Universidade do Minho
Escola de Ciências da Saúde

Sámia Issufo Sulemane

Schizophrenia, Comorbidities and Readmission

Esquizofrenia, comorbilidades e readmissão

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Dissertação de Mestrado
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Trabalho efetuado sob a orientação do
Professor Doutor António Pacheco Palha
e
Professor Doutor João Miguel Seiça Bessa Peixoto

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Abstract

Schizophrenia is a psychiatric disease with idiopathic aetiology, being the theory of the dopaminergic hyperfunction the most accepted one to explain its physiopathology. Recently, other theories have emerged: the glutamatergic and neurodevelopment theory. This disease has also been associated to several medical comorbidities (obesity, blood pressure changes and thyroid diseases) that contribute to the lack of therapeutic adhesion and posterior readmissions.

This study was performed by assessing 107 medical records admitted at Casa de Saúde do Bom Jesus (CSBJ), in Braga, throughout a period of five years (2007-2012). Patients were all women with ages between 18 and 64 years old. Statistical analysis was performed using SPSS (version 22); the significance was defined as $p < 0.05$.

Time of hospital stay, medical comorbidities, difference of admission days and social-demographic variables were analysed based on the descriptive statistics. One way ANOVA and a multinomial regression model were performed to assess readmission and determine the readmission predictors up to the third admission. Furthermore the test χ^2 was performed to assess the degree of association between readmission, medical comorbidities and the different types of antipsychotic treatments. Finally, a binary logistical regression model was used to assess the degree of association between the independent variables (different comorbidities, type of antipsychotic treatments and the different types of treatment) with the dependent variable (number of admissions).

Results show that most patients were young adult women with ages between 20 and 29 years old, single (54%), with a low level of school education (41.58%), residing in urban areas (55.95%), with unskilled employment and a high functional level, few readmissions (3) and a longer interval between readmissions (3 years), who showed several medical comorbidities (obesity, thyroid disease and blood pressure changes), being obesity.probabily related with genetic factors and aggravated by atypical antipsychotics. That treatment and thyroid dysfunction are supposed to contribute to the reduction of the risk of readmission. On the other hand, treatment with combined antipsychotics reduced the risk of patients developing thyroid disease. Regarding blood pressure changes, classic antipsychotics showed a lower risk of causing hypotension when compared to atypical ones.

Resumo

A esquizofrenia é uma doença psiquiátrica com etiologia idiopática, sendo a teoria da hiperfunção dopaminérgica a mais aceite para explicar a sua fisiopatologia. Recentemente surgiram outras teorias, a teoria glutamatérgica e a do neurodesenvolvimento. Esta doença também foi associada á várias comorbilidades médicas (obesidade, alteração na tensão arterial, e doenças da tiroide) que, contribuem para falta de adesão terapêutica, e posteriores readmissões.

Foi realizado avaliando 107 processos clínicos de pacientes internados na Casa de Saúde do Bom Jesus (CSBJ), em Braga, durante um período de cinco anos (2007-2012). Os pacientes eram todos do sexo feminino, com idades compreendidas entre os 18-64 anos. A análise estatística foi realizada usando SPSS (versão 22); a significância foi definida como $p < 0,05$.

O tempo de permanência hospitalar, as comorbilidades médicas, as diferenças de dias de internamento e variáveis socio-demográficas foram analisados com base nas estatísticas descritivas. Para avaliar a readmissão foi feita ANOVA a um fator e um modelo de regressão multinominal para avaliar quais eram os preditores de readmissão até o terceiro internamento. Finalmente, foi feito o teste χ^2 para avaliar o grau de associação entre a readmissão, comorbilidades médicas e os diferentes tipos de tratamentos antipsicóticos; como também o modelo de regressão logística binária para avaliar o grau de associação entre as variáveis independentes (diferentes comorbilidades, tipo de tratamento antipsicóticos e os diferentes tipos de tratamento) com a variável dependente (número de internamentos).

Os resultados mostram que a maioria das pacientes eram adultas jovens com idades compreendidas entre os (20-29 anos), solteiras (54%), com baixo nível de escolaridade (41.58%), residentes em zonas urbanas (55.95%), com trabalho não qualificado e com nível funcional elevado, com poucas readmissões (3) e um intervalo entre as readmissões mais longo (3 anos), que apresentavam várias comorbilidades médicas (obesidade, doença da tiroide e alteração da tensão arterial),sendo que provavelmente a obesidade resultante de fatores genéticos e é agravada pelos antipsicóticos atípicos. Este tratamento e as doenças da tiroide contribuíram para diminuir o risco de readmissão, por outro lado o tratamento com antipsicóticos combinados diminuem o risco dos pacientes desenvolver disfunção da tiroide. Relativamente as alterações da tensão arterial, os antipsicóticos clássicos apresentaram menor risco de causar hipotensão em relação aos atípicos.

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Abbreviations list

AMPA-acid-alpha-amino-hydroxy-5-methly-lisoxazolepropionic

BDNF- brain derived neurotrophic factor

BMI-body mass index

COMT - catechol -o-methyltransferase

CNS- central nervous system

CSF-cerebrospinal fluid

COPD- chronic obstructive pulmonary disease

CSBJ-Casa de Saúde Bom Jesus Braga

DF1 = Difference between days of hospitalization the 1st and 2nd admissions

DF2 = Difference between days of hospitalization the 2nd and 3rd admissions

DNA-deoxyribonucleic acid

DM- diabetes mellitus type II

DSM- Statistical Manual of Mental Disorders

DISC1-disrupted in schizophrenia

(DOPA) dihidroxifenilalanina

(DLPFC) dorsolateral prefrontal cortex

ECT-electroconvulsive therapy

EPS-extrapyramidal neurological

GABA-Gama aminobutyric acid

HPRL- hyperprolactinemia

IQ-intelligence quotient

ICD- international classification of disease

IL-interleukin

(LSD) Lysergic acid diethylamide

MS-multiple sclerosis

MHC- major histocompatibility complex

MARTA-multiple target receptors

MS-multiple sclerosis

mGLUR- glutamate metabotropic

NMDA-N-methyl-D-aspartate

NMS-neuroleptic malignant receptors

NRG1 -ERBB4 Neuregulin 1

OMR-oligodendrocytes-myelin-genes

PCP-phencyclidine

RA- rheumatoid arthritis

RNA-ribonucleic acid

RTN4R-reticulon 4-receptor

SPSS-Statistical Package for Social Sciences

SLE-Systemic erythematosus lupus

SBP - systolic blood pressure

DBP - diastolic blood pressure

TSH- thyroid stimulating hormone

TNF-tumor necrosis factor

THC-tetrahydrocannabinol

US- United States

VIH- human immunodeficiency virus

5HT-5-hydroxytryptamine

1. INTRODUCTION

1.1. THE EVOLUTION OF THE CONCEPT OF SCHIZOPHRENIA

Schizophrenia is a psychiatric disease whose definition, limits, causes and pathogenesis remain obscure (Silveira et al., 2012). The concept of schizophrenia originated in the mid-nineteenth century, when European psychiatrists described various psychotic disorders affecting young adults that were associated with deterioration and chronicity. Morel (1856) defined this condition as "early dementia" (Tandon, 2012). In 1893 Kraepelin proposed the designation of dementia praecox (Silveira et al, 2012; Tandon & Maj, 2008; Tandon, 2012), a clinical syndrome that included the hebephrenia, catatonia and paranoid conditions (Tandon, 2012). In 1911, Eugen Bleuler changed the concept of dementia praecox, noting the occurrence of a process that involves the loss of several psychic functions, the presence of emotional ambivalence but without a mandatory evolution to mental deterioration. Bleuler renamed this condition as Schizophrenia, meaning Split Mind, defining a basic set of 4 symptoms (affective ambivalence, affective incongruity, autism and loss of association of ideas), which were features of schizophrenia present in patients with this condition (Tandon, 2012). In 1959, Kurt Schneider established a hierarchy of important symptoms for diagnosis's of schizophrenia: symptoms of first rank (currently defined as positive symptoms) that include insertion, theft or dissemination of ideas, delusions (Andreasen, 1997; Silveira et al, 2012) and auditory hallucinations in dialogue; symptoms of second rank (currently defined as negative symptoms) that include the loss of affection, abulia (inability to make decisions), deficits in communication and attention, avolition (inability to formulate plans and pursue them), apathy and alogia (poverty of thought and expression) (Andreasen, 1997; Silveira et al, 2012.).

Current definitions of schizophrenia, including the International Classification of Diseases (ICD-11) and the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), incorporate the chronicity defined by Kraepelin, the negative symptoms defined by Bleuler and the positive symptoms defined by Schneider. This broad definition has led to discrepancy between the diagnosis of schizophrenia in the United States (US) and the rest of the world that used the ICD system and emphasized the chronicity by Kraepelin in ICD-7 as well as the positive symptoms of Schneider in ICD 8 (Tandon & Maj, 2008; Tandon, 2012). In Japan, the designation of early dementia name was changed in 2002 at the request of patients and family members to reduce the stigma and move away from the term "dementia praecox" (Van Os, 2009). Some authors postulate that the twentieth century expression referring to schizophrenia as split state of the mind is an inappropriate term for the diagnosis. The stigma associated with the term schizophrenia led to the adoption of other

denominations for the disease such as: Integration Disorder in Japan or Disorder of Dopamine dysregulation or Disorder of emotional neuro-integration (Silveira et al, 2012).

1.2. RISK FACTORS FOR SCHIZOPHRENIA

There are several risk factors for the occurrence of schizophrenia, in particular maternal risk factors (adverse effects during the prenatal and perinatal period), paternal old age, autoimmune diseases, factors associated with social risk (such as place of residence, migration, Childhood adversities, substance abuse and bullying) and genetic risk factors.

1.2.1. MATERNAL RISK FACTORS

With regard to maternal factors associated with increased risk of schizophrenia in their offspring, there are several that have been identified. Children born in the winter (Brown et al., 2011; Mura et al., 2012; Vallada Samaia, 2000) and early spring (Vallada & Samaia, 2000) have an increased risk (5-8%) to develop schizophrenia when compared to children born in the summer with risk between 1.01 to 1.08%. The increased risk of schizophrenia in the winter can be explained by the fact that the second trimester of pregnancy is associated with higher incidence of respiratory infections such as-, the flu virus A and B (Mura et al., 2012; Patterson, 2009). Other infections are associated with increased risk of occurrence of schizophrenia, such as exposure to influenza virus (Brown et al., 2011; Hamlyn et al., 2013; Richard & Brahm, 2012), Toxoplasma Gondi (Brown et al., 2011; Hamlyn et al., 2013; Richard & Brahm, 2012), rubella virus and Herpes Simplex virus type 2 (Hamlyn et al., 2013) during the first and second trimester of pregnancy (Hamlyn et al., 2013). The consequences of perinatal infection with the flu virus A and B can be reduced cognitive performance in children that can develop psychosis in adulthood (Mura et al., 2012). On the other hand, the maternal reproductive tract infections (Brown et al., 2011) and maternal infections with influenza viruses are both associated with memory deficits in their offspring (Brown et al., 2011; Patterson, 2009).

