends to be moderately high. Ziprasidone and aripiprazole are instead, associated with a low risk of weight gain. The mechanism of their action would seem secondary to both a central action at the hypothalamic level (blockage of D2 receptors, H1 histamine receptors and 5-HT<sub>2c</sub> receptors), that induces an increase in appetite; and peripherally through their sedative action, reducing physical activity and therefore energy expenditure. Moreover, anti-psychotic drugs leads to significant and dose-dependent increase in prolactin levels that could influence the percentage of body fat, directly through a decrease in insulin peripheral sensitivity, and indirectly through stimulation of the hypothalamic centers of appetite mediated by an altered testosterone /estradiol ratio. Finally, recent clinical and molecular evidence supports the hypothesis that the response to antipsychotic drugs in terms of weight gain can be genetically predetermined, because of genetic polymorphisms in receptors involved in satiety/appetite signaling.

There are very few tools to counteract weight gain in psychiatric patients, because diet programs are particularly complex to manage, and the use of anti-obesity drugs is complicated by their own pharmacodynamics and pharmacokinetic profile, and in particular, by their interference with the monoamines involved in the pathophysiology of psychotic disorders. A careful assessment of the clinical history and the antropometric parameters of the patients who were treated with antipsychotic drugs are needed, and prevention strategies to avoid weight gain (dietary counseling, physical activity) from the beginning of the pharmacological treatment are mandatory.

## Introduction

The increase in obesity among the Western population is a major health problem, given the epidemic characteristics that the phenomenon presents in countries such as the United States, where prevalence is currently estimated at around 18% without significant differences in both sexes, and age group 25-65 years.<sup>1</sup> Obesity is increasingly considered a behavioral disorder that leads to significant morbidity and mortality.<sup>2</sup> In this regard, it is known that cardiovascular and respiratory diseases, hypertension, dyslipidemia, cholelithiasis, sleep apnea, osteoarthritis, various types of cancer (endometrium, breast, colon), glucose intolerance and Type 2 diabetes are significantly associated with obesity.<sup>3</sup> The clinical picture and its management are particularly complex when obesity complicates a serious psychiatric disorder. People with a major psychiatric condition have a higher mortality rate than the general population as recently demonstrated by Dixon et al.<sup>4</sup> In particular, in this study, it was shown that people suffering from schizophrenia and bipolar disorder, show an incidence of overweight and obesity greater than the general population and therefore, theoretically, also related morbidity. This morbidity is further increased by tabagism and alcohol dependence.<sup>4</sup>

Antipsychotic drugs are an important therapeutic tool for patients with schizophrenia and other forms of psychosis: in fact, in recent

decades the quality of life for many of these patients have improved; thanks to the treatment with neuroleptics (traditional antipsychotics). Research on new generation antipsychotic drugs aims at reducing side effects, improving selectivity or expanding the field of action with respect to classical neuroleptics such as phenothiazines and butyrophenones. The so-called atypical antipsychotics (such as clozapine, olanzapine, risperidone, quetiapine, ziprasidone), characterized by specific pharmacological actions that will be described later, show a therapeutic efficacy equal to or greater than the traditional ones, a lower incidence of side effects and are indicated as a first choice in the pharmacological strategies of schizophrenia.<sup>5</sup> However, weight gain and obesity with different incidence according to the drug in consideration, remain part of the major problems related to antipsychotic therapy. Clinical studies following the introduction of the first antipsychotic drugs (fenotiazine, in particular chlorpromazine) highlighted the problem of weight gain related to the use of such drugs.<sup>6-8</sup>

Recently, Allison et al. performed a meta-analysis on 81 treatment trials lasting at least 10 weeks, in which weight gain in patients was compared, using traditional and atypical antipsychotics,<sup>10-12</sup> and interesting result was obtained.<sup>9</sup> Based on these studies, the clinical relevance of antipsychotic side effects such as weight gain and

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obesity and their related diseases is significant and should not be underestimated in the risk-benefit balance at the time of initiation of drug therapy. According to De Hert, from the publication of the first studies on the metabolic syndrome (MS) in schizophrenic patients in 2003, about 30 studies confirmed that the risk of developing MS is constantly increased up to two or three times compared to the general population, even compared to the type of drug used.

### Mechanisms of action of antipsychotics

Traditional antipsychotics are called neuroleptics because of their common characteristics of inducing neurolepsy, i.e. slows down movement and behavioral activities in the experimental animal, and in humans, reduces psycho-motor and induces emotional indifference. These drugs act by blocking dopamine D2 receptors at the mesolimbic and hypothalamic levels. Non-selective action on D2 receptors is responsible for the most significant side effects such as neuroleptic deficiency syndrome (mesocortical dopaminergic (DA) pathway), parkinsonism (via nigrostriatal DA), hyperprolactinemia (via tuber-infundibular DA). In addition to blockade of D2 receptors, classical antipsychotics perform, to varying degrees, antagonistic actions on cholinergic muscarinic receptors and  $\alpha_1$ - $\alpha_2$  adrenergic and histaminergic receptors, causing well known side effects (constipation, blurred vision, xerostomia, somnolence, hypotension, dizziness).

