

Systematic Review

*Corresponding author

Karine Zortea, PhD

Department of Schizophrenia Program
Hospital de Clínicas de Porto Alegre;
Postgraduate Program in Medicine:
Psychiatry, Universidade Federal do Rio
Grande do Sul, Porto Alegre 90035-903
RS, Brazil
Tel. +55 51 82433554
E-mail: karine.personaldiet@gmail.com

Volume 3 : Issue 2

Article Ref. #: 1000OROJ3124

Article History

Received: May 23rd, 2016

Accepted: July 12th, 2016

Published: July 13th, 2016

Citation

Franco VC, Zortea K, de Abreu PSB.
Obesity and clozapine use in schizo-
phrenia. *Obes Res Open J.* 2016;
3(2): 24-29. doi: [10.17140/OROJ-3-124](https://doi.org/10.17140/OROJ-3-124)

Copyright

©2016 Zortea K. This is an open access article distributed under the Creative Commons Attribution 4.0 International License (CC BY 4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Obesity and Clozapine Use in Schizophrenia

Viviane Carvalho Franco, MSc^{1,2}; Karine Zortea, PhD^{1,2*}; Paulo Silva Belmonte de Abreu, PhD^{1,2,3}

¹Department of Schizophrenia Program, Hospital de Clínicas de Porto Alegre, Porto Alegre 90035-903, RS, Brazil

²Postgraduate Program in Medicine: Psychiatry, Universidade Federal do Rio Grande do Sul, Porto Alegre 90035-903, RS, Brazil

³Hospital de Clínicas de Porto Alegre, Serviço de Psiquiatria, Laboratório de Psiquiatria Molecular, Porto Alegre 90035-903, RS, Brazil

ABSTRACT

Introduction: Schizophrenia is a chronic mental disorder, and treatment is based on the use of antipsychotics, such as clozapine. These drugs have been associated with obesity and metabolic changes.

Objective: A systematic review to assess the association of obesity with the use of clozapine in schizophrenic patients.

Method: It was made a search for articles in PUBMED and Capes of the regular databases with the keywords “Schizophrenia” “obesity” “clozapine” “weight gain”. The search included articles in English that were published between 2004 and 2015. We included only articles with retrospective studies and the following inclusion criteria: both sexes, patients older than 20 years, use of time of clozapine minimum of three months and sample size less than 50 individuals.

Results: They were selected 4 articles contemplated the inclusion criteria. In all items selected for this study, obesity was associated with clozapine.

Conclusions: There is a higher prevalence of overweight and obesity in patients with schizophrenia compared with the general population, this is due to some factors such as the use of atypical antipsychotics, such as clozapine.

KEYWORDS: Schizophrenia; Clozapine; Obesity.

ABBREVIATIONS: SZ: Schizophrenia; WHO: World Health Organization; BMI: Body Mass Index; IBGE: Brazilian Institute of Geography and Statistics; IMCI: Integrated Management of Childhood Illness; QoL: Quality of Life; WHR: Waist/hip ratio; WC: Waist Circumference.

INTRODUCTION

Schizophrenia (SZ) is a chronic mental disorder that affects about 1% of the world population, and mainly happens in the end of adolescence and the beginning of adulthood, regardless of gender or social groups.¹ It is a disease characterized by distortions in thoughts, bizarre delusions and changes in sensory perception and inappropriate emotional responses that lead patients to some degree of deterioration.²

Its symptoms differ among individuals and may afflict them gradually or explosively. These symptoms are still divided into negative or positive. Negative symptoms of SZ, facing decreased brain function, were described by Kaiser et al³ as defining this condition, as it often manifests itself together, and differs from other psychopathological conditions.

Negative symptoms described were: apathy, loss of pleasures in activities once the provided, unwillingness to start a behavior directed at a goal and poverty of speech. As the positives symptoms are the level of mental disorders such as delusions, distortion of thoughts, unreal perceptions, such as audio-visual hallucinations, excessive anxiety, impulses and aggression.

