Atypical antipsychotics: analysis of adverse events

Antipsicóticos atípicos: análise dos eventos adversos

Los antipsicóticos atípicos: análisis de eventos adversos

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Abstract

The aim was to identify adverse events arising from the continued use of atypical antipsychotics through cohort and case control studies, carried out on a worldwide level, in the period from 2013 and 2014. Method: A literature review was performed from an exploratory study seeking cohort and case control studies about atypical antipsychotics with bibliometrics application according to Bradford's Law. Results: The study resulted in 291 surveyed articles, of which 18 were selected and analyzed. Conclusion: the main findings were cardiovascular risk, QT interval prolongation, diabetes, increased body mass index, extrapyramidal effects.

Keywords: antipsychotic, schizophrenia, events.

Resumo

O objetivo foi identificar eventos adversos decorrentes do uso contínuo de antipsicóticos atípicos através de estudos de coorte e de caso-controle, realizados em nível mundial, no período de 2013 e 2014. Método: foi realizada revisão da literatura a partir de um estudo exploratório buscando estudos de coorte e caso-controle sobre antipsicóticos atípicos com aplicação de bibliometria, de acordo com a lei de Bradford. Resultados: O estudo resultou em 291 artigos pesquisados, dos quais 18 foram selecionados e analisados. Conclusão: os principais achados foram de risco cardiovascular, prolongamento do intervalo QT, diabetes, índice de massa corporal aumentada, efeitos extrapiramidais.

Palavras-*chave:* antipsicóticos, esquizofrenia, events.

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Resumen

El objetivo fue identificar eventos adversos derivados de la utilización continuada de antipsicóticos atípicos a través de estudios de cohortes y caso-control, llevó a cabo en todo el mundo en el período comprendido entre 2013 y 2014. Método: una revisión de literatura se llevó a cabo un estudio exploratorio para estudios de cohortes y caso-control sobre antipsicóticos atípicos con aplicación de bibliometría, según la ley de Bradford. Resultados: el estudio resultó en los 291 artículos encuestados, de los cuales 18 fueron seleccionados y analizados. Conclusión: los resultados principales fueron de riesgo cardiovascular, síndrome de QT largo, diabetes, aumento del índice de masa corporal, efectos extrapiramidales.

Palabras clave: antipsicótica, esquizofrenia, eventos.

Introduction

Antipsychotics are used in the primary treatment for all stages of schizophrenia. They are not absolute therapies and their use is not devoid of problems. The low therapeutic response and side effects are the main causes of relapse of patients, impairing the quality of life and generating extra care and hospital admissions that increase treatment costs. One type of classification for these drugs is according to their typicality, which may be typical or atypical. According to the Ministry of Health[(1)] this classification is obsolete, but it is observed that its use is largely found in the literature[(2)].

Schizophrenia is a chronic mental illness in which patients have difficulty recognizing reality, of behaving within the social parameters of normality and even to perform self-care and personal hygiene tasks. It is the most serious mental illnesses, affects around two million Brazilians and is surrounded by taboos and prejudices, due to the ignorance of most people about this disease[(3)].

Atypical antipsychotics (AA) have been used increasingly to treat patients with a variety of psychotic disorders and severe behavioral disorders. In the last decade, clinicians and researchers are on alert to the potential adverse effects from the use of AA, which may be related to weight gain, hyperlipidemia and glucose intolerance. The low therapeutic response of antipsychotics and side effects are the main causes of relapse of patients, impairing the quality of life and generating extra care and hospital

admissions that increase treatment costs[4-5].

Adverse events are defined as unintentional damage, which can lead to temporary or permanent disability, prolonged hospitalization or death, as a result of care provided to the patient and not by the evolution of the disease[6-7].

The cost of treating schizophrenia is 1.5 to 3.0% of the annual health budget in developed countries[8]. In a study conducted in three health services in the city of São Paulo(Brazil) - one state public hospital, one hospital that is linked to the Unified Health System and one psychosocial care center - showed the average direct cost medical and hospital of relapse in schizophrenia, per patient, which was R$ 8,167.58 (US$ 4,083.50) in the state public hospital, R$ 4,605.46 (US$ 2,302.76) in psychosocial care center and R$ 2,397.74 (US$ 1,198, 50) in the hospital linked to the Unified Health System. The main component was the daily cost (87% to 98%). The cost with atypical antipsychotics was higher than that with typical antipsychotics[9].