### Weight control mechanisms: role of adipose tissue and neuroendocrine regulation of hunger and satiety

Body weight seems to depend significantly on genetic factors. In this regard, it is known that the process of adipogenesis begins with a volumetric increase (hypertrophy) of the adipocytes, followed by an increase in their number (hyperplasia). The maximum volume of adipocytes is genetically determined and, when it becomes "critical", triggers the release of paracrine factors that lead to cell proliferation.<sup>13</sup> The adipose tissue is currently considered an endocrine organ that has two main functions; 1) storage of highly energetic molecules (triglycerides) which, through their hydrolysis to free fatty acids (FFA), can be used as an "energy substrate" by all cells in the human body; 2) production of different factors involved in the regulation of adipogenesis and food-intake such as leptin, resistin, insulin-like growth factor-I (IGF-I), transforming growth factor- $\beta$  (TGF- $\beta$ ) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ).

From a clinical point of view, the genetic component of body weight was suggested by studies carried out on twins raised separately, and showed a very high correlation (up to 70%) in their BMI, which was slightly lower than that present in twins raised in the same environment.<sup>14</sup> There has been considerable progress on past evidence and findings of genetic factors. Leptin and HTR2C genes are among the most promising and new evidence which suggest that DRD2, TNF, SNAP-25 and MC4R are significant risk factors. Among the most important susceptibility genes, CNR1, MDR1, ADRA1A and INSIG2 should also be considered. In any case, there are also many endocrine, environmental, psychological, behavioral and cultural components that must be considered because of their contribution to the maintenance of physiological weight, and unfortunately to weight gain and obesity. In the complex regulation of body weight, there are three main neuroendocrine components plus a fourth non-primarily endocrine component represented by the digestive system and the liver.<sup>13-15</sup>

The first neuroendocrine component includes an afferent system of satiety in food research, consisting of hormonal signals (insulin, leptin, cholecystokinin, ghrelin), and biochemical signals (noradrenaline, acetylcholine, serotonin, dopamine ...). The second consists in the "processing" of information located in the central nervous system, particularly in the hypothalamus; referred to as ventromedial hypothalamic nucleus (NVM) (center of satiety), ventrolateral nucleus (NVL) (center of hunger), arcuate nucleus (NA) and paraventricular nucleus (NPV). Finally, the third component involves an efferent system consisting of a complex set of appetite/satiety effectors, the autonomic system and thermogenesis. Briefly, the efferent signals stimulate both the sympathetic system through the  $\beta_3$  adrenergic receptors and the uncoupling proteins (UCP) of mitochondrial adipocytes to release energy through lipolysis, thermogenesis or physical activity, or stimulate the system parasympathetic (vagus nerve) to increase insulin secretion and promote liposynthesis and energy accumulation.<sup>13-15</sup> In this regard, the recent experimental evidence showed a high expression of  $\alpha_2$  adrenergic receptors combined with a reduced expression of  $\beta_3$  adrenergic receptors in adipose tissue of obese subjects, which could justify the unsatisfactory results of clinical trials with  $\beta_3$  adrenergic receptors agonists in such patients.<sup>15</sup>

Numerous neuropeptides and neurotransmitters that regulate the sensations of hunger and satiety by controlling body mass and the distribution of adipose tissue have been identified, which include; neuropeptide Y, galanine, dynorphin,  $\beta$ -endorphins, the release factor growth hormone (GHRH), noradrenaline, anandamide (endogenous cannabinoid ligand), GABA, agouti-related protein (AGRP), orexins A and B, melanin-concentrating hormone (MCH) and Ghrelin (a growth hormone secretagogue) stimulate hunger, while serotonin, insulin, neurotensin, corticotropin-releasing factor (CRF), dopamine, cholecystokinin (CCK), leptin, release of TSH (TRH), melanin stimulating hormone (MSH), amphetamine-regulated transcript cocaine (CART), prolactin-releasing peptide (PrRP). In addition, glucagon and somatostatin inhibit appetite and may increase expenditure or energy.<sup>13,15</sup> Interactions between antipsychotics and central and peripheral food-intake control systems. Among the peptides with an inhibitory action on food intake, leptin plays a pivotal role. Leptin (from Greek λεπτός leptos, "thin"), is an endocrine product synthesized by the adipose tissue in proportion to the number of adipocytes, and is involved in lots of mechanisms of regulation of body weight. Its primary role is to "indicate", in a saturable manner, information on energy reserves of adipose tissue at the NVM and NA, through a class of receptors of the cytokine family, existing in 6 different isoforms (Ob-Ra, b, c, d, e, f). In particular, at the NA level, leptin activates the neurons that produce proopiomelanocortin (POMC) and CART, while inhibiting those that secrete NPY and AGRP. At the peripheral level, the  $\beta_3$  adrenergic-UCP receptor axis represents a primary target of leptin action that leads to an increase in the expression of UCP-1 and thermogenesis.<sup>13</sup> Leptin synthesis is stimulated by dietary intake, insulin, glucocorticoids and estrogen, while it is inhibited by fasting, adrenergic stimulation and testosterone.<sup>14,15</sup>