The proposed mechanism for the increased risk of schizophrenia after maternal infection is that maternal antibodies can cross the placenta and interact with brain fetal antigens (Richard & Brahm, 2012) and thus present the ability to initiate immune disorders in early fetal development

(Patterson, 2009) and induce the release of pro-inflammatory cytokines (Richard & Brahm, 2012) such as tumor necrosis factor (TNF-α), interleukin 6 (IL-6) and interleukin 8 (IL8) (Brown et al., 2011) leading to persistent pro-inflammatory states. This pro-inflammatory state allows cytokines resulting from immune activation to cross the placenta and damage the fetal brain, producing an aberrant neurodevelopment (Richard & Brahm 2012; Venkatasubramanian & Debnath, 2014). IL-6 is involved in the regulation of the expression of the brain derived neurotrophic factor (BDNF) in the embryo and placenta. BDNF is expressed in brain regions implicated in the pathogenesis of schizophrenia (such as the prefrontal cortex and hippocampus) and interacts with neurotransmitters implicated in schizophrenia such as dopamine, glutamate, serotonin and GABA. Furthermore, the expression of IL-6 may be modulated by the estrogens, which in turn have neuroprotective effects on the hippocampus (Venkatasubramanian & Debnath, 2014) one of the regions implicated in the pathogenesis of schizophrenia.

In addition to the infections there are other risk factors associated with schizophrenia. Recently it was shown that prematurity, hypoxia, maternal infections (Mura et al, 2012.), prolonged labor, premature rupture of membranes, pre-eclampsia (Girgis et al, 2014; Hamlyn et al, 2013), complications of the umbilical cord, the vicious fetal presentations (Girgis et al., 2014), ante-partum hemorrhage, gestational diabetes, maternal-fetal incompatibility, low birth weight, decreased head circumference, uterine atony (Hamlyn et al, 2013; Piper et al, 2012) are some of the factors associated with the risk of developing the disease (Mura et al., 2012). Males display a higher number of early complications during birth that may explain the higher incidence of the disease in this sex (Brown et al., 2011).

Finally, it is also known that exposure to famine during the prenatal period, as well as increased homocysteine in the third trimester of pregnancy and decreased vitamin D prenatally increase the risk of schizophrenia. The deficit of vitamin D leads to changes in brain structure (Piper et al., 2012).

1.2.2. PATERNAL AGE

The paternal age was linked to schizophrenia in 1958 (Hamlyn et al., 2013). It has been reported that the greater the age of the parents, lower is the ability to produce psychosocial environments favorable to their children (Stilo & Murray, 2010) and the greater the risk of their children

developing schizophrenia (Hamlyn et al., 2013; Mura et al., 2012; Piper et al., 2012; Stilo & Murray, 2010). The risk for the occurrence of schizophrenia in the offspring is increased in parents over 30 years of age (Hamlyn et al., 2013; Piper et al., 2012). A possible explanation for the occurrence of schizophrenia associated with paternal age is the possible occurrence of *de novo* mutations in the paternal germ cells (Hamlyn et al., 2013; Mura et al., 2012; Naserbakht et, 2011; Piper et al., 2012), as well as the existence of epigenetic mechanisms that could explain this association, such as reversible changes in the methylation of deoxyribonucleic acid (DNA), ribonucleic acid (RNA) and proteins (histones) (Naserbakht et al., 2011).

1.2.3. AUTOIMMUNE DISEASES

The association between autoimmune diseases and psychosis has been investigated since 1950, when researchers were intrigued by the fact that rheumatoid arthritis (RA) seemed to protect against schizophrenia. Later it was confirmed that the combination of both was negative. This negative association between schizophrenia and RA is the result of genetic interaction, since different autoimmune diseases are associated with different markers of the complex region major histocompatibility complex (MHC) and therefore can have different combinations with different psychiatric diseases (Benros et al., 2014).

The polymorphism of a single nucleotide in the MHC genes located on chromosome (6p), is critical for the functioning of the immune system and therefore is regarded as a risk factor for schizophrenia (Benros et al., 2014; Ezeoke et al., 2013). The family history of autoimmune disease (Ezeoke et al., 2013), with the exception of RA, increases the risk of developing schizophrenia by 10% (Benros et al., 2014) to 45% (Richard & Brahm 2012). Furthermore, patients with schizophrenia are likely to have first degree relatives with autoimmune diseases (Richard & Brahm, 2012) and present some common clinical features between them (Chen et al., 2012). Regarding etiology, it was demonstrated that this group of diseases are complex and with some genetic influence, environmental and lifestyle factors (Chen et al, 2012; Richard & Brahm, 2012). With regard to clinical expression and onset, both are initiated after puberty and have an outbreak and cyclic reference. The last common feature is the presence of autoantibodies or chronic inflammation (Richard & Brahm, 2012).

Several autoimmune diseases are associated with increased risk for psychosis, including: systemic lupus erythematosus (SLE), autoimmune thyrotoxicosis, multiple sclerosis (MS), autoimmune hepatitis and psoriasis (Benros et al, 2014), celiac disease (Benros et al, 2014; Chen et al, 2012; Mura et al, 2012), autoimmune thyroiditis (Benros et al, 2014; Mura et al, 2012), psoriasis (Chen. et al., 2012), pernicious anemia (Chen et al., 2012), vasculitis (Chen et al., 2012) and Diabetes Mellitus (DM) type I (Benros et al., 2014).

1.2.4. EMIGRATION

Emigrant populations have a significant higher risk of developing schizophrenia compared with the natives, in particular the East African migrants, because they are subject to the effects of poverty, discrimination and racism (Mura et al., 2012). The first and second generation of emigrants have a higher risk of developing schizophrenia, being more pronounced in dark-skinned emigrants (Hamlyn et al, 2013; Mura et al, 2012; Piper et al, 2012) and in small emigrant communities, thus reinforcing the fact that the isolation and lack of social support are determining factors in the pathogenesis of schizophrenia (Mura et al., 2012). Concerning the age of emigration, a study has revealed that the risk of schizophrenia is higher if the migration occurs is very early (ages babies or children) and this risk will decrease if the age of the migrant is before 29 years (Piper et al., 2012).

1.2.5. RESIDENCE

The incidence of schizophrenia is higher in people born or raised in urban areas (Stilo & Murray, 2010) and people living in unorganized areas of the city (Lewis & Levitt, 2002; Piper et al., 2012; Stilo & Murray, 2010). It is unclear which are the associated factors between schizophrenia and residence in urban areas, but it is thought that the association between the two is secondary to exposure to factors such as infections, exposure to toxins or malnutrition that are common in urban areas (Lewis & Levitt, 2002).

1.2.6. SOCIAL CLASS AND SOCIAL ISOLATION

There is a strong association between schizophrenia and low social status. Underdeveloped countries have poor environmental conditions, such as unemployment, increased risk of infectious diseases and poor maternal and child care. These factors may contribute to the occurrence of schizophrenia (Lewis & Levitt, 2002).

1.2.7. DRUG ABUSE

Acute ingestion of cannabis or its tetrahydrocannabinol component (THC) (Piper et al, 2012; Stilo & Murray, 2010) and D-amphetamine (both act on the dopaminergic system) (Mura et al, 2012) can cause acute psychotic effects and their continued use exacerbates pre-existing psychotic illness. The risk of schizophrenia is increased in people who started early abuse of cannabis (Piper et al, 2012; Stilo & Murray, 2010) particularly high power cannabis (sinsemilla or shunk) (Stilo & Murray, 2010). Lysergic acid diethylamide (LSD) abuse, which acts on the serotonin system may also cause psychotic symptoms, suggesting that dysregulation of dopamine is not the only factor responsible for the occurrence of schizophrenia. This theory was supported by the fact that antipsychotics used to treat schizophrenia, such as clozapine and olanzapine, both feature high serotonin antagonist actions (5HT2) compared to their dopamine antagonist actions (D2) (Mura et al., 2012).

1.2.8. ADVERSITY CHILDHOOD

Separation by death of one or both parents increases the risk of schizophrenia three times (Stilo & Murray, 2010).

1.2.9. BULLYING

Victims of bullying between 8-10 years have a two-fold risk of developing schizophrenia (Stilo & Murray, 2010).

1.2.10. INTELLIGENCE QUOTIENT (IQ)

Offspring of schizophrenic parents have low IQ reduction in general cognitive function and low educational qualifications. The decreased IQ in children is associated with increased risk of schizophrenia when they reach adulthood (Lewis and Levitt, 2002).

1.2.11. GENETIC FACTORS

Schizophrenia is a complex genetic disease resulting from the combined effect of environmental and genetic factors (Mura et al., 2012; Venkatasubramanian & Debnath, 2014; Mura et al., 2012), each with a small effect on the individual's phenotype. Among the genetic factors, it has been demonstrated that the risk of schizophrenia is higher among first-degree relatives of affected individuals and in monozygotic twins (Lewis & Levitt, 2002; Vallada & Samaia, 2000). Multiple polymorphisms contribute to the occurrence of schizophrenia in particular 311Cys Ser polymorphism of the dopamine receptor gene, which is particularly evident in patients with no negative symptoms (Mura et al., 2012). The other polymorphism associated with schizophrenia is Val108/105Met, the COMT enzyme gene, involved in catabolism of various molecules including dopamine. The catechol -o-methyltransferase (COMT) gene is located on chromosome 22q11 and when deleted contributes to occurrence of schizophrenia (Mura et al., 2012). This deletion (22qDS) increases the risk of schizophrenia about 25 and is associated with a reduction in both white and gray matter in the brain (Bartzokis, 2002).

Other genes involved in the pathogenesis of schizophrenia are the oligodendrocytes-myelin genes (OMR). The OMR genes with strong genetic association with schizophrenia are (Roussos & Haroutunian, 2014): Neuregulin 1 (NRG1) -ERBB4 - The NRG1 is important as a trophic factor and in the myelination of glial cells. The NRG1-ERBB4 signaling has multiple roles in the development of the central nervous system (CNS) (Jaaro-Peled et al., 2009; Roussos & Haroutunian, 2014) , in the modulation of neuronal migration and neurotransmission); Disrupted in esquizofrenia1 (DISC1) is a gene associated with schizophrenia and has a role in oligondregolial differentiation during development (Roussos & Haroutunian, 2014); Reticulon 4 receptor (RTN4R) is a myelin-associated protein that inhibits the growth of nervous terminals and has a role in the pathogenesis of schizophrenia (Roussos & Haroutunian, 2014);

1.3. ETIOLOGY OF SCHIZOPHRENIA

The etiology and pathophysiology of schizophrenia are still widely unknown (Snyder & Gao, 2013). For decades, the dopaminergic theories prevailed. With the paradigm shift in the etiology of this disease, evidence showed that environmental and genetic risk factors converge in particular with new evidence on the glutamatergic receptors or another angle considered schizophrenia as a neurodevelopmental disorder (Jaaro-Peled et al., 2009). These theories are discussed herein.

1.3.1. THE ROLE OF GLIAL CELLS

It is thought that glial cells (astrocytes and oligodendrocytes) are changed in psychotic disorders (Duncan et al., 2014). The activation of glial cells is responsible for the induction of a number of pro-inflammatory molecules that can lead to neuropathological changes observed in schizophrenia (Venkatasubramanian & Debnath, 2014).

Postmortem, in vivo and brain imaging studies have showed that the white matter is reduced and disorganized in psychoses, and that these changes are more pronounced in schizophrenia. Oligodendrocytes are responsible for brain myelination, and maintenance of the white matter. The location and function of oligodendrocytes may be the cause of malfunctions of the white matter observed in schizophrenia (Duncan et al., 2014). Some examples of these white matter disorders are, for example, metachromatic leukodystrophy, the 22q11 deletion syndrome (22qDS) and demyelination diseases. These diseases have been associated with the schizophrenic syndrome in early adolescence, adulthood and possibly in old age (Bartzokis, 2002). It is known that myelination increases the speed of the transmission of nerve impulses and decreases the refractory period (Roussos & Haroutunian, 2014). Postmortem and human neuroimaging revealed abnormalities of myelin-oligodendrocytes (OMR) in schizophrenia contributing to these changes in nerve impulse conduction between brain neurons (Roussos & Haroutunian, 2014).

