ANTIPSYCHOTIC TREATMENT AND WEIGHT GAIN IN ADOLESCENTS WITH VERY EARLY AND EARLY ONSET SCHIZOPHRENIA

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ABSTRACT

The use of antipsychotic drugs (ADPs) in younger patients has steadily increased in recent years. These drugs are associated with a considerable increase in patient body weight. Their endocrine and metabolic side-effects are of particular concern, especially within today’s pediatrics population that appears to be at greater risk as compared to adults for antipsychotic-induced metabolic adverse effects. To evaluate weight-related changes in a group of adolescents diagnosed with early onset schizophrenia who received atypical antipsychotic treatment with risperidone. We included 19 patients (age between 12 and 17) with very early-onset and early-onset schizophrenia diagnosed according K-DSATS. During this trial they received treatment with risperidone in doses up to 2 to 4 mg/day. Their weight and BMI were measured at baseline and after 6 months of antipsychotic treatment. After 6 months of antipsychotic treatment all 19 patients gained weight. Weight higher than, or equal to 5 kg was considered significant weight gain. 58% of patients experienced a weight gain exceeding 5 kg. The results confirm clinically significant and substantial weight gain induced by antipsychotic treatment Monitoring body weight early in treatment will help predict those at high risk for substantial weight gain.

Keywords: antipsychotic treatment, weight gain, adolescent.

INTRODUCTION

The use of antipsychotic drugs (APDs) has been increasing considerably during recent years, not only as a result of growth in the population that uses such substances, but also because of expanded use of such medication in other clinical situations in which they are considered to be of potential benefit for patients. A newer class of drugs known as atypical antipsychotic medication can be lifesaving for young people with schizophrenia, bipolar disorder or severe aggression associated with autism, according to an editorial accompanying the study in Wednesday's issue of the Journal of the American Medical Association [1].

The use of ADPs in younger patients has steadily increased in recent years. Data collected from the US Food and Drug Administration (FDA) regarding outpatient prescription of ADPs demonstrates a 22% increase in atypical antipsychotic prescriptions from 2004 to 2008 for patients younger than 17 years of age. Risperidone was the most common drug prescribed [2].

However, the evidence to date suggests that antipsychotic, or at least some of the most widely used APDs, are associated with a considerable increase in patient body weight (>7%) and with the development of glucose and lipid metabolic alterations. This in turn can imply an increased risk of premature death among such patients due to cardiovascular events [3].

Obesity has become one of the most important public health problems in a lot of countries. As the prevalence of obesity increases, so does the prevalence of the comorbidities associated with obesity. More
than a third of children and teenagers taking certain ADPs became overweight or obese in the first three months of treatment, as a new U.S. study has found [1].

"Overweight" technically refers to an excess of body weight, whereas "obesity" refers to an excess of fat. However, the methods used to directly measure body fat are not available in daily practice. For this reason, obesity is often assessed by means of indirect estimates of body fat. The body mass index (BMI) is the accepted standard measure of overweight and obesity for children two years of age and older. Adults with a BMI between 25 and 30 are considered overweight; those with a BMI ≥30 are considered to be obese. Unlike adults, children grow in height as well as weight. Thus, the norms for BMI in children vary with age and sex. In 2000, the National Center for Health Care Statistics and the Centers for Disease Control (CDC) published BMI reference standards for children between the ages of 2 and 20 years [4].

Atypical antipsychotics have a favorable risk/benefit profile in early onset schizophrenia (EOS). However, despite the increasing use of psychotropic medication in children and adolescents, their endocrine and metabolic side-effects (weight gain, obesity, and related metabolic abnormalities such as hyperglycemia and dyslipidemia) are of particular concern, especially within this pediatric population that appears to be at greater risk as compared to adults for antipsychotic-induced metabolic adverse effects - youths are still developing at the time of psychotropic drug exposure. In addition to medication, many factors contribute to weight gain in psychiatric patients, including sedentary lifestyle and poor diet. Excessive weight gain has psychosocial consequences such as a sense of demoralization; physical discomfort and being the target of substantial social stigma are so intolerable that they may discontinue the treatment even if it is effective.

Furthermore, excessive corpulence may evolve to a metabolic syndrome with a high-risk state for future cardiovascular morbidity and mortality in adult age [5].

The evidence is that different antipsychotic have different propensities for weight gain, and that children, adolescents, and first-episode patients are at higher risk for weight gain associated with antipsychotic treatment [6].

Atypical antipsychotics tend to cause more weight gain than conventional ones and weight gain, diabetes, dyslipidemia, seem to be most severe with clozapine and olanzapine [7].

ADPs may contribute to weight gain in children and adolescents. In 21 articles linking weight gain and obesity with newer ADPs among youths, risperidone was the most commonly cited agent. Weight gain from olanzapine was the largest among the more commonly prescribed newer agents. All studies reported absolute weight gain. Risperidone is associated with less weight gain than olanzapine [8].