A reduction in leptin levels, which reflects a decline in energy reserves, signals to the NVM and the NA, the reduction of energy expenditure and metabolic processes and stimulates the increase in appetite, by reducing the inhibitory inputs on the neurons secreting the

NPY and the AGRP. Despite the central inhibitory role on food-intake highlighted in many experimental studies, the clinical applications of leptin in the treatment of obesity were disappointing, since mutations of its gene or its receptors are rare in obesity (which is considered a form of leptin-resistance). Interesting, although not conclusive, correlations were recently highlighted between the use of classical antipsychotics such as haloperidol and atypical antipsychotics such as clozapine, olanzapine and high levels of leptin. This increase could represent a direct effect of antipsychotics on the feedback mechanisms for this hormone, or an effect resulting from the increase in food intake and weight gain. In these patients, hyperleptinemia could represent an essential link in the development of overweight/obesity and insulin resistance both directly and through the pituitary, to stimulate the release of prolactin.<sup>13,15,16–20</sup> Dopamine, released by neurons located in the NA and the medial back nucleus, exerts a central inhibitory effect on the appetite through the D2 receptors. This experimental finding led to the use of drugs with dopamine-agonist activity such as amantadine in subjects that showed significant weight gain, related to the use of an atypical antipsychotic such as olanzapine.<sup>21</sup>

Hypothalamic histaminergic receptors exert an inhibitory regulation on appetite; this experimental evidence justifies the detection of changes in body weight, which is secondary to the use of high-affinity drugs for histaminergic receptors (such as phenothiazines or, among antidepressants, mirtazapine). Because of their anti-histaminergic action, these molecules stimulate appetite; moreover, their sedative action, reducing physical activity and therefore energy expenditure, contributes to weight gain. On the other hand, the antagonist action on histaminergic receptors is present in a different measure, as well as in traditional neuroleptics, also in the new antipsychotics, particularly clozapine and olanzapine, which, in the context of this new pharmacological class, are associated with a more pronounced weight gain. In this regard, significant correlations between weight gain induced by atypical antipsychotics and affinity for H1 histamine receptors have been highlighted.<sup>22</sup> The weight increase associated with olanzapine is dose-dependent resulting in about 12 kg after one year of therapy at the dosage of 12.5–17.5 mg/day and about 3 kg with 1 mg/day.<sup>23</sup> Moreover, this molecule appears to cause direct damage to the  $\beta$  pancreatic cells, favor insulin resistance and eventually result in type 2 diabetes.<sup>23</sup>

Similar weight gains (7–11 kg) were observed after clozapine therapy at a dose of 175–600 mg/day for 4–6 months.<sup>23</sup> Finally, both of these molecules are associated with lipid metabolism disorders such as hypercholesterolemia and hypertriglyceridemia,<sup>23</sup> often worsened by poor eating habits and alcohol abuse.

Another molecule involved in the mechanisms of regulation of body weight and dietary behavior is serotonin.<sup>24</sup> This neurotransmitter, mainly produced by the nuclei of the dorsal raphe, is a well-known satiety factor and the increase in its concentrations in the brain produces in the animal, an attenuation of the stimulus for food research. Experimental evidence suggests that 5-HT<sub>2c</sub> receptors are the most involved in the pharmacological action of serotonin, and for this reason, they are the subject of numerous studies. Observations on knockout mice for 5-HT<sub>2c</sub> receptors showed a progressive tendency to increase food intake and the development of obesity.<sup>25</sup> In humans, the antagonist action on 5-HT<sub>2c</sub> receptors located in the NVM and NPV are responsible for weight gain due to the use of atypical

antipsychotics (high receptor affinity of olanzapine, risperidone and ziprasidone and moderate clozapine), which is higher than that of classic drugs such as haloperidol which has minimal antagonist activity on these receptors. Another way in which antipsychotic drugs determine weight gain is the alteration in sex steroid milieu, particularly of the androgen/estrogen ratio related to the increase in prolactin. In this regard, there is a certain role for sex steroids, as it has been shown that hyperprolactinemia occurs with a greater frequency and at significantly lower dosages in women than in men. The variable but generally significant and dose-dependent increase in prolactin levels associated with the use of traditional and atypical antipsychotics such as risperidone could influence the percentage of body fat directly through a decrease in insulin peripheral sensitivity, and indirectly through stimulation of the hypothalamic centers of appetite mediated by an altered testosterone/estradiol ratio.<sup>16,17</sup> In addition, other morbidities associated with hyperprolactinemia related to antipsychotics should be mentioned, such as osteoporosis (in both sexes), oligo-amenorrhea and galactorrhea (in female sex) and changes in libido and potency, retrograde ejaculation and anorgasmia (in males).<sup>26</sup>