Astrocytes are the other glial cells that may also be involved in schizophrenia. These cells are responsible for stabilizing the glutamatergic synapses, through its role in glutamate metabolism. The change in glutamatergic signaling is secondary to the deficit in the recycling of this neurotransmitter by astrocytes, instead of being assigned only to the release of glutamate abnormalities in presynaptic and postsynaptic terminals (Duncan et al., 2014).

1.3.2. SCHIZOPHRENIA AS A NEURODEVELOPMENTAL DISORDER

It is believed that schizophrenia was neurodevelopment disease caused by brain damage occurring in the early phase of life that interferes with normal developmental stages (Lewis & Levitt, 2002; Mura et al., 2012).

The minor anomalies of neuronal cytoarchitecture are accompanied with little proliferation of glia cells (gliosis) in autopsied brains of patients with schizophrenia (Jaaro-Peled et al., 2009). The gliosis is a marker of neurodegeneration involving loss of cell apoptosis by different mechanisms. Patients with schizophrenia do not exhibit this marker of the neurodegeneration (Bartzokis, 2002), and schizophrenia is a disease of the neurodevelopment and not a degenerative disease (Bartzokis, 2002; Jaaro-Peled et al., 2009; Piper et al., 2012).

Morphological and macroscopic postmortem studies have shown decreased cell asymmetry in patients with schizophrenia, this change is the first to emerge in the prenatal period, and is consistent with alteration of normal brain development (Piper et al., 2012). There are other data showing that this psychiatric disorder is associated with brain development. Thus, it has been observed that the offspring of schizophrenic at high risk of contracting the disease show delay development of certain motor skills (such as walking later than the time allotted) (Lewis & Levitt, 2002) and bearing in mind that the pathophysiology of schizophrenia is the result of molecular changes that occur in the neural circuits that are responsible for cognitive functions (such as working memory, attention and context representation) that are altered in this disease (Piper et al., 2012) .These changes in these circuits are the result of anomalies in the formation of glutamatergic synapses, and consequently there is a hypofunction of these receptors, which contributes to the abnormalities of the dopaminergic system (Howes et al., 2013).

1.3.3. DOPAMINE

The dopaminergic hyperfunction is the neurochemical model more accepted to explain schizophrenia. The sources of evidence to explain this hypothesis are namely the fact that amphetamines induce dopamine release and thus originate psychotic symptoms and on the other the fact that the therapeutic blockade of antipsychotic drugs are made through the dopamine

receptor type 2 (D2) (Bressan & Pilowsky, 2003). Positive psychotic symptoms result from hyperactivity of the mesolimbic dopaminergic neurons and negative, cognitive and affective symptoms of result from underactive mesocortical dopaminergic neurons (Howes et al, 2013; Snyder & Gao, 2013).

The dopaminergic system is modulated by the glutamatergic system, as noted by the increase of glutamate in the prefrontal cortex after systemic administration of ketamine resulting in the increased release of dopamine in schizophrenic individuals (Bressan & Pilowsky, 2003; Stone, 2011). It is accepted that changes in glutamatergic modulation via NMDA receptor antagonism can be the determining mechanism for the increased activity of the dopaminergic system (Bressan & Pilowsky, 2003).

1.3.4. GLUTAMATE

Glutamate is the excitatory brain neurotransmitter (Bressan & Pilowsky, 2003; Duncan et al., 2014; Stone, 2011), that acts on ionotropic and metabotropic glutamate (mGluR) (Bressan & Pilowsky, 2003; Stone, 2011). The glutamate ionotropic receptors of are divided into two groups: receptor N-methyl-D-aspartate (NMDA) receptors and non-NMDA which include receptors acid-alpha-amino-3-hydroxy-5-methyl-4-lisoxazolepropionico (AMPA), and kainate (Bressan & Pilowsky, 2003).

It is thought that glutamate abnormalities are associated with psychotic and mood disorders. This association was demonstrated in postmortem studies suggesting that the synthesis and catabolism of glutamate were altered in schizophrenia and bipolar disorder. These changes were also supported by genetic studies, which revealed an association of genes for glutamatergic neurotransmission in psychotic and bipolar disorders (Duncan et al., 2014) and concluded that the candidate genes for schizophrenia were not related to the dopaminergic system, but converging on the molecules involved in glutamatergic transmission (Stone, 2011). Among these molecules is the ionotropic receptor (NMDA) (Bressan & Pilowsky, 2003). This finding was supported by extensive evidence. The first observation was that the drugs which act as non-competitive antagonist at NMDA receptors, such as phencyclidine (PCP) and ketamine induced psychotic symptoms similar to the symptoms of schizophrenia only in adults, such as changes of thought, occasional delusions, hallucinations, cognitive impairment, emotional withdrawal, blunted affect, social withdrawal (the latter which has been compared to the negative symptoms of schizophrenia)

(Bressan & Pilowsky, 2003; Stone, 2011). The negative symptoms were the result of NMDA receptor blockade by ketamine, suggesting that glutamate and dopamine originate different symptoms in schizophrenia (Stone, 2011). The second observation was that in the first psychotic episode there was an increase of glutamatergic transmission in the cingulate gyrus and the frontal cortex, but the same was not true in the chronically ill who had normal or reduced cortical glutamate levels. The decrease of glutamate in the hippocampus was correlated with increased the dihidroxifenilalanina (DOPA) uptake in the striatum, a marker of presynaptic dopamine function.

After these observations, we conclude that the glutamatergic hypothesis of schizophrenia are the result of evidence presented that changes in glutamatergic neurotransmission may occur in schizophrenia, as well as the change in glutamatergic neurotransmission may lead to changes in other neurotransmitter systems, such as dopamine (Stone, 2011).

1.4. CLINICAL ASPECTS OF SCHIZOPHRENIA

The diagnosis of schizophrenia is based primarily on clinical criteria. Clinical symptoms include positive symptoms (hallucinations, delusions), disorganized speech and behavior, negative symptoms such as affective flattening, apathy, social withdrawal, loss of motivation, deficits in communication, lack of initiative, cognitive symptoms (Jaaro-Peled et al., 2009; Naserbakht et al., 2011; Silveira et al., 2012) and changes in mood and motor function (Silveira et al, 2012). Schizophrenic patient's exhibit premorbid schizoid personality in 25% of cases and 35% of these patients meet the criteria of personality disorder seconds DSM IV (Mura et al., 2012).

Psychotic symptoms usually manifest themselves in late adolescence and early adulthood (Tandon & Maj, 2008; Tandon, 2012) in men (15-25 years), and have a longer latency period in women (25-35 years) (Carpenter & Koenig, 2008). This longer latency in females is attributed to the protective effects of estrogens. An example of this is the fact that schizophrenia is more frequent in the postpartum period and menopause, coinciding with the time when estrogen levels are lower (Venkatasubramanian & Debnath, 2014).

Males tend to have a lower amount of myelin in the temporal lobe as well as a slower brain myelination compared to females in the same age group, which may explain the reason for increased vulnerability to early onset of schizophrenia in males (Bartzokis, 2002). The receptors of

sexual steroids (estrogen and progesterone) are present in the glial cells are produced locally in the brain. Progesterone stimulates brain myelination and this hormone is found in lower concentrations in the brain in males than in females, thus explaining the pathophysiology of schizophrenia associated with differences in gender (Bartzokis, 2002).

1.4.1. PSYCHOPATHOLOGY

1.4.1.1. POSITIVE SYMPTOMS

Delusions are ideas or beliefs irrefutable by logical argument and not shared by people of the same culture, involving misinterpretation of perceptions or experiences. Delusions arise from the need of trying to explain auditory hallucinations and are incongruent with the mood. The most common contents of delusions are persecutory and self-referential but can include various topics: somatic, religious, hypochondriac, etc. (Monteiro, 2014; Renca & Cherry, 2014).

Hallucinations are perceptions without the presence of an object. Can occur in any sensory modality (auditory, visual, olfactory, gustatory and tactile). Auditory hallucinations in the form of voices and utterances are the most common in schizophrenia (Monteiro, 2014; Renca & Cherry, 2014).

1.4.1.2. DESORGANIZATION OF THOUGHT AND SPEECH

Changes in thought form and course are also present in schizophrenia. Among the changes, we can describe (Monteiro, 2014; Renca & Cherry, 2014):

• Loss of association of ideas - are considered nonsensical ideas that can translate into a confused and incoherent speech;

• Derailment of ideas - in which contribute changes of the course of thought, such as blocking of thought;

• Tangential thought - the thought circulates irrelevant details and never reaches the central ideas;

• Insertion of thought - the patient believes that thoughts are being inserted into the mind and recognizes that the thoughts come from outside;

• Diffusion of thought – the patient thinks that other people are aware of his thoughts;

• Eco of thought - the patient ears his thoughts out loud and believes that other people are also listening.

1.4.1.3. NEGATIVE SYMPTOMS

Negative symptoms may occur five years before the onset of psychotic symptoms (Mura et al., 2012). Negative symptoms are the most important and fundamental in schizophrenia because they are of cognitive nature (Andreasen, 1997; the 2009). Kraepelin and Bleuler said the cognitive basis of abnormality could explain the positive and negative symptoms of schizophrenia and the latter symptoms are closely related to basic cognitive deficits (Andreasen, 1997). Furthermore neuro-cognitive impairments are present in relatives of schizophrenic patients in the first degree and are preceding the onset of illness (The 2009).

The primary negative symptoms of schizophrenia refer to the poverty of speech, restricted affect and decreased emotional range and social indifference. However, these primary negative symptoms can be distinguished from secondary negative symptoms, resulting from extrapyramidal side effects of antipsychotic treatment, social exclusion and stigma related factors the illness. (Van Os, 2009).

Negative symptoms include:

• Blunted affect – that consists in the reduction of the extent and intensity of emotional expression (Miller, 2014; Renca & Cherry, 2014);

• Social isolation - characterized by reduced interest in social interaction ,involvement and affective commitment (Jaaro-Peled et al, 2009);

• Avolition - which is characterized by lack of motivation and non-compliance with targets (Andreasen, 1997);

• Alogia or deficit in communication - in which the patient has poor speech with brief and laconic answers (Silveira et al, 2012; Monteiro, 2014; Renca & Cherry, 2014);

• Anhedonia – inability to exprience pleasure (Monteiro, 2014; Renca & Cherry, 2014);

• Deficits in motor, language and cognitive development - that are seen early in life (Mura et al., 2012), which result from the activation of the dorsolateral prefrontal cortex (DLPFC) in patients with schizophrenia (Piper et al., 2012).

1.5. CLASSIFICATION

According to the clinical syndrome described by Bleuler, in schizophrenia there are primary and secondary symptoms (Silveira et al., 2012) and according to Andreasen, fundamental and accessory symptoms (Andreasen, 1997). The main symptoms should be the key for diagnosis (Tandon & Maj, 2008) and include loss of thought association, inappropriate affect, loss of attention avolition, ambivalence, and autism (Andreasen, 1997; Silveira et al., 2012). These are currently considered as negative symptoms, and reflect changes in cognitive and emotional processes. Hallucinations and delusions were regarded as secondary for the diagnosis of schizophrenia (Andreasen, 1997).