The results of the studies confirm clinically significant and substantial weight gain induced by antipsychotic treatment in drug-naive patients with first-episode schizophrenia and identify several risk factors for weight gain such as lower BMI scores, use of olanzapine, and a diagnosis of undifferentiated schizophrenia [9].

Another systematic review search of randomized, placebo controlled trials of ADPs in children and adolescents (<18 years old) was conducted until February 2010. In total, 31 randomized, controlled studies including 3595 pediatric patients were identified. A review of these data confirmed that APDs are associated with relevant cardiometabolic and endocrine side-effects, and that children and adolescents are more likely to experience antipsychotic induced hyperprolactinaemia, weight gain and associated metabolic disturbances. Ziprasidone was associated with the lowest weight gain, followed by aripiprazole, quetiapine and risperidone, which were intermediate, while olanzapine was associated with the highest weight gain. Significant weight gain appeared to be more prevalent in patients with autistic disorder who were also younger and likely less exposed to ADPs previously [10].

One pilot study focuses on the metabolic effects of risperidone in children and adolescents up to 16 years of age. Twenty-six children and adolescents aged 7 to 15.5 years were included. They all received risperidone from 1mg/day to a maximum of 6 mg/day. The results confirm a strong link between prescription of risperidone in EOS and risk of obesity [11].

These repercussions are more notorious in the case of second generation APDs (atypical drugs), though the risk level tends to
vary according to the different drug substances used. These drugs increase the activity of AMP kinase within the hypothalamus, blocking the activity of the H₁ histamine receptors [3]. In this way, medication might interfere with central nervous functions regulating energy balance; patients report an increase of appetite for sweet and fatty foods or “food craving”.

According to current concepts, appetite and feeding are regulated by a complex of neurotransmitters, neuromodulators, cytokines and hormones interacting with the hypothalamus, including the leptin and the tumor necrosis factor system. The pharmacologic mechanisms underlying weight gain are currently poorly understood: it may be induced by different activities at some receptor systems, but it may also be genetic predisposition. Understanding the metabolic consequences of ADPs (weight gain, diabetes, dyslipidemia) is essential: treatment with antipsychotic medication increases the risk of impaired glucose tolerance and diabetes mellitus [7]; ADPs affect satiety and energy homeostasis signaling; the specific peptides mediating these effects are unknown but probably overlap with those involved in idiopathic obesity; and single nucleotide polymorphisms in genes encoding known neurotransmitter receptors and metabolic proteins are promising pharmacogenomics targets for countering adverse affects. However, sophisticated molecular studies and genome-wide association studies, ideally in antipsychotic-naïve/first episode samples, are needed to further advance the field [8].

**OBJECTIVE**

In this study we propose to evaluate weight-related changes in a group of adolescents diagnosed with early onset schizophrenia who received atypical antipsychotic treatment with Risperidone.

**METHOD**

We included 19 patients (age between 12 and 17) with very early-onset and early-onset schizophrenia diagnosed according K-DSATS. During this trial they received treatment with risperidone in doses up to 2 to 4 mg/day and trihexifenidinum (2 to 4mg/day) to prevent extrapyramidal adverse effects. Their weight and BMI were measured at baseline and after 6 months of antipsychotic treatment.

**RESULTS**

The group included in the study had the following gender distribution (Figure 1):
55% of patients are male; 45% of patients are female.

**Figure 1. Distribution by gender of the lot**

The evolution of weight after 6 months of antipsychotic treatment is represented in figure 2:

**Figure 2. Evolution of body weight after 6 months of treatment**

After 6 months of antipsychotic treatment all 19 patients gained weight. Weight higher than, or equal to 5 kg was considered significant weight gain. 58% of patients experienced a weight gain exceeding 5 kg (Figure 3).
After 6 months of antipsychotic treatment with risperidone 16% of patients were considered obese and 31% overweight (Figure 6).

A comparison between BMI at baseline and after 6 months of treatment is showed in figure 7.

**DISCUSSIONS**

After 6 months of antipsychotic treatment with risperidone the following results were obtained: 58% of patients experienced a significant increase in weight over 5 kg; the percentage of overweight patients increased from 28% to 31%; the percentage of obese patients increased from 5% to 16%.

Consistent with the literature data it can be concluded that antipsychotic treatment may be correlated with a significant weight gain and metabolic complications of obesity.

Understanding the side effects of APDs, including their metabolic consequences (weight
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gain, diabetes, dyslipidemia) is essential for psychiatrics to avoid, on the one hand, a risk of lack of compliance, a discontinuation of the pharmacological medication and also a risk of relapse and hospitalization.

CONCLUSIONS

Alternative treatment should be considered in some cases. Other antipsychotics may have a better benefit/risk ratio and they may be prescribed as a first prescription or as a switch.

A good collaboration between child- and adolescent psychiatrists, general practitioners and paediatricians is essential to maximize overall outcomes and to reduce the likelihood of premature cardiovascular morbidity and mortality especially in child and adolescents patient; The study is limited by the small number of patients included.

REFERENCES