Because of the strong relation between the use of AA and the incidence of adverse events in the treatment of schizophrenia, it is necessary to characterize these events to the appropriate monitoring of patients using these drugs.

The aim of the study was to identify adverse events arising from the continued use of atypical antipsychotics through cohort and case control studies, carried out on a worldwide level in the years 2013 and 2014.

Methodology

A literature review was performed from an exploratory study seeking cohort and case control studies about AA with application of bibliometry.

The bibliometry has three basic laws: Bradford's Law (periodicals productivity), Lotka's Law (authors productivity) and Zipf's Law (frequency of words occurrence)[10].

The bibliometry technique was applied, according to Bradford's Law. The emergence of bibliometry took place in the early twentieth century in order to study and evaluate the production and scientific communication activities. Bibliometry is understood as the "quantitative technique and statistical measurement of production index and dissemination of scientific knowledge"[11].

Scientific publications were collected using to search the

descriptors: antipsicóticos atípicos coorte, antipsicóticos atípicos caso controle, atypical antipsychotics cohort, atypical antipsychotic case control, cohorte antipsicóticos atípicos, antipsicóticos atípicos casos y controles. Searches were conducted in the databases US National Library of Medicine's® (MEDLINE, PubMed), Scientific Electronic Library Online (SciELO), Virtual Health Library (BVS).

The inclusion criteria of used articles were: have been found by the descriptors; published between January 2013 and December 2014; are published in Portuguese, English or Spanish in any country in the world; and are characterized as cohort studies or case control studies.

The exclusion criteria used were: those who not fit as cohort and case control studies, not having types of adverse events to the AA use and articles not available as full text.

It was found 291 articles in Pubmed database by descriptor *Atypical antipsychotics cohort* with 27 in 2013 and 14 in 2014 (August) and 275 by descriptor *Atypical antipsychotics case control* being 15 in 2013 and 6 in 2014. In the Scielo database was found only 1 article.

Articles in duplicate were excluded as well as those who had no adverse events to AA use.

Although they have limitations, observational cohort and case-control studies were chosen for providing evidence on the incidence in chronic conditions such as the use of drugs for the treatment of psychiatric disorders, in the case of schizophrenia.

Results

Through the methodology were found 18 articles that fall within the established criteria (Table 1).

Table 1: Selected articles with their respective authors, countries, years of publication and type of study.

Author	Article	Country	Year	Type of Study
12	Antipsychotics and the Risk of Diabetes Mellitus Type 2 in Children and Youth.	USA	2013	cohort
13	Endothelial nitric oxide synthetase genetic variants, metabolic syndrome and endothelial function in schizophrenia.	USA	2013	cohort

14	Psychotropic drug initiation or increased dosage and the acute risk of falls: a prospective cohort study of nursing home residents.	USA	2013	cohort
15	Antipsychotics Prescription and Cerebrovascular Events in Italian Older Persons.	Germany	2013	Case control
16	Atypical Antipsychotic Drugs and Pregnancy Outcome: A Prospective, Cohort Study.	Germany	2013	cohort
17	Investigation of Peripheral Hypothalamic Neurohormone Levels in Psychotic Patients.	Turkey	2013	Case control
18	Risk of incident stroke in patients with Alzheimer disease or vascular dementia.	USA	2013	Case control
19	Antipsychotics and the Risks of Sudden Cardiac Death and All- Cause Death: Cohort Studies in Medicaid and Dually-Eligible Medicaid-Medicare beneficiaries of Five States.	USA	2013	cohort
20	Risk of Mortality (Including Sudden Cardiac Death) and Major Cardiovascular Events in Atypical and Typical Antipsychotic Users: A Study with the General Practice Research Database.	UK, USA	2013	cohort
21	Comparative Safety of Antipsychotics: Another Look at the Risk of Diabetes.	Canada	2013	cohort
22	Length of mechanical restraint following haloperidol injections versus oral atypical antipsychotics for the initial treatment of acute schizophrenia: a propensity-matched analysis from the Japanese diagnosis procedure combination database.	Japan	2013	Case control
23	The Association between Cataract Surgery and Atypical Antipsychotic Use: A Nested Case-Control Study.	Canada	2013	Case control
24	Associations between risk of mortality and atypical antipsychotic use in vascular dementia: a clinical cohort study.	UK	2013	cohort
25	Older men with dementia are at greater risk than women of serious events after initiating antipsychotic therapy.	Canada	2013	cohort
26	Antipsychotic Drug Use and the Risk of Venous Thromboembolism in Elderly Patients With Dementia.	Germany	2013	Case control
27	Depot Typical Antipsychotics versus Oral Atypical Antipsychotics in Relapse Rate Among Patients with schizophrenia: A Five - Year Historical Cohort Study.	Iran	2014	cohort
28	Atypical antipsychotics and hyperglycemic emergencies: Multicentre, retrospective cohort study of administrative data.	Canada	2014	cohort