In 1959 Kurt Schneider introduced the psychotic symptoms in a hierarchical way, and the diagnosis of schizophrenia was based on a hierarchy of symptoms as it was already presented

The DSM IV has classified Schizophrenia in nine clinical subtypes (Paranoid, Hebephrenic, Catatonic, Undifferentiated, Residual, Simple, Post-schizophrenia depression, other schizophrenia and schizophrenia unspecified (Monteiro, 2014) and ICD-10 ranked schizophrenia in five subtypes (Paranoid, Disorganized, Catatonic, Undifferentiated and Residual). In addition to these five subtypes ICD 10 also added two categories: latent and simple (Silveira et al, 2012).

In 1974, Strauss proposed the concept of positive and negative symptoms of schizophrenia. Positive symptoms corresponded to the symptoms of first order of Kurt Schneider that included: delusional perception, auditory hallucinations, delusions and echo of thought, integration and dissemination of ideas (Silveira et al., 2012). Negative symptoms corresponded to loss of affection, cognitive changes, apathy, communication deficit, avolition and apathy (Silveira et al., 2012).

In 1980, Crow classified schizophrenia into two subtypes. A positive syndrome or subtype I (hallucinations and delusions) which would be secondary to a biochemical imbalance in the dopamine hyperactivity and the other as the negative syndrome or II subtype associated with neural

tissue damage and brain atrophy. In 1988, Carpenter et al. introduced the classification of deficit schizophrenia and non-deficit forms of schizophrenia (Silveira et al., 2012).

The current DSM-V in the definition of schizophrenia advocates several changes from the DSM IV. Three changes are proposed in the criterion A (Monteiro, 2014):

1. Catatonia ceased to be a subtype of schizophrenia and considered to be applicable to various pathologies, whether the schizophrenic spectrum or the bipolar spectrum disorders:

2. The medical causes associated with catatonia should be diagnosed as well as catatonia unspecified;

3. Elimination of the special attention given to bizarre delusions and symptoms of the first order for because they were not considered specific to schizophrenia. The criteria A for schizophrenia has become more demanding in requiring the presence of two or more of the following symptoms: delusions, hallucinations, disorganized speech, disorganized or catatonic behavior and negative symptoms present.

1.6. HISTORICAL PERSPECTIVE OF THE TREATMENT OF SCHIZOPHRENIA

The treatment of schizophrenia has undergone various periods, since the admissions phase of mental patients in asylums in the nineteenth century up to their integration in the community care system today. In that time there was no effective treatment and in the attempt to find an appropriate therapy for these patients, the convulsant therapies were developed (third the case of twenty centenary) and later in the fifties antipsychotic drugs revolutionized the treatment of this disorder.

1.6.1. CONVULSANT TREATMENTS

The first convulsant therapy used in clinical practice has been proposed by Meduna using cardiazol and metrazol in 1933. The seizures induced by them had been used for some time and replaced by eletroconvulsive therapy (ECT) because seizures induced were dangerous and poorly tolerated by patients (Metastasio, 2013; Perizzolo et al., 2003). ECT was developed by two Italian psychiatrists (Ugo Carletti and Lucius Bini) was well accepted for treating affective disorders and schizophrenia until the introduction of antipsychotic medication (Harold & Fink, 1996). This

technique made without anesthesia brought discomfort to the patient, as well as fractures resulting from the motor activity during the seizure act, which later disappeared with the use of ECT technique modified by anesthesia in 1950 (Perizzolo et al., 2003). The role of ECT in the treatment of schizophrenia has diminished in the last two decades (Metastasio, 2013), however it can increase the antipsychotic efficacy in some patients. It is used to treat catatonic symptoms, as an adjunctive treatment to clozapine in cases of patients refractory to antipsychotic drugs (Tandon et al., 2010), in major depressive disorder, in manic episodes, neuroleptic malignant syndrome and depression in the elderly (Perizzolo et al., 2003).

In the late 80s, the prefrontal leucotomy, a neurosurgical method, was implemented by Burkhardt (1980) in the case of two patients without great therapeutic success (Sargant & Slater, 1972). Subsequently, Moniz proposed the section of nerve fibers in patients with certain abnormal behavior in the case of schizophrenia. In a first step, ethanol was introduced in the subcortical white matter in the frontal lobe and later a *leucotome* was used for cutting synaptic connections in the same area. Later, Freeman and Watts in the United States developed their application to debatable clinical and operative conditions and the prefrontal leucotomy fall into disuse (Sargant & Slater, 1972).

1.6.2. THE DISCOVERY OF ANTIPSYCHOTICS

In the nineteen century and early century, patients with schizophrenia were subjected to institutional long-term treatment and provided to be a safe and supportive environment until the patient was obtained spontaneous amelioration of mental illness (Harvey et al, 2013; Tandon el ., 2010). At that time, there were no effective treatments for the symptoms of schizophrenia, thereby contributing to increased hospital stay (Harvey et al., 2013).

Thereafter it was added electroconvulsive treatment (ECT) which was then discredited and treatment with insulin coma and the frontal leucotomy (Tandon et al., 2010) which were described above. Before the introduction of chlorpromazine the mentally ill were treated with barbiturates and sedatives (Minns & Clark, 2012).

While the use of chlorpromazine was initiating in Europe, reserpine was introduced in America (Moreira & Guimaraes, 2007) .This antihypertensive drug was the first drug to be used in the

treatment of schizophrenia, which acts by decreasing the release of synaptic dopamine. This allowed the discovery of the antipsychotic properties of chlorpromazine (Carpenter & Koenig, 2008). Antipsychotics introduced in the decade 1950 were initially baptized as neuroleptics or major tranquilizers (Moreira & Guimaraes, 2007). It was at this time that chlorpromazine and other phenothiazines such as fluphenazine and thioridazine were introduced for the treatment of schizophrenia (Bishara & Taylor, 2008a; Carpenter & Koenig, 2008; Tandon et al, 2010), contributing to reducing hospitalization time from months to weeks. However, patients not sensitive to the treatment with chlorpromazine continued with prolonged hospitalization (Harvey et al., 2013). With the introduction of typical antipsychotics, classical or first generation there was an improvement in the treatment psychotic symptoms which contributed to the deinstitutionalization of people with schizophrenia since the late 1960 (Tandon et al., 2010). Later in the 70 and 80 second-generation antipsychotics or atypical were introduced (Tandon et al., 2010).

Clozapine was the first atypical antipsychotic to be developed and was introduced in 1970. In 1974, it was taken off the market because of its association agranulocytosis (Minns & Clark, 2012). In 1989 it was found that was higher compared to other drugs for the treatment of schizophrenic refractory patients to the treatment and suicides (Bishara & Taylor, 2008; Tandon et al, 2010) and was re-approved its use by the FDA (Minns & Clark, 2012). In 1990 some other atypical antipsychotics have been developed with the goal of treating the positive and negative symptoms (risperidone, olanzapine, quetiapine, ziprasidone) and more recently aripiprazole and paliperidone. Although these drugs exhibited some improvement in negative symptoms, this benefit has been accompanied by the occurrence of other effects, including metabolic side, such as weight gain and impairment in glucose metabolism (Bishara & Taylor, 2008).

1.6.2.1. ROLE OF CLASSICAL ANTIPSYCHOTICS

Antipsychotic drugs are classified into classic, typical or first-generation antipsychotics and atypical or second-generation antipsychotics taking into account the chemical structure. The classic antipsychotics are divided into 5 groups: butyrophenones which includes droperidol and haloperidol, phenothiazines including chlorpromazine, promethazine, fluphenazine, thioridazine and prochlorperazine and the thioxanthene group cloroproxitene, benzamides (sulpride, tiapride) and reserpinics (riserpine) (Mauri et al, 2014;. Minns & Clark, 2012).

There are five types of dopamine receptors in humans: subtype (D1 and D 5) which are designated as Class D1. The D1 receptor (located on cortico-limbic-mesoestrial regions) has shown no clinical relevance in schizpohrenia. The blockade of D2 receptors (which are located in mesoestrial-limbica region) is the pharmacological target of all antipsychotics (Mauri et al., 2014). The classical have high affinity for D2 receptors and a strong correlation between clinical efficacy and its affinity to this receptor (Bishara & Taylor, 2008). Phenothiazines, the first group synthetized with block receptors D1 and D2 dopamine (Minns & Clark, 2012). Blockade of dopamine and the level and area of occupancy of the D2 receptor by antipsychotics are the factors responsible for many side effects of extra-pyramidal neurological order (EPS) such as tardive dyskinesia, Parkinsonism, dystonia and akathisia. Other side effects include cognitive and hormonal effects such as increased prolactin (Currell & Kane, 2014) and the neuroleptic malignant syndrome (NMS). These side effects occur with either high doses or in some cases with effective clinical doses of antipsychotics (Mauri et al., 2014). On the other hand, it should be noted that classical antipsychotics are less effective for improvement of negative symptoms and the opposite is valid for positive symptoms. Indeed, the positive symptoms of schizophrenia improve with drugs which reduce the transmission of serotonin agonists (5-HT 1A), of which increase the activity of dopamine in the prefrontal cortex of which reduce the hyperactivity of the mesolimbic pathway and blocking receptors from presynaptic dopamine (Bishara & Taylor, 2008).

1.6.2.2. THE SECOND-GENERATION ANTIPSYCHOTICS

The atypical antipsychotics are characterized by less avidity to bind to the D2 receptor (Mauri et al., 2014) so they are D2 dopamine receptor antagonist (Bishara & Taylor, 2008) and serotonin 5-HT2A, alleviating negative symptoms of schizophrenia (Minns & Clark, 2012) .It is due to this antagonism serotonin (5-HT2A) – dopamine (D2) and its affinity more to the serotonin (5-HT2A) receptor than for the dopamine (D2) that was proposed the separation between the classic and atypical; as an, exception to this rule the following antipsychotics amisulpride and remoxipride (Mauri et al., 2014). The higher affinity of atypical antipsychotics, to block the 5-HT2A receptors are responsible for increasing the output of dopamine in the striatum which contributes to the reduction of EPS effects (Mauri et al., 2014) and increased dopamine activity in the cortex prefrontal, improving negative symptoms (Bishara & Taylor, 2008). Atypical antipsychotics have minimal effects extrapyramidal or no effect on clinical doses (Mauri et al, 2014; Minns & Clark,

2012) with the exception of risperidone (Ishigooka, 2004). However it is associated with increased weight and decreased glucose tolerance (Ishigooka, 2004). Others show 5-HT2A receptor affinity, D2, and other systems affinity (cholinergic, antihistamine, 5-HT1A and 5-HT1C) are called multiple target receptors (MARTA); belong to this class: clozapine, olanzapine, quetiapine and asenapine. The blocking receptors D2 and D3, subtype receptors are called combined antagonist (amisulpride) (Mauri et al., 2014). And finally, a class of dopamine partial agonists such as aripiprazole and cariprazina (Mauri et al. 2014).

1.7. COMORBIDITIES

Comorbidity is defined as the independent coexistence of psychiatric and organic disease in the same patient, and each with influences on morbidity and mortality (Testa & Giannuzzi, 2013). It is estimated that 50% of patients with schizophrenia exhibit at least one comorbid psychiatric or general medical condition (Kozumplik et al., 2009). Psychiatric comorbidities associated with schizophrenia are: depression, anxiety disorder, obsessive compulsive disorder, and substance abuse that contribute negatively to the course of schizophrenia, worse psychotic symptoms and contribute to non-adherence therapy (Buckley, Miller, Lehrer, & Castle, 2009). The presence of anxiety is very common in these patients, including panic disorder, post-traumatic stress disorder and obsessive-compulsive disorder (Buckley et al., 2009).

