Review

RESP

Influence of the use of atypical antipsychotics in metabolic syndrome

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ABSTRACT

Objectives: To describe the possible relationship between the use of antipsychotic drugs and the presence of metabolic syndrome. Other objectives are to list the main side effects of antipsychotic treatment, and to determine if there is any pharmacological treatment that can contribute towards counteracting metabolic syndrome.
Material and method: A narrative bibliographic review was carried out of the following databases: PubMed, Cochrane, CINAHL, IBECS, LILACS and HealthCare. Preference in the selection process was given to clinical trials and systematic review articles or review articles and some articles that were considered relevant because of their content. The time period was limited to between January 2014 and November 2019. The languages were English and Spanish. Repeated articles and those that were not related to the objectives were rejected. The search criteria were: "antipsychotic AND metabolic syndrome"; "schizophrenia AND metabolic syndrome"; "bipolar disorder AND metabolic syndrome"; "metabolic syndrome AND suicide NOT disorder"; "metabolic syndrome AND prisons"; "metabolic syndrome AND prolactin".
Results: 24 articles were selected out of the 510 that were consulted. The relationship between atypical antipsychotics and metabolic syndrome was evident. Other anticholinergic, antidopaminergic effects, extrapyramidal syndromes, neuroleptic malignant syndrome, hypotension, arrhythmias, sedation, hypovitaminosis D, increased prolactin, sexual dysfunction, sleep disturbances, etc. are also highlighted. Pharmacological associations with other drugs were also found.
Discussion: There is a relationship between the use of atypical antipsychotics and weight gain, lipid disorders, glucose and high blood pressure. There are some associated drugs that decrease some symptoms (ranitidine, topiramate, metformin, melatonin, modafinil). Patients taking this type of medication should be monitored and encouraged to lead healthy lifestyles.

Keywords: metabolic syndrome; antipsychotics; schizophrenia; bipolar disorder; prolactin; prisons.

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INTRODUCTION

The term metabolic syndrome (MS) was first used by the Swedish physician, Eskil Kylin, in 1923, to refer to the association between high blood pressure, increased blood glucose and the appearance of hyperuricemia[1]. At the end of the 1980s it was called "syndrome X" by Dr. Gerald Reaven, in reference to a set of metabolic changes and high blood pressure, to which insulin resistance was added as a principal factor[2].

Different classifications[3] were added over the years, depending on the bodies that defined them or the criteria used, as shown in Table 1.

In order to group the different definitions together, a unification of criteria was established in 2009, which was published under the title of "Harmonising metabolic syndrome"[4], in which the presence of at least three of the following criteria were regarded as a diagnosis of metabolic syndrome:

- Increase of abdominal circumference: specific definition depending on the population and country.
- Increase of triglycerides equal to or over 150 mg/dL (or receiving specific lipid lowering treatment).
- Reduction of HDL (high-density lipoproteins) cholesterol to below 40 mg% in men and 50 mg% in women (or receiving treatment with drugs that act on HDL cholesterol).

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- Systolic blood pressure (SBP) ≥ 135 mmHg and diastolic blood pressure (DBP) ≤ 85 mmHg (or receiving treatment for high blood pressure).
- Fasting blood glucose ≥ 100 mg/dL (or receiving treatment for high blood sugar).

Metabolic syndrome is currently considered to be a set of risk factors that contribute towards the onset of cardiovascular diseases, and the development of diabetes mellitus 2.

The increase of MS over the course of the decade has taken on alarming dimensions. The prevalence of metabolic syndrome in the USA is estimated to be 34-50% of the population, and 10-30% in Europe. The syndrome is more common amongst men and increases notably with age. The current estimated prevalence in Spain is considered to be 24.3% of the adult population, and a major increase is expected to take place in the next few years as the result of an ageing population[5].

The use of neuroleptic and antipsychotic medication, especially the so called second-generation or atypical antipsychotics, also appear to be related to the onset of metabolic syndrome.

The prison population includes a large number of patients who present mental illnesses, as was shown in a recent study carried out at prisons in the Region of Valencia (Spain), where patients referred to psychiatric consultancies were monitored, of whom 81.4% presented a diagnosis of dual pathology, 67.2%, B cluster personality disorders, 13.7%, affective and/or anxiety disorders and 13.0% schizophrenic disorders[6].