The treatment of SZ, focused on minimizing the symptoms, is based on the use of antipsychotics. These drugs are inhibitors of psychomotor functions (in excitation and stirring conditions) and minimize psychotic symptoms, such as delusions and hallucinations. These drugs can be classified as typical or atypical.

The major typical antipsychotic drugs block only D2 receptors. The atypical antipsychotic drugs are associated to lower risks of extrapyramidal effects, not block D2 receptors only, but also other monoamines, such as the 5HT-2. These include: Clozapine, Olanzapine, Quetiapine and Respiridona.⁴

Clozapine is a reference atypical antipsychotic, having distinct characteristics of the medications available before its release, which showed effective in 30% to 60% of psychoses that do not respond to traditional drugs, and low incidence of adverse effects, becoming the main indication for refractory schizophrenia. Atypical offer several important advantages over typical, including its characteristics of low risk of extrapyramidal symptoms such as akathisia, dystonia, parkinsonism and tardive dyskinesia, improved cognition, reduced suicide and minor depression compared with typical antipsychotics at clinically relevant doses.⁵

The use of antipsychotics is an important component in the clinical treatment of patients with schizophrenia, but has been associated with metabolic abnormalities⁵ and also obesity, diabetes, dyslipidemia, metabolic syndrome and high mortality.⁶

Associated with pharmacological treatment, nutritional and psychological treatments are very important in the improvement of the condition of these patients.⁷ Obesity is a non-transmissible chronic disease, which presents itself not only as a scientific problem, but also as a public health problem. The modern lifestyle with a more westernized diet, associated with a decrease in physical activity, converges to the increase in worldwide obesity.⁸

According to World Health Organization (WHO), obesity is defined as an abnormal fat accumulation that may impair health.⁹ Body mass index (BMI) is an index which correlates weight and height (kg/m²), thereby obesity is classified as BMI ≥ 30 kg/m².

The World Health Organization (WHO) projected that in 2005 the world would have 1.6 billion people over the age of 15 overweight (Integrated Management of Childhood Illness (IMCI) ≥ 25 kg/m²) and 400 million obese (BMI ≥ 30 kg/m²). The projection for 2015 is even more pessimistic: 2.3 billion people overweight and 700 million obese. These data indicate a 75% increase in obesity cases in 10 years.⁹

In 2010, the Brazilian Ministry of Health and the Brazilian Institute of Geography and Statistics (IBGE) released two large surveys of the numbers of overweight and obesity in Brazil, called "VIGITEL Brazil 2009: Risk and Protective Factors

Surveillance for Chronic Diseases using Telephone Survey and Household Budget Survey 2008-2009 (POF)".¹⁰

Studies showed an excess weight in 46.6% of the population, was higher among men (51.0%) than among women (42.3%). Already the POF (2008-2009) shows a steady increase of overweight and obesity in the population over 20 years of age over 35 years. Overweight nearly tripled among men, 18.5% in 1974-1975 to 50.1% in 2008-2009. In women, the increase was smaller: from 28.7% to 48%.⁹

Obesity is associated with a lower quality of life both in schizophrenic patients and the general population. This is due to eating disorders and metabolic disorders such as oxidative stress. These patients deserve greater attention in the management and intervention in weight.⁵

The objective of this study is to evaluate the association of obesity with the use of clozapine in schizophrenic patients, as explained above, there is an increasing prevalence of obesity in recent decades, which compromises the expectation and quality of life (QoL) of these patients.

MATERIALS AND METHODS

A review of the literature was conducted between 2004-2015 on obesity in schizophrenic patients with clozapine, and the association of this atypical antipsychotic with these conditions was the main target of this study.

This research used two databases: PubMed (MEDLINE) and Journal of Capes. The terms used in the search were: "Schizophrenia", "Obesity", "Clozapine" and "Weight gain".

The selection of items was conducted by a researcher, taking into account the following inclusion criteria: English language, both sexes, retrospective study, patients aged over 20 years, the minimum clozapine use time of three months and sample size equal or higher than 50 individuals.

For the extraction of data from the articles was prepared a card (Table 1).