29	Predictors of mortality in atypical antipsychotic-treated community-dwelling elderly patients with behavioural and psychological symptoms of dementia: a prospective population-based cohort study from Italy.	Italy	2014	cohort

Source: Elaborated by the authors

In the studies were evaluated the effects of atypical antipsychotics for schizophrenia and other conditions such as dementia in the elderly, bipolar disorder, etc. The evaluated populations are mostly adults and elderly and were also present children and pregnant women. The works were found only in the English language and published in 8 countries, and in Brazil was not identified any study.

The atypical antipsychotics included in the studies are described in Figure 1 with the respective article numbers.

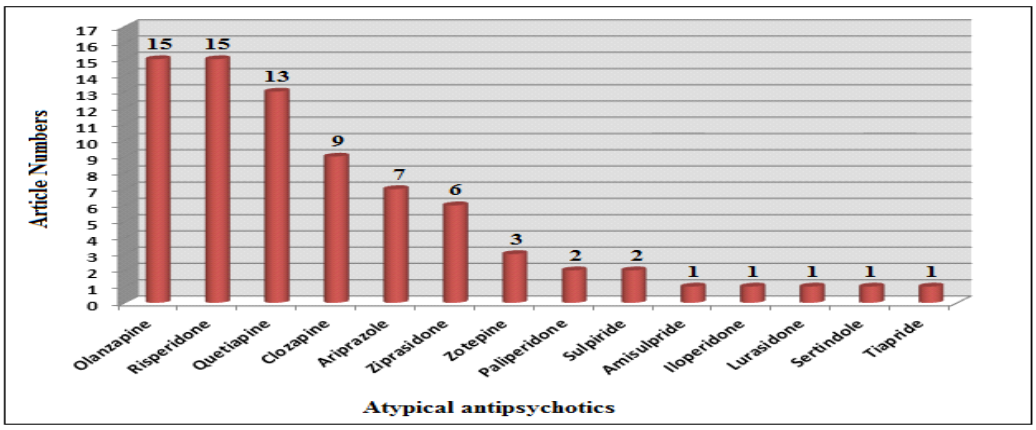

Figure 1 - Number of citation of articles by atypical antipsychotic.

Source: Elaborated by the authors

The cohort study of Bobo et al.[12] showed an increased risk of developing Diabetes Mellitus type 2 in children and adolescents using risperidone, quetiapine and olanzapine (HR = 3.14 [95% CI = 1.50 – 6.56]). In another cohort study of Lipscombe et al.[28], it was found a higher risk of hyperglycemia in elderly patients with diabetes using risperidone [adjusted hazard ratio, 95% confidence interval (CI): 0.69, 0.53 - 0.90]. The risk for hyperglycemic emergencies is low after the onset of antipsychotic drugs, but patients with pre-existing diabetes may be at higher risk. The lower risk

appeared with the use of quetiapine in older patients, but the clinical significance of the results requires further study. Another cohort study of Moisam et al.[21] opposed to the studies cited previously because it was not shown higher risk of Diabetes type 2 with the use of atypical antipsychotics in adults taking clozapine, olanzapine, quetiapine and risperidone. The use of antipsychotics was also related to cardiac and vascular events. In cohort study of Burghardt et al.[13] was researched the endothelial dysfunction due to loss of genetic protection afforded by nitric oxide. A significant association was demonstrated, where the variant eNOS T-786C (F = 3.65, p = 0.02) and smoking (F = 6.03, p = 0.01) for those without metabolic syndrome, contributed to the meaning of the entire model (F (6,108) = 3.39, p = 0.004). The study was conducted with adult patients using AA olanzapine, clozapine, quetiapine, risperidone, ziprasidone, iloperidone, paliperidone and ariprazol.