In severe mental illnesses such as schizophrenia medical diseases also occur, especially cardiovascular disease, diabetes mellitus type II, obesity (Kozumplik et al., 2009), infections (human immunodeficiency virus "VIH" ,Hepatitis C and tuberculosis), arteriosclerosis, ischemic heart disease, hypothyroidism ,hyperthyroidism ,contact dermatitis, (Kozumplik et al, 2009;. Leucht et al., 2007), essential hypertension and chronic obstructive pulmonary disease (COPD). COPD is secondary to smoking habits present in these patients and infections by VIH (Kozumplik et al, 2009; Leucht et al, 2007) are the result of risk behaviors such as unprotected sexual intercourse with multiple partners, and substance abuse (Kozumplik et al, 2009.).

1.7.1. OBESITY

Obesity is twice more frequent in patients with schizophrenia than in the general population (Robillard et al., 2012) and is a risk factor for DM type II, heart disease, osteoarthritis, hypertension and diseases of the gallbladder (Kozumplik et al., 2009).The factors associated with obesity in these patients are: poor eating habits, physical inactivity, (Robillard et al, 2012.), The side effect of classical antipsychotics (chlorpromazine and thioridazine) that are responsible for increasing the weight gain (Yogaratnam et al. 2013) by 40%, and the effects of the atypical antipsychotics (Kozumplik et al., 2009). Clozapine and olanzapine have greater propensity to increase the weight, followed by quetiapine, risperidone (Reynolds and Kirk, 2010; Yogaratnam et al., 2013) and chlorpromazine that have intermediate risk, and finally, ziprasidone, aripiprazole, amisulpride, asenapine and haloperidol that have little effect on weight gain (Kirk & Reynolds, 2010).

Obesity induced by antipsychotics is thought to be associated with increased caloric intake and antagonism of atypical antipsychotics at the receptor of histamine H1 (Lean et al. 2003; Scigliano & Ronchetti, 2013), 5-HT2C serotonin and D2 dopamine (Scigliano & Ronchetti, 2013).

Clozapine and olanzapine exhibit 5-HT 2C antagonism associated with antagonism D2 (Reynolds & Kirk, 2010) and high affinity for the histamine receptor H1 (Yogaratnam et al., 2013), which may explain the increase in weight secondary to increased intake food (Kirk & Reynolds, 2010) .On the other hand, aripiprazole, ziprasidone have lower affinity for the histamine H1 receptor agonists and are partial antagonist (D2/ 5-HT1A), partial agonists shared in the serotonin (5HT1B) receptor and (D2 / 5-HT2C) receptor observed in the aripiprazole (Kirk & Reynolds, 2010). Pharmacological mechanisms that could explain the lower propensity for weight gain by these drugs (Yogaratnam et al., 2013). Asenapine has little effect on weight gain despite its strong affinity to the 5HT2C receptor.

Whatever the pharmacological mechanism, there are many differences between individuals in their susceptibility to weight gain induced by drugs that cannot be explained by differences in drug treatment or lifestyle or environmental factors (Reynolds & Kirk, 2010), as patients with schizophrenia before starting treatment with antipsychotics already had three times more intra-abdominal fat (Yogaratnam et al., 2013).These differences suggest the involvement of genetic factors. The gene associated with obesity is Leptin. This gene acts as an anorexigenic signal of adipocytes by activating the α-melanocyte-stimulating hormone. It is thought that the stimulation of the leptin receptors in the hypothalamus result of the secondary stimulation of hormones

melanin, endogenous cannabinoids and neuropeptide Y, which are associated with decreased appetite (Jin et al., 2008), but antipsychotics may induce resistance to leptin and subsequently lead to disinhibition of dietary intake (Reynolds & Kirk, 2010).

The peripheral metabolic hormones (leptin in the adipose tissue), ghrelin (in the intestinal tract) and central signals pancreatic insulin (histamine and serotonin) converge in the hypothalamus and modulate the activity of orexigenic neurons (ghrelin) and anorexigenic (leptin) in the arcuate nucleus. The active ghrelin and Y neuropeptide in the hypothalamic neurons are associated with increased appetite (Britvic et al., 2013). Patients with schizophrenia treated with antipsychotics have increased on the levels of ghrelin, in the appetite stimulating hormone and this factors were associated with increased body fat (Robillard et al., 2012). In addition, leptin has an overlap between serotonergic signaling and melanocortin signaling resulting in consumption and altered energy expenditure (Britvic et al., 2013).

Serotonin affects energy homeostase by stimulating neuronal melanocortin through receptor antagonism at the serotonin receptor 5HT2C and agonism at serotonin receptors 5HT1A, which explains the tendency of olanzapine and clozapine in weight gain (Britvic et al., 2013) and the opposite is observed by the 5HT2C serotonin agonists and H1 histamine. Cortisol is also thought to have a role in obesity and schizophrenia patients have increased levels of cortisol. The cortisol receptors are stored in visceral fat and potentiate the activity of lipoprotein lipase (an enzyme involved in the deposition of fat) (Robillard et al., 2012).

1.7.2. BLOOD PRESSURE

Hypertension is defined as the increase in systolic blood pressure greater than 140 mmHg and diastolic pressure greater than 90 mmHg. This disease is more common in patients with schizophrenia, and affects 9-27% of patients (Lan & Chen, 2012). The factors associated with high blood pressure in these patients may be attributed to increased levels of anxiety that increase diastolic blood pressure and heart rate (Robillard et al., 2012). The anxiety activates the hypothalamic-pituitary-adrenal axis and the sympathetic system (Graeff, 2007). Sympathetic hyperactivity can elevate blood pressure by peripheral vasoconstriction and increase in renal tubular reabsorption of sodium (Carvalheira, 2008). The dopamine system is a regulator of blood pressure through its direct action on the kidneys, controlling water balance and electrolytes but also has action on hormones with vasoactive capacity, such as aldosterone, renin, prolactin, and catecholamines (Alessi, 2003).

The peripheral dopaminergic system is modulated by the endogenous dopaminergic and cardiovascular system. During sympathetic stimulation, endogenous dopamine is secreted and modulates sympathetic discharge. The chronic blockade of D2 receptor dopamine by antipsychotic drugs that bind to this receptor, interrupting the peripheral dopaminergic modulation (in the heart, kidneys, adrenals, liver, endocrine pancreas and vessels), resulting in an increase in sympathetic tone and increase chronically blood pressure. These hypotheses are supported by the fact that patients with schizophrenia present increase in catecholamine levels in CSF and plasma after long-term treatment with antipsychotics and reduce these effects when the drug is withdrawn (Scigliano & Ronchetti, 2013).

In hypertension antipsychotics are also associated with orthostatic hypotension. Hypotension is defined as a reduction of ≥ 20 mmHg SBP or decreasing the SBP <90 mmHg while standing for three minutes (Mackin, 2008) .The hypotension occurs with all antipsychotic depending on the degree of α-1-adrenergic receptor antagonism, particularly with classic low power and atypical (clozapine, risperidone, quetiapine) (Muench & Hamer, 2010) and those with cholinergic antagonism (Khasawneh & Shankar, 2014; Mackin, 2008). The antipsychotics clozapine, olanzapine and quetiapine increase the risk of hypotension resulting from the α-adrenergic blockade (Jana et al, 2015; Mackin, 2008), and D2 agonist (aripiprazole), also reduce blood pressure, glucose and blood lipids.

The D2 receptors are located presynaptically on ganglion postsynaptic neurons, adrenal chromaffin cells, when activated indirectly induce vasodilation, reducing the cardiac contractility. As well, stimulation of the peripheral D1 receptors located in postsynaptic renal arteries, mesenteric and splenic direct cause vasodilation and decrease peripheral vascular resistance and blood pressure (Scigliano & Ronchetti, 2013).

The risk of orthostatic hypotension may be aggravated by combined antipsychotics, and is more common with the classic low power compared to middle or high power and atypical antipsychotics, which could worsen if they are associated with antihypertensive drugs (Khasawneh & Shankar, 2014).

1.7.3. THYROID DISEASE

We must point out that schizophrenic patients have a high prevalence of positive versus negative thyroid antibodies (Ezeoke et al., 2013). The prevalence of Graves' disease is increased in patients with schizophrenia (Chen et al., 2012), and can be attributed to genetic, environmental factors (linked to sedentary lifestyle), the side effects of drugs and immunological (Chen et al., 2012). The thyroid hormones play an important role in the regulation of dopamine and serotonin receptors, major neurotransmitters involved in the pathogenesis of schizophrenia (Santos et al., 2012). This is a negative feedback in which the thyroid hormones regulate levels of dopamine receptors, and this neurotransmitter inhibits in turn the secretion of thyroid stimulating hormone (TSH) leading to a state of hyperthyroidism. On the other hand, treatment with dopamine blockers increases TSH levels, leading to subclinical hypothyroidism (Santos et al, 2012.) and hypothyroidism increases the sensitivity of receptors of dopamine (Radhakrishnan et al, 2013; Santos et al, 2012), and decreases the activity of 5-Hydroxy-treptamina (5HT) (Santos et al., 2012).

1.8. READMISSION

Half of schizophrenic patients clinically stabilized after hospital discharge can be readmitted one year after. Factors associated with relapse in these patients are many, including the lack of adherence to treatment (Conley et al., 1999; Lafeuille et al, 2014.). Non-adherence which is defined as stopping the use of antipsychotic medication in a range equal to or exceeding one month during the first three months of treatment (Lafeuille et al., 2014).

The rates of lack of medication adherence in the clinic are greater than 50%, and may be associated with disease itself, such as the lack of insight, lack of adequate family support and also the side effects of antipsychotics. Adherence can be improved with the use of atypical antipsychotics or long-acting injectable antipsychotics (Conley et al., 1999; Lafeuille et al, 2014). Typical antipsychotics also reduce the readmission rate in the short and long term in a manner similar to the atypical. However, results in readmission rates are still lower than with classical antipsychotics (Conley et al., 1999). A study comparing the readmission rates between classical antipsychotics (haloperidol and fluphenazine) and atypical (clozapine, olanzapine and risperidone), over a 2 year period in acute and chronic schizophrenic patients, found no difference in the readmission rate in that time period (Herceg et al., 2008). However, they were different in the first year of readmission. Atypical drugs were significantly superior in reducing the readmission rate (Herceg et al., 2008). A

possible explanation for these differences in readmission rates between the two classes of antipsychotics may be because of the classical antipsychotics among patients with psychosis contribute to deterioration of cortical and related functional deficits, which occur more frequently than with atypical antipsychotics such as clozapine which reduces the risk of degeneration of cortical and psychosis (Harvey et al., 2013). Besides adherence other factors are associated with readmission such as gender. The differences between male and female point for women to be more vulnerable to readmission one year after discharge; and men 14 days to 5 years after discharge. This early readmission in males is attributed to alcohol and substance abuse. The social factors are also associated with readmission in a range of 1-5 years in patients with schizophrenia. The social factors contribute to 38.9% of readmission, followed by factors related to psychiatric illness and physical 31.1%, and substance abuse 9.7% (Lin et al., 2010).

2. OBJECTIVES

2.1. GENERAL OBJECTIVE:

Evaluate the effect of different antipsychotics in schizophrenic patients treated in Casa de Saúde do Bom Jesus (CSBJ) and study the most common medical comorbidities.

2.2. SPECIFIC OBJECTIVES:

1. Compare the length of initial admission with number of subsequent readmissions;
2. Study the relationship of different types of antipsychotic treatments prescribed (classical, atypical and combined) with the number of admissions and readmission period;
3. Understand the influence of different types of antipsychotic treatment with the incidence of the following comorbidities - obesity, hypertension and thyroid disease.