Data extraction form
Article Title: _____
Design: _____
Medication And Use Time: _____
Tracking Time: _____
Sex: _____
Patient Age: _____
Parameters Used to Evaluate Obesity: _____
Sample Size: _____
Study Outcome: _____

Table 1: Data extraction form.

RESULTS

They were found 323 articles, of which 306 in English in the initial search. After careful selection, 57 were excluded because they did not conform to the proposed theme (different diseases or medications), 94 were excluded after reading the title because they are from different areas, 32 to be another type of resource, such as reviews or Congress act, 57 repeated, 54 previously published for 2004, the remaining 12 articles, which were read and examined again taking into account the inclusion criteria, with only 4 items selected and included in this review (Figure 1).

Thus, the individual description of each study was made, following the reverse chronological order of publication as shown in Table 1 and their outcomes in Table 2.

The study Villanueva et al¹¹ measured the change in BMI induced by clozapine, in both sexes, in two stages, 18 and 56 weeks follow-up. They analyzed 76 patients at 18 weeks and 57 in 56 weeks.

At first it was determined baseline BMI and then was made periodic reviews weight, height, BMI and clozapine dos-

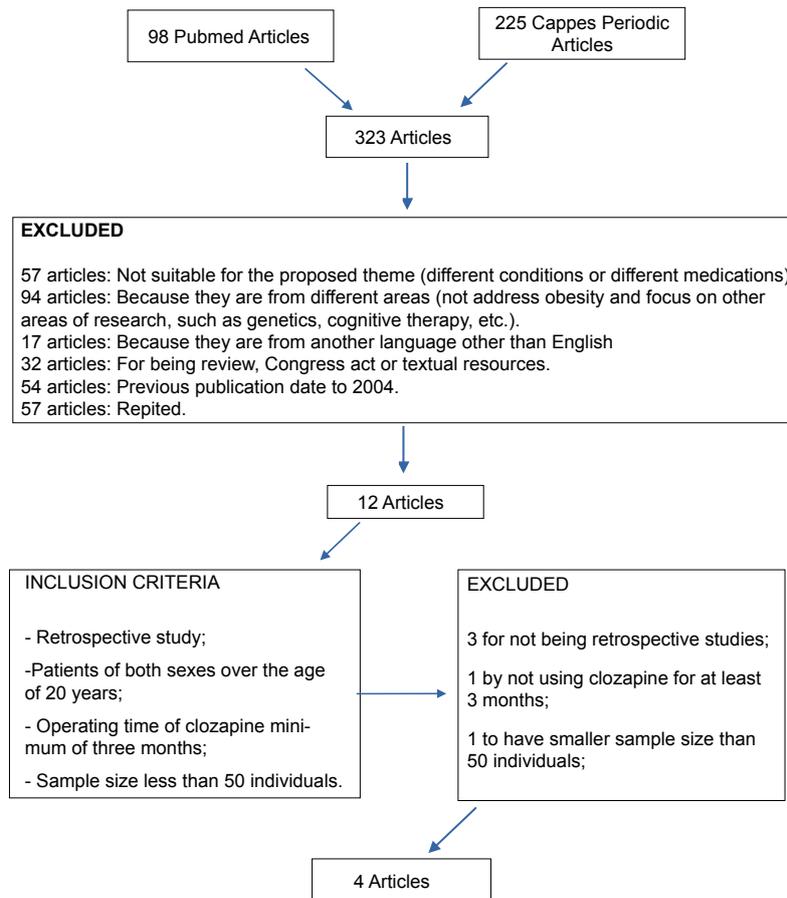


Figure 1: Organization chart of items excluded.