A higher risk of transient ischemic attack development in patients with Alzheimer's disease [4.5 (2.1-9.2) CI 95%] was evidenced in the case-control study of Imfeld et al.[18] with elderly patients using risperidone, quetiapine and olanzapine.

In case control study of Schemedt and Garbe[26] an increased risk of venous thromboembolism (VTE) was observed in patients using the combination of AA and conventional antipsychotics. Increased VTE risk was found for current users (OR, 1.23; confidence interval of 95% [CI], 1.01 Y 1.50) and for users with a combination of AA and conventional antipsychotics (OR, 1.62; 95% CI, 1.15 Y 2.27). In the current users of that study, the use was associated with an increase of the risk (OR, 1.63; 95% CI, 1.10 Y 2.40). In a cohort study of Sultana was found that the AA use in vascular dementia does not significantly increase the mortality risk (HR = 1.05) of elderly patients using olanzapine, quetiapine and risperidone.

The risk was also identified in the cohort study of Thomas et al.[20] that identified a higher mortality for any cause, cardiac death and sudden cardiac death with antipsychotics in general compared to non-psychiatric control population, but the risk with AA is lower than the risk with typical antipsychotics. The RR of cardiac mortality is 2.39 in patients between 30 and 64 years of age.

However, in relation to vascular events, was obtained lower association with the use of AA for cerebrovascular

events (typical OR, 1.3 [95% CI, 0.9 Y 1.9]; atypical OR, 0.9; [95% CI, 0.7 Y 1.2]) in cohort study of Franchi et al.[15].

Yanik et al.[24], in his case-control study, found an increase in BMI (body mass index) of patients using risperidone. The treatment led to a significant increase in the levels of leptin in patients. The increase was about 60% after treatment (T 1.68 0.35 ng / mL) versus before the beginning of treatment (T 0.99 0.17 ng / mL), 0.05 LP.

Other types of adverse events found were: birth defects identified in infants born to mothers who used olanzapine, clozapine, quetiapine, risperidone, ziprasidone, aripiprazole, zotepine, amisulpride [16,30]. Postnatal disorders (considering exposed live births, at least during the last week of gestation): cohort study against comparison cohort II: crude OR, 4.18 (95% CI, 2.62 Y 6.65); Adjusted OR (95% CI, 3.51 Y 11.10) 6.24; Comparison cohort I versus comparison cohort II: crude OR, 6.21 (95% CI, 3.54 Y 10.89); Adjusted OR (95% CI, 2.21 Y 11.44) 5.03 [30].

In addition, a protective association of the AA use and a lower risk of cataract were observed. According Pakzad-Vaezi et al.[23], a lower cataract surgery rate (adjusted proportion, 0.70; 95% of confidence interval, 0.65 - 0.75) was found in patients taking clozapine, olanzapine , quetiapine and risperidone in a case-control study with an elderly population.

The AA were more effective in the acute treatment of schizophrenia. There was less need for mechanical restraint with adult patients using risperidone and olanzapine. Compared with the AA group, the relative risk (RR) for the haloperidol group was 1.15 (95% CI, 0.95 - 1.40, p¼ 0.15)[22].

In Table 2 were cited other adverse events and associations identified in the articles.

Table 2. Adverse events and other associations related to the use of AA and respective authors.

Author	Adverse events and other associations
12	Diabetes Mellitus type 2
13	Endothelial dysfunction
14	Risk of falling equal to atypical and typical
15	Lower association of atypical with cerebrovascular events
16	Postnatal Disorders
17	Mortality in vascular dementia
18	Higher risk of transient ischemic attack development in patients with Alzheimer's disease
19	Cardiovascular events and death
20	Mortality for any cause, cardiac death and sudden cardiac death
21	It was not demonstrated increased risk of Type 2 Diabetes
22	Less need for mechanical restraint in the acute treatment of schizophrenia.
23	Lower risk of developing cataracts
24	Increased BMI (body mass index)
25	Risk of serious adverse events (not specified)
26	Risk of venous thromboembolism
27	Lower number of relapses with AA oral doses than deposit AT
28	Hyperglycemia in diabetics
29	Deaths, Extrapyramidal symptoms, Strokes

Source: Elaborated by the authors

Discussion

The AA have unique benefits in relation to typical, reduced risk of extrapyramidal effects and tardive dyskinesia, but its use has been associated with the increase of cardiovascular risk because of other complications such as: weight gain, diabetes mellitus and dyslipidemia. Because of the association between these metabolic alterations and the cardiovascular disease, the AA have received growing attention from the psychiatric literature, and just recently clinicians and researchers began to assess the relation between the use of drugs and schizophrenia within the cardiovascular risk context [4,12,19-20,21-24].