Many of these patients receive treatment with second generation neuroleptics. The prescription rates for antipsychotics in prisons vary between 4% and 70% of the population, depending on the centres, and the most widely used ones are as follows: aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone, sulpiride and ziprasidone. It should be pointed out that in recent years the use of long-acting injectable antipsychotics (depot) has intensified in order to achieve better adherence to treatment[7].

Establishing links between MS and the use of second-generation neuroleptics opens up channels towards preventing a higher risk of cardiovascular disease and diabetes mellitus 2 in the prison population by monitoring patients who receive this type of treatment.

The main aim of this study is to describe the possible relationship between the use of second-generation antipsychotic drugs and the presence of metabolic syndrome.

The secondary objectives of the study include:

- List the main side effects of treatment with atypical antipsychotics.
- Determine the existence of a drug treatment that counteracts metabolic syndrome.

Table 1. Criteria for classification of metabolic syndrome.

WHO (1999)	NCEP (2005) ATP III	IDF (2006)
High glucose and 2 or more of following criteria:	3 or more of following criteria:	High risk abdominal circumference and 2 or more criteria:
Glucose >110 mg/dL	Glucose >100 mg/dL or receiving treatment for diabetes	Glucose >100 mg/dL or diagnosed with diabetes
HDL chol. <35 mg/dL (men)	HDL chol. <40 mg/dL (men)	HDL chol. <40 mg/dL (men)
HDL chol. <40 mg/dL (women)	HDL chol. <50 mg/dL (women) or undergoing treatment	HDL chol. <50 mg/dL (women) or undergoing treatment
Triglycerides >150 mg/dL	Triglycerides >150 mg/dL or undergoing treatment	Triglycerides >150 mg/dL or undergoing treatment
BP >140/90 mmHg	BP >130/85 mmHg or undergoing treatment	BP >130/85 mmHg or undergoing treatment
Abd. C >90 cm (men)	Abd. C >102 cm (men)	Abd. C >94 cm (men)
Abd. C >85 cm (women)	Abd. C >88 cm (women)	Abd. C >80 cm (women)

Note. ATP III: Adult Treatment Panel III; chol.: cholesterol. HDL: high density lipoproteins; IDF: International Diabetes Federation; NCEP: National Cholesterol Education Program; WHO: World Health Organisation; P. Abd. C.: abdominal circumference; BP: blood pressure.

MATERIAL AND METHOD

A narrative bibliographical review of the scientific literature was carried out by running a bibliographical search of the following date bases: Cochrane, PubMed, CINAHL, IBECS, LILACS, HealthCare, in the Library of the Jaume I University of Castellon.

Descriptors in Spanish included in the Descriptores en Ciencias de la Salud (Health Sciences Descriptors) were used, along with the English descriptors in Medical Subject Headings (MeSH), as shown in Table 2.

Combinations were made with Boolean operators using "AND" and sometimes the operator "NOT", which discards references that are not wanted in the search and so reduce the number of references.

The combinations used in the searches were: "antipsychotic AND metabolic syndrome"; "schizophrenia AND metabolic syndrome"; "bipolar disorder AND metabolic syndrome"; "metabolic syndrome AND suicide NOT disorder"; "metabolic syndrome AND prisons"; "metabolic syndrome AND prolactin".

The language limits consisted of publications in Spanish and English and the period of publication was limited to between January 2014 and November 2019.

The inclusion criteria used were: preferably all randomised clinical trials with a comparison group, as well as original systematic review or review articles, original articles that were relevant for their content or related to the objectives of this study.

The exclusion criteria consisted of rejecting those articles that were repeated in different searches, those that had no relationship with metabolic syndrome, articles that discussed genetic links or biochemical processes with different products, and descriptive studies that were limited to a very specific population or sample, along with editorials, letters and opinion articles.

After applying these strategies, a total of 510 articles were identified, of which 478 were eliminated for not meeting the inclusion criteria or because they had one or more of the exclusion criteria (Figure 1).

Twenty four articles were selected for the review, of which: 3 were clinical trials, 11 were review articles; 2 were quasi-experimental studies, and 8 were cross-sectional studies.