3. MATERIAL AND METHODS

3.1. TYPE OF STUDY

The study was quantitative, descriptive and retrospective cross-sectional through the study of the clinical of the date of 300 cases records of female patients hospitalized in period of five years in the Casa de Saúde do Bom Jesus (CSBJ) in Braga (2007-2012), with diagnosis of schizophrenia according to the International System of Classification of Diseases, 9th edition (ICD-9). After approval by the ethics committee of the CSBJ, was selected 107 clinical processes following; the inclusion criteria

3.1.1. INCLUSION CRITERIA

Patients clinically diagnosed with schizophrenia according to ICD-9 with aged 15-64 years with complete clinical records.

3.1.2. EXCLUSION CRITERIA

Patients chronically hospitalized in CSBJ, with the abuse of alcohol or psychoactive substances and neurological diseases were excluded from the study.

3.1.3. SAMPLE CHARACTERIZATION

The data collection was based on medical records of patients diagnosed with schizophrenia treated in CSBJ Braga between 2007-2012 who met the selection criteria. Data were entered in a database allowing the sample and the study definition. The variables studied were age in different admissions, marital status, race, profession, residence, education level, weight for admission, height, blood pressure in admission, type of treatment with antipsychotics (classical, atypical or combined), major medical comorbidities, number of hospital days per admission and differences of days between the first and second and second and third hospital admission.

3.2. EVALUATION OF COMORBIDITIES

3.2.1. OBESITY

Obesity was defined based on the weight up to the third admission, and the height of the clinical process, by means of the following formula (BMI = weight/height^2). Obesity was defined if the BMI was ≥30 kg/m^2, and pre-obesity was defined if the BMI ranged from 25-29.9 kg/m^2 (Norlelawati et al., 2012).

3.2.2. BLOOD PRESSURE

The blood pressure was taken directly from the records. It was considered if the pressure value TA was ≥ 140/90mmHg (Tschoner et al, 2007; Newcomer & Haupt, 2006).and hypotension if the TA was less than 100/60 mmHg in females.

3.2.3. THYROID DISEASE

It was evaluate from the clinical date of each process (clinical and analytical study).

3.2.4. OTHER COMORBIDITIES

Diabetes mellitus, smoking and hypercholesterolemia were not possible to assess due to lack of consistent records.

3.3. EVALUATION OF TREATMENT

The different treatments were registered in each admission carried out and were subsequently analyzed and graded according to the type of inpatient treatment with classical antipsychotic drugs, atypical or in combination.

3.4. STATISTICAL STUDY

The analysis was conducted with the introduction of the study variables withdrawn from medical records with the statistical package for social sciences (SPSS version 22). For all statistical tests used a significance level of 5% ($p < 0.05$) was considered.

The hospital stay, comorbidity and socio-demographic variables were analyzed based on the descriptive statistics. The age and differences of days (DF1 and DF2) among admissions were evaluated until the third admission because there are few records in other admissions. The variables of differences days of hospitalization were calculated by the formula, (DF1 = Difference between days of hospitalization the 1st and 2nd admissions divided by 360 days; DF2 = Difference between days of hospitalization the 2nd and 3rd admissions divided by 360 days) in order to obtain age in years.

To evaluate the period of initial admission to the number of subsequent readmissions was made ANOVA test one way with the dependent variable(length of the first hospitalization) and independent variables (number of subsequent readmissions) and a model of multinomial regression to assess what were the readmission predictors until the third hospital. It was used as the dependent variable (number of hospitalization) and the independents variables (length of stay in the first admission, age class, marital status, residence setting and level of education). It was considered the 1st internment as a reference.

The χ^2 test was used to assess the degree of association between readmission and the different co-morbidities (obesity and thyroid pathology) and readmission and the different types of antipsychotics (classical, atypical and combined). The degree of association between different antipsychotic treatments with medical comorbidities (orthostatic hypotension, pre-obesity, obesity and thyroid pathology) was also assessed. Finally a binary logistic regression model was used to assess the degree of association between the covariates: blood pressure (normotensive, hypertension), obesity (without, pre-obesity and obesity), antipsychotics (classical, atypical and combined) and a dependent variable (1-3 admissions which was coded as "0" and more than three admissions which was coded as "1").

4. RESULTS

4.1. GLOBAL DESCRIPTION OF THE SAMPLE

The table 1 show descriptive statistic for the sample. Most of the patients in this sample [(n = 40 (37.38%)] were young adults, single [n = 59 (54.13%)], residing in an urban area (n = 61 (55.95%)] with primary education (n = 42 (41.58%)] and had unskilled jobs (n = 34 (49.28%)].

Table 1 - Global Description of the Sample

	n (%)
Age	
≤19 years	10 (9.35)
20 to 29 years	40 (37.38)
30 to 39 years	22 (20.56)
40 to 49 years	23 (21.5)
50 to 59 years	9 (8.41)
≥ 60 years	3 (2.8)
Marital status	
Single	59 (54.13)
Married	32 (29.36)
Divorced	2 (1.83)
Widow	16 (14.68)
Residence setting	
Urban	61 (55.96)
Rural	42 (38.53)
Unknown	6 (5.5)
Formal education	
Primary education	42 (41.58)
Basic education	24 (23.76)
Secondary education	20 (19.8)
Higher education	15 (14.85)
Occupation	
Student	5 (7.25)
Unemployed	13 (18.84)
Unskilled worker	34 (49.28)
Skilled worker	14 (20.29)
Retired	3 (4.35)

Until the 3rd hospitalization 64.2% (n = 70) of participants were readmitted and from the fourth hospitalization only less than half of the initial sample were readmitted (n = 45; 41.28%). We also observed that the highest averages of days of hospitalization correspond to the 10th admission (Mean = 70.6; SD = 64.18; n = 10) and the 5th admission (Mean = 48.83; SD = 49.61; n = 36)

and were lower in the 9th (Mean = 25.19; SD = 20.37; n = 16) and 8th (Mean = 25.74; SD =11.62; n = 19) hospitalizations. Since after the 4th hospitalization more than an half of the initial sample was not readmitted we decided to merge the subsequent hospitalizations and classify them as 4 or more hospitalizations.

Table 2 - Descriptive Statistics of Inpatient Hospital Days

Length of hospitalization (days)	n(%)	Mean (SD)
1st hospitalization	109 (100)	38.31 (41.21)
2nd hospitalization	88 (80.73)	39 (41.37)
3rd hospitalization	70 (64.22)	37.32 (23.99)
4th hospitalization	45 (41.28)	31.73 (27.59)
5th hospitalization	36 (33.03)	48.83 (49.61)
6th hospitalization	27 (24.77)	44.44 (49.03)
7th hospitalization	21 (19.27)	41.29 (33.78)
8th hospitalization	19 (17.43)	25.74 (11.62)
9th hospitalization	16 (14.68)	25.19 (20.37)
10th hospitalization	10 (9.17)	70.6 (64.18)
11th hospitalization	6 (5.5)	34.83 (16.41)
12th hospitalization	4 (3.67)	35.75 (7.37)

The averages of days between periods when patients were not readmitted were similar for the three intervals between readmissions despite a decrease in the size of the sample [(Mean $_{1st/2nd}$ = 1381.6; SD = 1637.01; n = 88); (Mean $_{2nd/3rd}$ = 1167.5; SD= 1732.34; n = 70) and (Mean $_{3rd/4th}$ = 1128.36; SD= 1497.50; n = 47)].

Table 3 - Difference in days among the admissions

	n	Mean (SD)
Days between 1st and 2nd admission	88	1381.63 (1637.01)
Days between 2nd and 3rd admission	70	1167.53 (1732.34)
Days between 3rd and 4th admission	47	1128.36 (1497,50)

There was no significant differences between the duration of the first hospitalization among patients that had 1,2,3, 4 or more number of admissions (F=1.69; p=,17).

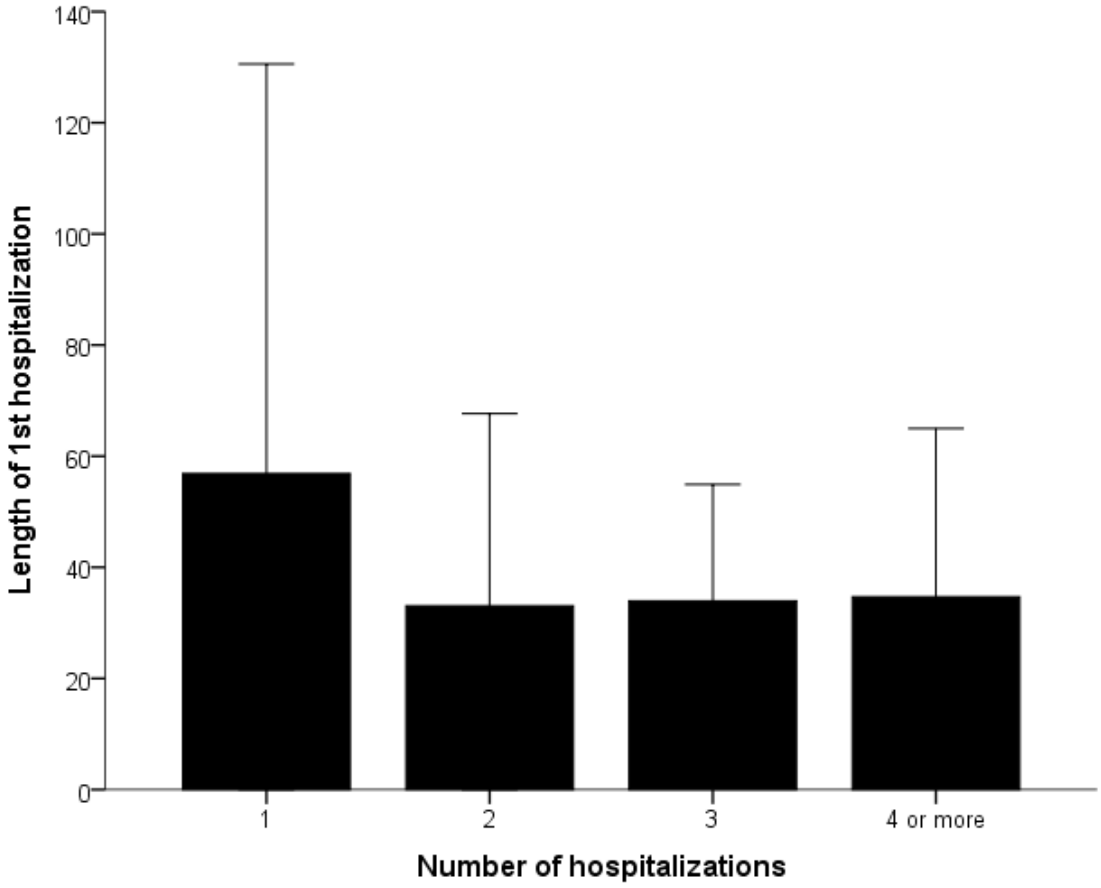

Figure 1 - Duration of the first hospitalization and the number of subsequent readmissions

A model of multinomial regression between the dependent variable (number of hospitalization) and the independent variables was made (length of stay in the first admission, age class, marital status, residence setting and level of education). It was considered the 1st internment as a reference, and it was observed that the education level was significant predictor of the second admissions (OR = 0041; p = .007) which means that the higher education level decrease the risk of the patient have a second readmission. The age group was significant predictor of the third (OR=0.45; p=.02) and fourth hospitalization (OR=0.25; p=.001), meaning that the older patients have lower risk of having three or more admissions.