The atypical antipsychotics more used in the studies are olanzapine, risperidone and quetiapine. This is due to the highest frequency of use of these drugs compared to other atypical, this same relation is found in other studies [9,12,28].

A study carried out in Santa Catarina showed that the antipsychotic haloperidol and risperidone presented best cost-effectiveness compared to olanzapine. Haloperidol is most likely to adverse effects, relapses and hospitalizations, situations that affect the patient's quality of life compared to AA, and olanzapine, in spite of showed

a higher effectiveness than haloperidol, has a higher cost[32].

Clozapine was also quite found in studies what is justified for being the reference antipsychotic in refractory cases of schizophrenia having greater efficacy on positive symptoms of the disease[33]. However, the use of clozapine is associated with a significant increase of the risk of incident diabetes mellitus 2 compared with the use of haloperidol and risperidone. Regarding to quetiapine, there is less association with the risk of incident diabetes mellitus to the use of conventional antipsychotic.

Antipsychotics are related to a higher cardiovascular risk. Olanzapine has a higher cardiac safety profile compared to chlorpromazine and haloperidol. Risperidone has cardiac safety profile similar to olanzapine, and quetiapine is associated with a lower risk[19].

The risk of acute cardiovascular event in young and middle-aged patients using olanzapine, quetiapine or risperidone are similar, being 5.3 / 1000 to olanzapine, 3.4 to quetiapine and 5.2 to risperidone, when used as single drugs [5,31].

The use of AA in the study by Wang et al [34] in Taiwan was associated with a decrease in the rate of mortality after ischemic stroke by 86% (OR 0.14; 95% CI 0.12-0.17), however, with typical antipsychotics the decrease in the mortality rate was 78% (OR = 0.22; 95% CI 0,18-0,26).

The association between the use of atypical antipsychotics and weight gain are due to an early deficiency in glucose metabolism induced by these drugs (TEFF) and to the increase of leptin levels during treatment[4].

The use of AA can bring risks to the fetus during pregnancy. According to the Food and Drug Administration (FDA), newborns exposed to these drugs in the last week of pregnancy are at increased risk of postnatal disorders[35] .This brings concerns about the safety of pregnant women, since the prescription of atypical antipsychotics before and during pregnancy is increasing. However, pregnancy is strongly associated with women discontinuing treatment with antipsychotics[30].

It was evident that AA may represent safer initial options than the typical, after the alternative therapies have been exhausted[36].

Conclusion

In the study were not found cohort and case-control articles published in Portuguese and Spanish

within the search parameters, which shows a low production on the subject in Latin speaking countries and in the period surveyed.

Most studies were conducted in North America and Central Europe demonstrating the need for cohort and case-control studies in South America (Brazil) and Latin America and other countries in accordance with the socioeconomic and cultural context.

There is great difficulty in managing the treatment of schizophrenia, with high rates of relapse and modest pattern of improvement in efficacy assessments. AA have advantages over typical mainly by a superior safety profile, which can lead to a better treatment compliance.

The study showed that AA drugs are widely used in the world for the treatment of schizophrenia and other psychiatric diseases. These drugs are not immune to adverse events according to the Table 3 studies. It is necessary to emphasize the need for frequent monitoring of antipsychotic users with pre-existing morbidities or not.

The main findings are cardiovascular risk, QT interval prolongation, diabetes, increased body mass index and extrapyramidal effects. These effects can lead to relapse of patients if not properly monitored, being in this case less frequent with AA.

The contribution of the study was to provide more updated and systematized information at level of clinical evidence about adverse events arising from the use of AA, facilitating access for multidisciplinary teams and health managers.

Among the study's limitations are the difficulty in identifying an association between an adverse event and a single drug due to poly pharmacy.

There is no conflict of interest.

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