RESULTS

The studies of Ijaz et al, and those carried out by Jeon and Kim described changes related to metabolic syndrome in the form of weight gain, changes in lipid metabolism, glucose levels and blood pressure[8,9].

Alongside these changes, there were also a number of cognitive disorders in schizophrenics such as: changes in processing speed, attention, working memory, verbal learning and memory, visual learning and memory, reasoning, problem-solving, social cognition, etc., whose relationship with the antipsychotics was not entirely clear, since there were variables in the studies that could act as confounding factors, such as: the patients' age, duration, stage of the disease, degree of adherence to medication, appearance of extrapyramidal effects, etc., that could complicate the relationship of improvement between the antipsychotics and cognitive functions. There is evidence in the scientific literature that highlights the fact that the relationship between antipsychotics, cognition and

Table 2. Terms used in bibliographical search.

Key words			
MesH		DeCS	
Spanish	English	Spanish	English
Antipsicótico	*Antipshycotic*	Antipsicótico	*Antipshycotic*
Síndrome metabólico	*Metabolic syndrome*	Síndrome metabólico	*Metabolic syndrome*
Esquizofrenia	*Schizophrenia*	Esquizofrenia	*Schizophrenia*
Trastorno bipolar	*Bipolar disorder*	Trastorno bipolar	*Bipolar disorder*
Prolactina	*Prolactin*	Prolactina	*Prolactin*
Suicidio	*Suicide*	Suicidio	*Suicide*
Prisiones	*Prisons*	Prisiones	*Prisons*

Note. DeCs: Descriptores en Ciencias de la Salud; MeSH: Medical Subject Headings

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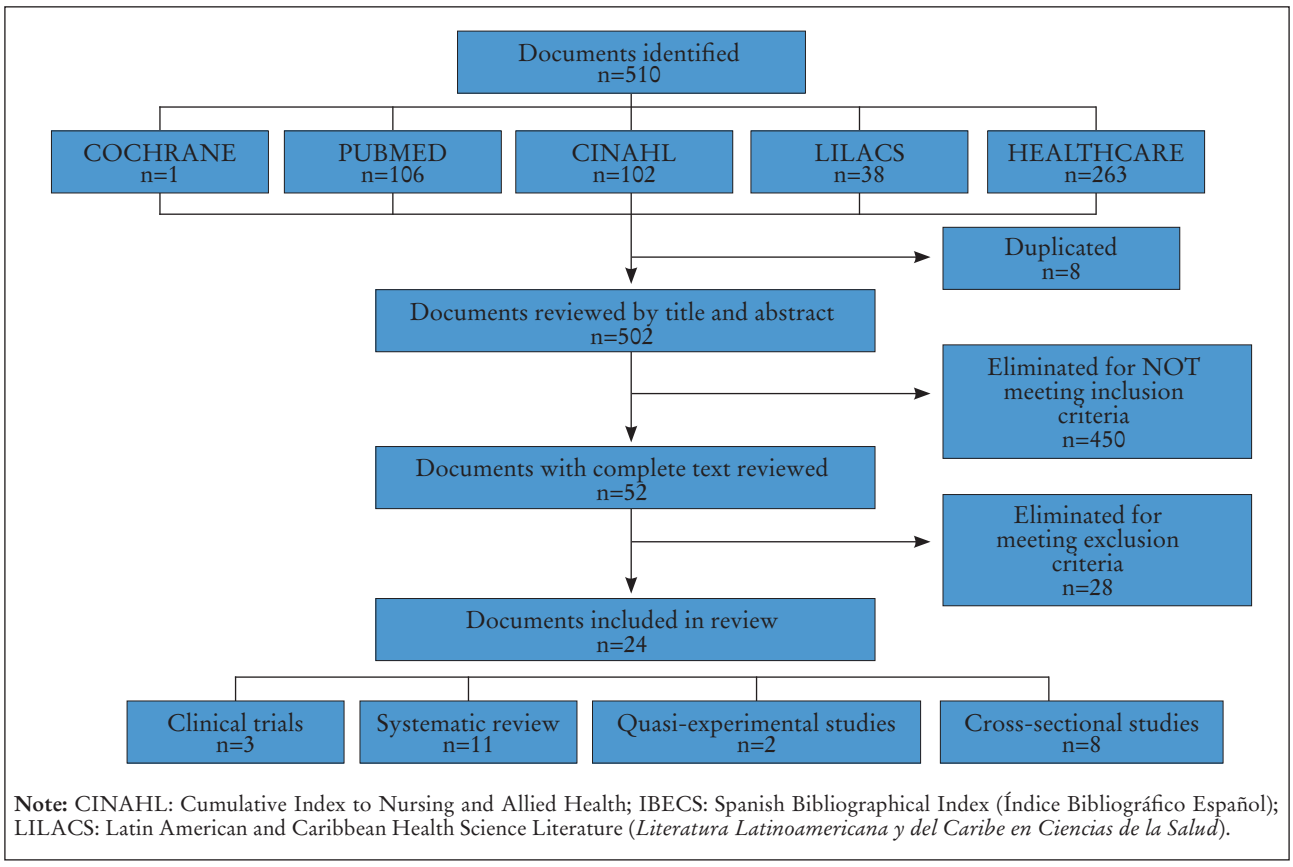