## Clinical implications and conclusions

Authors agree that weight gain and obesity are both side effects of most therapies with all traditional or atypical antipsychotic. Moreover, the latter, with the exception of ziprasidone, seem to cause a greater weight increase compared to traditional neuroleptics. The mechanism of their action would seem secondary to both a central action at the hypothalamic level that induces an increase in appetite and peripherally through a reduction in energy expenditure.<sup>20,21</sup> Other factors can modulate the magnitude of weight gain caused by antipsychotics: gender, age, initial body weight, concomitant endocrine diseases (type 2 diabetes, hypothyroidism, ovarian polycystosis) and associated drug therapies (lithium salts and other antidepressants). Weight gain and obesity, like other side effects, can affect compliance with pharmacological treatments of psychotic patients, complicating the known problems related to poor awareness of the disease and thus increasing the risk of interruption of therapy and the incidence of relapses. In this regard, Allison et al.<sup>9</sup> pointed out that, although there is no precise quantification of the effect of weight gain on treatment compliance, a certain number of patients attribute the interruption of therapy to this phenomenon. Recent clinical and molecular evidence supports the hypothesis that the response to antipsychotic drugs in terms of weight gain can be genetically predetermined. In fact, gene polymorphisms of molecules such as the 5HT<sub>2c</sub> serotonergic receptor, the H1 and H2 histamine receptors and the  $\beta$ 3 adrenergic receptor appear to be associated with a more considerable weight increase during therapy with an atypical antipsychotic such as clozapine.<sup>24</sup> Various techniques have been studied to avoid weight gain during treatment with antipsychotics.<sup>16</sup> Unfortunately, given the known difficulties encountered in the control or weight reduction in the general population, it is understandable that diet programs are particularly complex to manage in psychiatric patients. However, successes in nutritional counseling programs have been reported in patients treated with risperidone and olanzapine.<sup>16</sup>

The use of pharmacological treatments to avoid weight gain induced by antipsychotics is complicated by their own pharmacodynamic and pharmacokinetic profile, and in particular by their interference

with the monoamines involved in the pathophysiology of psychotic disorders. In fact, drugs for obesity usually reach their effect by stimulating noradrenergic, dopaminergic and/or serotonergic activity, while antipsychotic drugs act with inhibitory actions on the same systems. The use of anti-obesity drugs with these characteristics in schizophrenic patients may, therefore, exacerbate psychotic symptoms and is highly discouraged.<sup>9,17</sup> In this regard, the authors recommend a careful assessment of the clinical history and the anthropometric parameters of the patient who initiates treatment with antipsychotic drugs, in which the problem of possible weight gain and associated morbidity contributes to the orientation of the pharmacological choice. In patients with a BMI that is compatible with overweight (BMI 25-29 kg/m<sup>2</sup>), obesity (BMI ≥30 kg/m<sup>2</sup>), or with a family history of obesity or type 2 diabetes, it is useful to look for molecules that present a minor risk of inducing weight gain as well as changes in glucose and lipid metabolism. In any case, the monitoring of body weight in psychiatric patients should be considered as primary while associated prevention activity from the beginning of the pharmacological treatment to dietary counseling programs be aimed at controlling or modifying dietary behavior and exercise.

Comparing eight different drugs belonging to the SGA category (clozapine, olanzapine, risperidone, quetiapine, zotepine, amisulpride, ziprasidone, and aripiprazole), based on the risk of weight gain but also relative to hyperglycemia and dyslipidemia, randomized controlled trials have highlighted significant differences between the drugs mentioned. Clozapine and olanzapine tends to be the most dangerous in terms of weight gain, while the risk of weight gain during therapy with risperidone and quetiapine tends to be moderately high. Ziprasidone and aripiprazole, are instead, associated with low risk.<sup>27</sup> The complex reciprocal action between psychiatric illness and weight brings into play; neurobiology, psychology, and sociological factors. The analysis of the predominant variables among people with mental disorders is an urgent necessity since mortality attributable to physical causes is the most common among the causes of premature death among people suffering from chronic mental illnesses.<sup>28,29</sup>

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## Conflict of interest

None.

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