Analysis of the articles included				
Authors in studies year	Outline	Population sample size	Medication and time use	Parameters used to evaluate obesity
Villanueva et al ¹¹	Coorte retrospective study	Men and women 76 patients	Clozapine 18 to 56 weeks	BMI and body weight
Choong E et al ¹²	Cross retrospective study	Men and women 196 patients	Clozapine, olanzapine, quetiapine, risperidone, lithium and valproate. >3 months of use	BMI and body weight
Ya Mei Bai et al ¹³	Retrospective study	Men and women 96 patients, 55 being accompanied.	Clozapine 8 years	BMI and body weight
Covell NH et al ¹⁴	Retrospective study	Men and women 38 patients	Clozapine 2 years	BMI and body weight

BMI: Body Mass Index

Table 2: Analysis of the articles included.

age. As a result at 18 weeks of follow-up there was a variation in BMI of 1.83 kg/m², and of these 18 patients (19.7%) had a decrease in BMI. There was no difference between sexes in BMI changes. At 56 weeks of follow-up there was a BMI range of 2.67 kg/m², and of these 10 patients (17.5%) had a decrease in BMI. There was no difference between sexes in BMI changes, also this time. There was a statistically significant inverse relationship between BMI and baseline BMI in both times. In this study, the authors concluded that despite the increase in weight with the use of clozapine, physicians should not discourage the use for refractory patients.

Choong et al's¹² study evaluated the importance of side effects associated with weight gain psychotropic drugs and their metabolic consequences. Patients received for more than three months drugs: Clozapine, olanzapine, quetiapine, risperidone, lithium and/or valproate. 196 patients were analyzed. The weight gain ($\geq 10\%$ of initial body weight) after treatment with clozapine was reported in 47% of patients.

The prevalence of obesity (BMI ≥ 30) was present in 38% of patients. The highest dose, an increase in appetite after the introduction of medication, type of medication (clozapine or olanzapine > quetiapine, or risperidone > lithium or valproate), and sex was significantly associated with the development of BMI.

Yamei Bai¹³ study tested whether the initial clozapine response is related to weight gain. This study was a retrospective study of 8 years of 96 hospitalized patients with schizophrenia. There was a loss of 41 patients (death, incomplete weights, unavailable medical records, change of antipsychotic). The monthly weight change data were analyzed, the initial clinical response, age, sex, clozapine, and concomitant use of mood stabilizers and other antipsychotics. To analyze the weight gain BMI was used.

The patients receiving clozapine (55 patients, 57.3%) throughout the study period, achieved an average weight gain of 11.7 kg (SD=1.6). The multiple linear regression analysis showed significant initial clinical response and lower initial body mass index was associated with higher weight gain. The results show that the initial response to the antipsychotic clozapine is associated with higher weight gain in the long term, measured over 8 years.

Covell NH¹⁴ study analyzed the percentage weight gain of 138 randomized patients taking clozapine for 2 years and 89 who continued to receive first-generation antipsychotics.

In each group, 39% of participants were women. Two patients who were randomized to clozapine, did not start its use and were excluded and 3 patients had their weight measured outside the patterns and were also excluded from the analysis Table 2.

Demographic data were collected, the daily log of med-

ications and weight from information available through chart review. When more than one weight measurement was available in a given month, we used the latest weight for analysis. It also calculated body mass index.

The groups did not differ significantly from the initial weight and average BMI. The random regression analysis showed that patients who switched to clozapine gained more weight than patients who remained in the first generation of antipsychotic agents.

DISCUSSION

In the four studies selected in this systematic review, BMI was used as a parameter to assess weight gain. However, this parameter measures the weight as a whole, and does not assess body composition. Thus, the weight increase may be associated with increased lean body mass or fat mass, and only the latter being associated with obesity.

According Garn and colleagues¹⁵ there are three limitations to the use of BMI: The correlation with height, the correlation with the fat-free mass and the influence of body proportionality (size ratio of the legs/trunk), such that individual less leg length have a higher BMI. These limitations could jeopardize the use of BMI as body fat indicator.

To get a real idea of the incidence of obesity in these studies, the authors should associate with BMI, bioimpedance test or skin folds (done with skinfold), and then perform the comparison of these parameters before and after the use of clozapine Table 3.