Note: CINAHL: Cumulative Index to Nursing and Allied Health; IBECS: Spanish Bibliographical Index (Índice Bibliográfico Español); LILACS: Latin American and Caribbean Health Science Literature (*Literatura Latinoamericana y del Caribe en Ciencias de la Salud*).

Figure 1. Flowchart of study.

metabolic effects is scarce, but that there is some kind of link between metabolic comorbidity and worsened cognitive function[10].

Reese et al. highlighted the anticholinergic, antidopaminergic and extrapyramidal effects, neuroleptic malignant syndrome, low blood pressure, arrhythmias and even sedation during treatment with antipsychotics[11]. Furthermore,, Rohatgi et al. included the respiratory variable in this group of effects, where according to their study the link between metabolic syndrome caused by drug treatment and the likelihood of developing obstructive sleep apnoeas was 15 times higher than in the rest of the population[12].

Fond et al. showed that 27.5% of the subjects who suffered from schizophrenia, severe depressive disorder and cognitive disorders and who were treated with antipsychotics presented hypovitaminosis D[13].

In a study by Auriemma et al., mention is made of another effect of metabolic syndrome in this type of pathology: changes in levels of glucose related to increased prolactin caused by treatment with antipsychotics in approximately one third of patients, thus creating a situation of overweight and obesity[14].

Osmanova et al. calculated that 48.1% of patients receiving antipsychotic treatment presented sexual dysfunctions as a result of increased prolactin in the bloodstream, attributed to the use of some atypical antipsychotics such as risperidone, which are more likely to create hyperprolactinaemia, due to the blockage they cause in type D2 dopaminergic receptors[15]. Kirino discovered that the use of aripiprazole (alone and in combination with other drugs) was advisable in that it reduced this type of effect thanks to its low affinity to D2 receptors acted on by dopamine, which enabled it to act as a functional agonist and antagonist at the same time, depending on the levels of circulating dopamine, but independently of the levels of serum prolactin, such as the dopamine agonists[16]. Thus, the use of aripiprazole prevented hyperprolactinaemia and any resulting secondary sexual dysfunction.

Porfirio et al. suggested nocturnal administration of melatonin to patients treated with second-generation antipsychotics. This idea was based on

the fact that melatonin is a nocturnally secreted endogenous indolamine that regulates the circadian cycle. One curious effect of antipsychotics is that they can cause sleep disorders, and circadian imbalances can influence the hormones involved in metabolic regulation, such as insulin, leptin and ghrelin. A link has also been demonstrated between obesity and reduced sleep, and sleep deprivation in rats has been associated with hyperphagia. The central and peripheral, direct and indirect metabolic effects of melatonin are geared towards most of the metabolic disorders reported during and after treatment with second-generation antipsychotics in children, adolescents and adults[17].

Sağlam Aykut and Özkorumak Karagüzel discovered that the use of second-generation antipsychotics in injected form with depot properties created greater adherence to them, making them very useful for all types of patients. This study, in which depot formulae were compared to habitual drugs taken orally, showed that the abdominal circumference and triglycerides were lower when using depot preparations than when taking daily oral doses. HDL cholesterol was also seen to increase more in patients using depot preparations[18].