Table 4 - Multinomial Regression Model

Number of hospitalizations		Odd's ratio	95% CI		*p*
			Lower	Upper	
2	Length 1st hospitalization	.983	.961	1.006	.142
	Age class	1.065	.544	2.086	.854
	Marital status	.631	.285	1.398	.257
	Residence setting	1.173	.341	4.033	.800
	Education	.407	.210	,786	007
3	Length 1st hospitalization	.993	,975	1.012	.482
	Age class	.453	.232	.884	.020
	Marital status	.859	.415	1.774	.680
	Residence setting	.976	.290	3.289	.969
	Education	.714	.425	1.199	.202
4 or more	Length 1st hospitalization	,997	,981	1.014	.744
	Age class	.250	.126	.497	.000
	Marital status	1.415	.744	2.693	.290
	Residence setting	1.094	.341	3.511	.880
	Education	.922	.766	1.111	.395

4.2. EVALUATION OF MEDICAL COMORBIDITIES

The figure 2 shows that the average body mass index (BMI) increases from the first (Mean = 25.69; SD=4.95; n = 66) to the fourth hospitalization (Mean = 27.91;SD=6.75; n = 31), although there is a decrease in the number of patients in the same order.

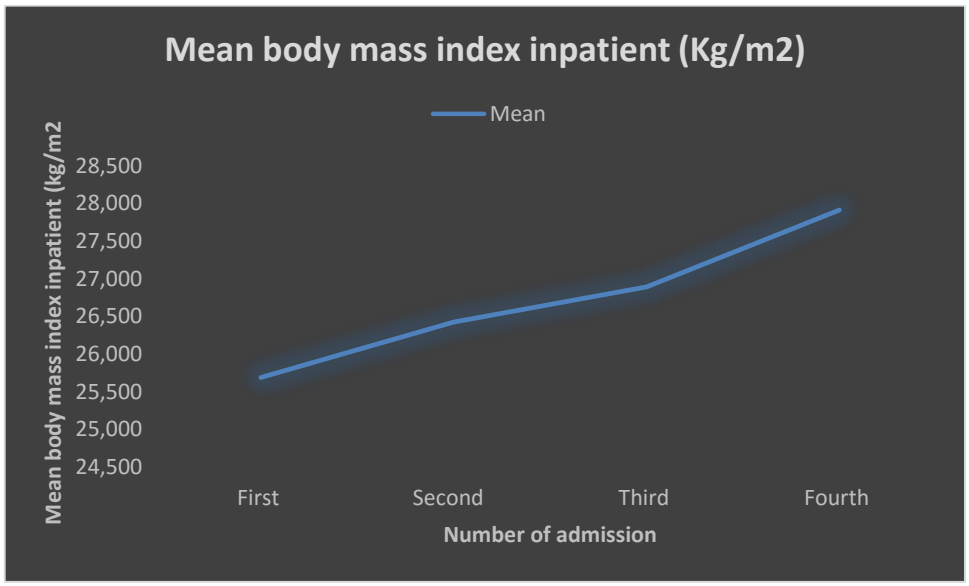

Figure 2 - Mean Body Mass index by Admission

The percentage of patients without obesity decreases from the second to the fourth hospitalization and the percentage of overweight patients increased from the second to the third admission. From the third admission, the percentage of obese patients increased also until the fourth admission.

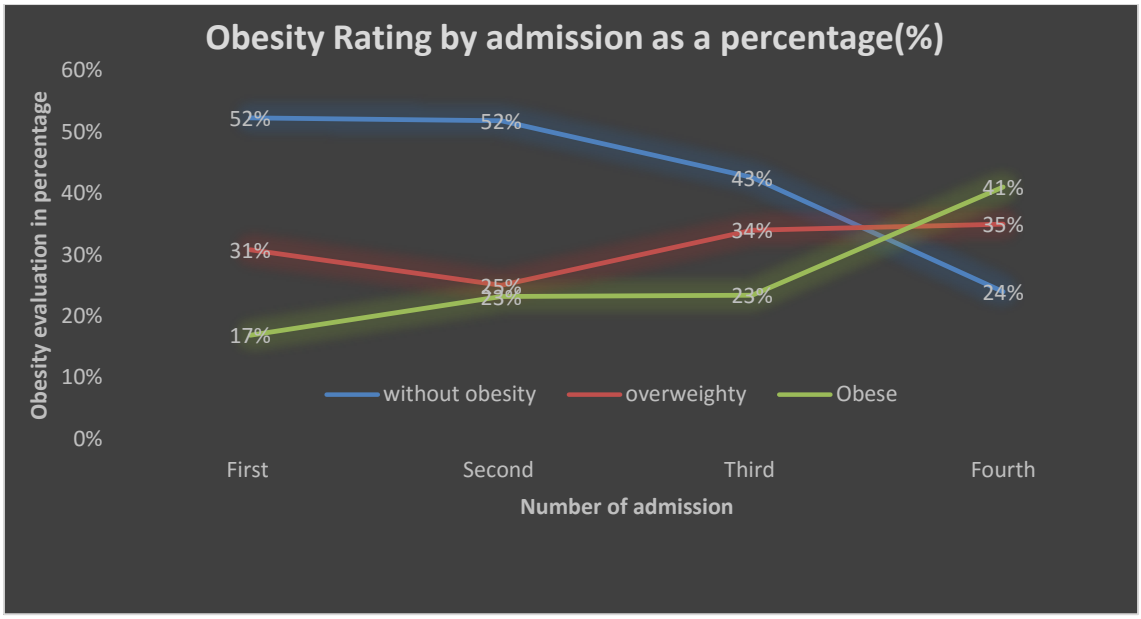

Figure 3 - Obesity classification inpatient as percentage (%)

The percentage of patients without comorbidities is high, showing a decreasing trend from the Third (69%) to the fifth hospitalization (54.7%). The Obesity represented the comorbidity with the higher percentage and showed an increasing tendency from the 1st (7.2%) to the 4th hospitalization (21.4%). The other comorbidities that rose from 1st to 4th relocation was the diabetes mellitus type II (9.9%; 11.9%) and. also the thyroids diseases which increases to almost double the 1st (3.6%) to the 4th (6.1%) hospital admission. The remaining was stable with a percentage lower than (7%).

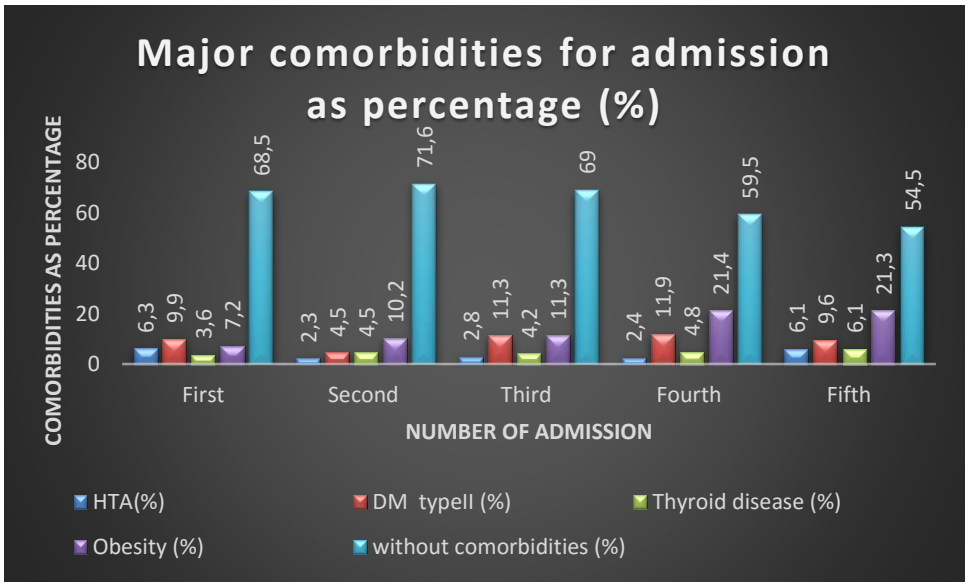

Figure 4 - Comorbidities in inpatient as percentage (%)

The percentage of schizophrenic patients with thyroid disease (n = 39; 35.8%) was lower compared to those without the disease (n = 70; 64.2%) (Figure 5).

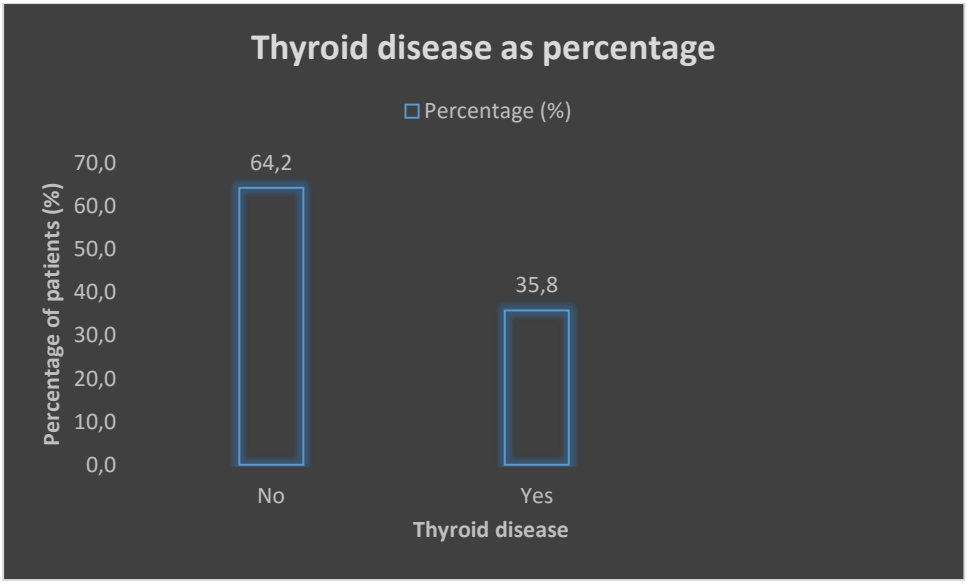

Figure 5 - Proportion of patients with thyroid diseases

The normotensive patients were the largest group presenting an opposite trend in relation to hypertensive patients. However, the percentage of hypotensive patients was the lowest among the three and remained stable over time (Figure 6).

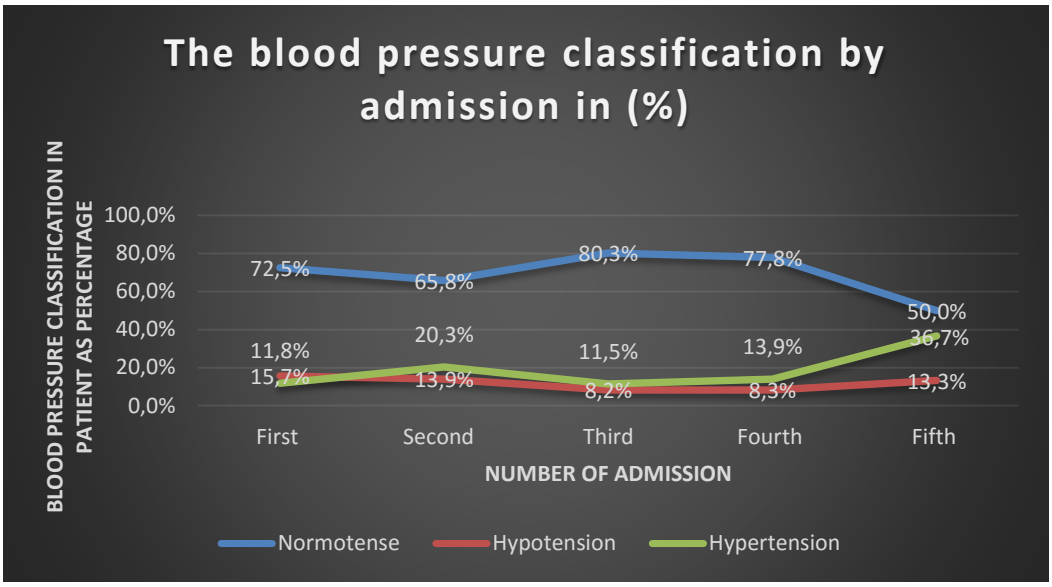

Figure 6 - Blood pressure rating inpatient in percentage (%)

4.3. EVALUATION OF TREATMENT

The percentage of schizophrenic patients who received combined antipsychotic was the highest, followed by classical antipsychotics. In relation to percentage of patients who received atypical antipsychotics was the smallest of all and remained stable until the third admission, when there was an increase in the percentage of patients receiving this treatment (Figure).