To Cerve,¹⁶ although BMI has high correlation with body mass, it has low with height, so it is important to correlate with other independent measures of body composition, which determine the composition in terms of body fat and muscle mass to have greater reliability as anthropometric parameters, such as bioelectrical impedance, skinfold thickness, waist/hip ratio (WHR) and waist circumference (WC).

And the study of Choong,¹² comparison was made with other antipsychotic drugs, and the results showed that clozapine and olanzapine are those with largest increase of appetite and consequent increased weight gain.

Studies show a high prevalence of obesity, hyperglycemia, dyslipidemia and metabolic syndrome in patients treated with atypical antipsychotics, with evidence of greater effect for those using clozapine and olanzapine.⁶

Like clozapine, olanzapine is also associated with weight gain, an increase from baseline of 6.12 kg in 6 to 12 months of treatment.¹⁷

In the study Covell¹⁴ significant difference in weight gain after Clozapine especially in women, unlike other studies.

Analysis of outcomes	
Studies and authors	Outcomes
Villanueva et al ¹¹	There was a change in BMI in both periods. In the 18 th week this change was 1.83 kg/m ² and in the 56 th week of 2.67 kg/m ² . Only 18 patients (19.7%) had decreased BMI at 1 time and 10 patients (17.5%) had decreased this index in the 2 nd time. There were no gender differences in observed changes in BMI.
Choong E et al ¹²	The weight gain was reported in 47% of patients, greater than or equal to 10% of their initial weight. The prevalence of obesity (BMI≥30 kg/m ²) was present in 38% of patients and clozapine or olanzapine were the drugs had a greater increase in appetite.
Ya Mei Bai et al ¹³	The patients (55 patients - 57.3% of the sample) received clozapine throughout duration of the study, 8 years, increased on average 11.7 kg body weight.
Covell NH et al ¹⁴	Patients who used clozapine had higher weight gain (13.7%) of those taking medications 1 st generation (5.4%). Patients with normal weight were more likely to become obese (BMI≥30 kg/m ²), especially among women.

*BMI: Body Mass Index

Table 3: Analysis of outcomes.

This may have been because it was a study with the smaller sample size of the four selected. In the other there was no difference between the sexes in both studied moments.

The databases used periodicals and CAPES, PUBMED is quite academic relevance, encompassing medical articles from various fields, which increases the credibility of the review further.

CONCLUSION

In all items selected for this study, obesity was associated with clozapine. However, this fact is directly related to lack of information on healthy eating and physical inactivity.

It has been noted the growing interest of researchers in exploring non-pharmacological treatments for psychiatric patients, since we have seen significant improvements in the quality of life of these patients, when reduced dosage or deleted the indication of these drugs. Thus, it is necessary greater awareness of physicians indicate these multidisciplinary treatments to their patients, such as nutritional care, exercise, behavioral and occupational therapy (art and music).