Rakhshan et al. found in a randomised clinical trial that establishing an education programme based on perceptions of the disease and lifestyle of patients with metabolic syndrome provided significant improvements in every dimension[19]. Schmitt et al. also found that physical exercise (principally aerobic), along with psychosocial and dietary interventions, improved cognitive deficits, severity of symptoms, depression quality of life and overall functioning of people who suffer from these types of disorders[20].

As regards the second objective, some studies were found, such as the one by Siskind et al., which showed certain associations of drugs to minimise the effects of metabolic syndrome. An example is the use of an oral anti-diabetic such as metformin taken in conjunction with clozapine, which reduces the level of metabolic syndrome amongst patients[21].

Gu et al. also commented on the association of ranitidine and antipsychotics that cause weight gain to bring about a reduction in weight[22], which is also related to the study by Narula et al. with the association of topiramate to reduce weight gain caused by olanzapine[23].

Auger et al. observed that nutritional doses of curcumin (contained in Curcuma longa extract) given to mice partially counteracted metabolic disorder induced by risperidone, which suggests that curcumin should be tested to establish if it reduces the capacity of risperidone to generate metabolic syndrome in humans[24].

Modafinil is a non-stimulant drug that is marketed mainly for narcolepsy and daytime sleepiness associated with obstructive sleep apnoea. Clinical experiences and the summary of the characteristics of the drug also mentioned anorexia as one of the side effects. This could have a direct impact on the consumption of carbohydrates and fats, which may in turn regulate the dyslipidaemia caused by antipsychotics and hyperglycaemia. Prasuna et al. carried out a clinical trial on patients being treated with antipsychotics in which one branch was treated with modafinil and an antipsychotic, while the other received an antipsychotic with a placebo. It was found that the group treated with modafinil had a significant drop in fasting serum cholesterol from week 3 to week 12. However, it should not be regarded as a medication for high cholesterol as statins are in controlling hyperlipidaemia[25].

DISCUSSION

There is evidence in the scientific literature that provides a degree of proof that the treatment of patients with schizophrenia, bipolar disorders and pathologies that require the use of atypical or second-generation antipsychotics can also lead to changes related to metabolic syndrome in the form of weight gain, changes in lipid metabolism, glucose levels and blood pressure[8,9]. There are other drugs, such as the ones described in the previous section that, taken in combination with some atypical antipsychotics, can contribute towards reducing the symptoms of metabolic syndrome. There is a growing body of knowledge about the functional mechanisms although more research is needed in this regard.

For all these reasons, monitoring systems need to be implemented for all patients undergoing treatment with atypical antipsychotics, with adequate adjustments to dosage, avoiding the use of multiple combinations of antipsychotics, checking weight, BMI, abdominal circumference, blood pressure, prolactin levels and ECG tests[26]. This type of monitoring has been carried out on prison patients, and has brought about a decrease in the prevalence of metabolic syndrome, along with a drop in the number of prescriptions for neuroleptic drugs over time[27].

The importance of nursing staff cannot be overemphasised, especially those specialising in mental health, in terms of monitoring patients undergoing treatment and in having sufficient knowledge and

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strategies to act using scientific evidence and so eliminate those risk factors that can be avoided[28,29].

It should be borne in mind that one of the major problems facing public health comes from overweight and obesity, which some authors have not hesitated in referring to as "the epidemic of the 21st century".

A pioneering multi-centre study was carried out on the Spanish prison population to detect chronic diseases and risk factors. One of the most striking findings was weight, showing percentages of overweight of 39.6% and obesity of 12.3% in the populations studied. This means one out of every two inmates'[30] weight is abnormal (51.9%). If the amount of atypical antipsychotics used in this setting is added, then it is more than necessary to transmit how important it is to control and monitor such patients, in order to reduce the risk of mortality and morbidity.

The main methodological limitation of this narrative review is the heterogeneous nature of the study designs, in which the quality of the scientific evidence given was not evaluated, and although most of the review articles were included, clinical trials were few in number.

Reviews such as this one should also raise awareness of the important role played by nursing professionals in proposing and establishing programmes geared towards eliminating the risk factors that can be avoided. They should also actively participate in raising awareness of daily physical exercise, provide education about eating habits and generally contribute towards promoting an adequate culture of health[20].

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