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

- Mari JJ, Leitão RJ. A epidemiologia da esquizofrenia [In Portuguese]. *Rev Bras Psiquiatr.* 2000; 22(1): 15-17. doi: [10.1590/S1516-44462000000500006](https://doi.org/10.1590/S1516-44462000000500006)
- DSM-IV. *Manual Diagnóstico e Estatístico de Transtornos Mentais* [In Portuguese]. 4th ed. Porto Alegre, Brazil: Artes Médicas; 1995. Web site: <http://c026204.cdn.sapo.io/1/c026204/cld-file/1426522730/6d77c9965e17b15/b37dfc58aad8cd-477904b9bb2ba8a75b/obaudoeducador/2015/DSM%20V.pdf>. Accessed May 22, 2016
- Kaiser S, Heekeren K, Simon JJ. The negative symptoms of schizophrenia: Category or continuum? *Psychopathology.* 2010; 44: 345-353. doi: [10.1159/000325912](https://doi.org/10.1159/000325912)
- Oliveira IR. Antipsicóticos atípicos: Farmacologia e uso clínico [In Portuguese]. *Rev Bras Psiquiatr.* 2000; 22(1). doi: [10.1590/S1516-44462000000500013](https://doi.org/10.1590/S1516-44462000000500013)
- Zortéa K, Bock PM, Moreno DB, Belmonte de Abreu PS. Avaliação antropométrica e bioquímica em pacientes com esquizofrenia usuários de clozapina [In Portuguese]. *Rev Nutr.* 2009; 22(5): 697-705. Web site: <http://www.lume.ufrgs.br/handle/10183/69895>. Accessed May 22, 2016.
- Leitão-Azevedo CL, Guimarães LR, Lobato MI. Ganho de peso e alterações metabólicas em esquizofrenia [In Portuguese]. *Rev Psiquiatr Clin.* 2007; 34(2): 184-188. Web site: <http://www.lume.ufrgs.br/handle/10183/20468>. Accessed May 22, 2016
- Mojtaba IR, Nicholson RA, Carpenter BN. Role of psychosocial treatments in management of schizophrenia: A meta-analytic review of controlled outcome studies. *Schizophr Bull.* 1998; 24(4): 569-587. Web site: <http://schizophreniabulletin.oxfordjournals.org/content/24/4/569.long>. Accessed May 22, 2016
- Francischi RPP, Pereira LO, Freitas CS, et al. Obesity: updated information about its etiology, morbidity and treatment. *Rev Nutr.* 2000; 13(1): 17-28. doi: [10.1590/S1415-52732000000100003](https://doi.org/10.1590/S1415-52732000000100003)
- Ministerio da Saude. *Prevalência Obesidade* [In Portuguese]. Web site: <http://portal.saude.gov.br/404.html>. Accessed May 22, 2016

10. Pesquisa de Orçamentos Familiares 2008-2009. *Antropometria e estado nutricional de crianças, adolescentes e adultos no Brasil* [In Portuguese]. Web site. http://www.ibge.gov.br/home/estatistica/populacao/condicaodevida/pof/2008_2009_encaa/. Accessed May 22, 2016

11. Villanueva API, Romero A, Goti J, et al. Should obesity be a limiting factor for clozapine treatment? *Rev Psiquiatr Salud Ment.* 6(2): 75-79. doi: [10.1016/j.rpsm.2012.05.005](https://doi.org/10.1016/j.rpsm.2012.05.005)

12. Choong E, Bondolfi G, Etter M, et al. Psychotropic drug-induced weight gain and other metabolic complications in a swiss psychiatric population. *J Psychiatr Res.* 2012; 46(4): 540-548. doi: [10.1016/j.jpsychires.2012.01.014](https://doi.org/10.1016/j.jpsychires.2012.01.014)

13. Bai YM, Lin C-C, Chen J-Y, Lin C-Y, Su T-P, Chou P. Association of initial antipsychotic response to clozapine and long-term weight gain. *Am J Psychiatry.* 2006; 163: 1276-1279. Web site. <http://ajp.psychiatryonline.org/doi/pdf/10.1176/ajp.2006.163.7.1276>. Accessed May 22, 2016

14. Covell NH, Weissman EM, Essock SM. Weight gain with clozapine compared to first generation antipsychotic medications. *Schizophr Bull.* 2004; 30(2): 229-240. Web site. <http://schizophreniabulletin.oxfordjournals.org/content/30/2/229.full.pdf>. Accessed May 22, 2016

15. Garn SM, Leonard WR, Hawthorne VM. Three limitations of the body mass index. *Am J Clin Nutr.* 1986; 44(6): 996-997. Web site. <http://ajcn.nutrition.org/content/44/6/996.long>. Accessed May 22, 2016

16. Cervi A, Franceschini SC, Priore SE. Critical analysis of the use of the body mass index for the elderly. *Rev Nutr.* 2005; 18(6). doi: [10.1590/S1415-52732005000600007](https://doi.org/10.1590/S1415-52732005000600007)

17. Grupta S, Droney T, AL-Samarrai S, Keller P, Frank B. Olanzapine: Weight gain and therapeutic efficacy. *J Clin Psychopharmacol.* 1999; 19(3): 273-275. Web site. <http://www.ncbi.nlm.nih.gov/pubmed/10350036>. Accessed May 22, 2016