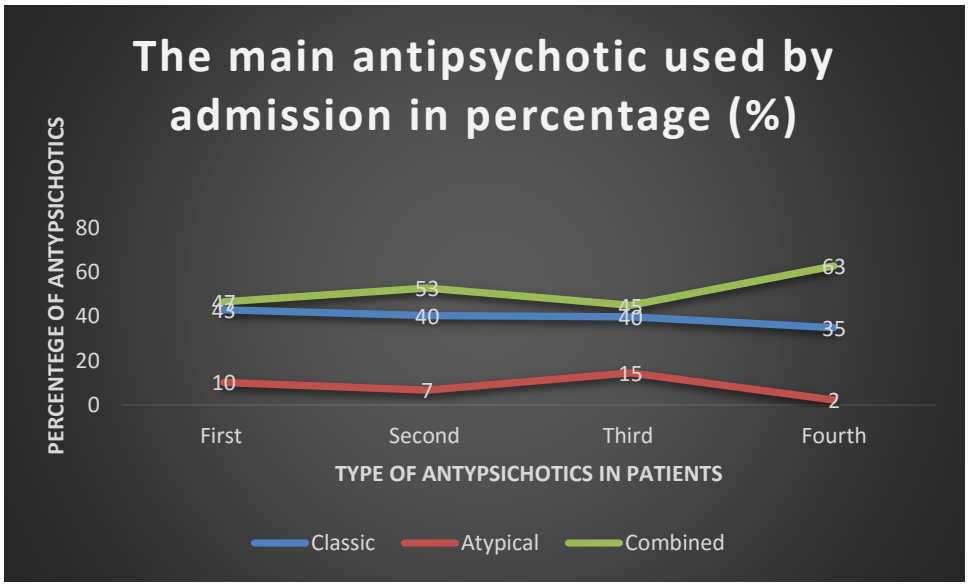

Figure 7 - The main antipsychotic's used in schizophrenic patients in percentage (%)

The classical antipsychotics used in ascending order were: Haloperidol, Chlorpromazine, Melperone, Levomepromazine, Pimozide, Thioridazine, Fluphenazine decanoate and Clotiapine.

Atypical antipsychotics were least prescribed compared to classical and their use decreased in the following order: Olanzapine, Risperidone, Quetiapine, Clozapine, Amisulpride, Aripiprazole and Ziprasidone (Figure 8).

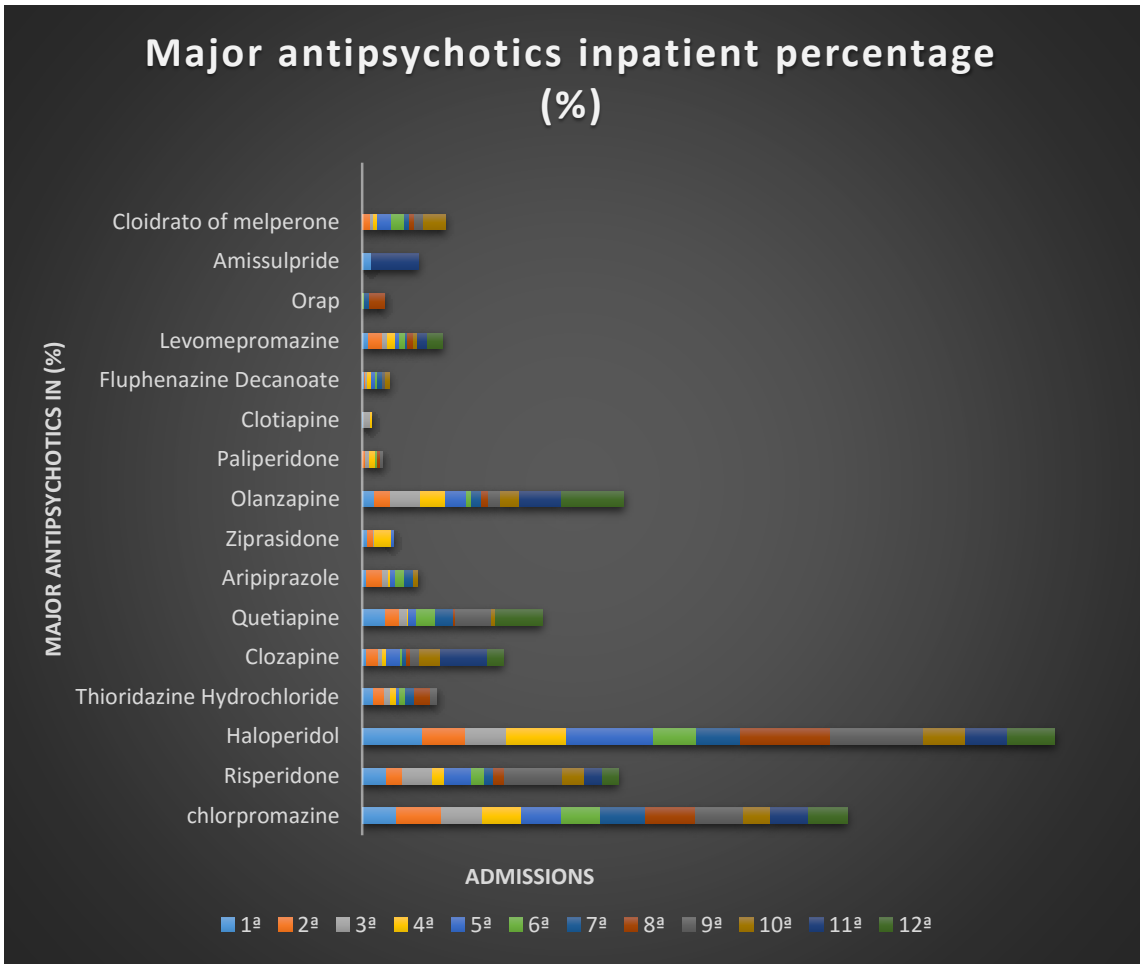

Figure 8 - Treatment in different admissions

4.4. EVALUATION OF READMISSION BY COMORBIDITY AND TREATEMENT

There was a significant association between patients who were obese and those who were readmitted ($\chi^2_{(df)} = 5.376_{(1)}$; $\varphi = .25$; $p = 0.02$). Of the total readmitted patients (n = 75), 19 (21.84%) were obese and 56 (64.37%) were not. Within the obese, 19 (21.84 %) were readmitted and 7 (8.05%) were not. Based on the relative risk, patients without obesity are 4.13 (OR: 4.13; CI: 1.170 - 14.548) more likely to be readmitted compared to obese.

There is a significant association between patients with thyroid pathology and those who were readmitted and high and significant effect size ($\chi^2_{(df)} = 42.09_{(1)}$; $\varphi = .64$; $p < 0.001$). The Table shows that the total readmitted patients (n = 89), 19 (17.43%) had thyroid disease and 70 (64.22%) did not. Of those who had thyroid pathology 19 (17.43%) were readmitted and 20 (18.35%) were not. Based on the relative risk, there was a decrease in readmission in patients with thyroid pathology in 78.7% (OR: .213; CI: .143 - .318) and estimation of variability was 68.2 to 85. 7%.

There is no significant association between the readmitted patients and those who received classical antipsychotics, ($\chi^2_{(df)}$ = 0.23 $_{(1)}$; φ= .13; p =.63).

There is a significant association between patients who received atypical antipsychotics and those who were readmitted, ($\chi^2_{(df)}$ = 6.61 $_{(1)}$; φ= .37; p =.10).Table 5 shows that the total readmitted patients (n = 69), 18 (24.66%) were treated with atypical antipsychotics and 51 (69.86%) were not. Of the patients who were treated with atypical antipsychotics 18 (24.66%) were readmitted and 4 (5.48%) were not. Based on the relative risk, there was a decrease in readmission of patients who received atypical antipsychotics in 73.9% and estimate of the variability was 61.2% to 82, 5% (OR: .261; CI: .175 - .388).

There is a significant and small association between patients who were treated with combined antipsychotics and those who were readmitted, ($\chi^2_{(df)}$ = 3.019 $_{(1)}$; φ= .22; p =.082). Table 5 shows that from the total readmitted patients (n = 81), 61 (64.89%) were treated with combined antipsychotics and 20 (21.28%) were not. Among the patients who were treated with combined antipsychotics 61 (64.89%) patients were readmitted and 13 (13.83%) were not. Based on the relative risk, there was a 24% reduction in readmission of patients who were submitted to combined antipsychotics and estimate of the variability was 14.7% to 33, 5% (OR: .753; CI: .147 - .335).

Table 5 - Readmission assessment taking into account the different types of antipsychotics treatments and different comorbidity's.

Variables	Readmited	Not readmited	
Obesity (n; %)			$\chi^2_{(df)}$; p; φ
No	56 (64.37)	5 (5.75)	$5.376_{(1)}$; .020; .249
Yes	19 (21.84)	7 (8.05)	
Thyroid pathology (n; %)			$\chi^2_{(df)}$; p; φ (Continuity Correction)
No	70 (64.22)	0 (0)	$42.086_{(1)}$; <.001; .643
Yes	19 (17.43)	20 (18.35)	
Classical antipsychotics (n; %)			$\chi^2_{(df)}$; p; φ (Continuity Correction)
No	23 (29.11)	0 (0)	$0.234_{(1)}$; .628; .127
Yes	53 (67.09)	3 (3.8)	
Atypical antipsychotics (n; %)			$\chi^2_{(df)}$; p; φ (Continuity Correction)
No	51 (69.86)	0 (0)	$6.614_{(1)}$; .010; .367
Yes	18 (24.66)	4 (5.48)	
Combined antipsychotics (n; %)			$\chi^2_{(df)}$; p; φ (Continuity Correction)
No	20 (21.28)	0 (0)	$3.019_{(1)}$; .082; .215
Yes	61 (64.89)	13 (13.83)	

4.5. EVALUATION OF THE COMORBIDITIES BY TREATMENT

4.5.1. PATIENTS TREATED WITH DIFFERENT TYPES OF ANTIPSYCHOTICS WITH THYROID DISEASE

There is a significant and small association between patients with thyroid disease and those who received classical antipsychotics, ($\chi^2_{(df)} = 5.25_{(1)}$; φ= .025; $p = 0.022$). The total number of patients who received classical antipsychotics (n = 56), 11 (13.92%) had thyroid disease and 45 (56.96%) did not have a thyroid condition. Of those who had thyroid pathology 11 (13.92%) had treatment with classical antipsychotics. Relying on relative risk, patients who had thyroid pathology have 1.24 less likely to have made treatment with classical antipsychotics (OR: 1.244; CI: 1.093 – 1.416).

There is a significant association between the patients with thyroid pathology and those receiving atypical antipsychotics, ($\chi^2_{(df)} = 8.59_{(1)}$; φ= .034; $p = 0.022$). The table that the total number of

patients who were treated with atypical antipsychotics (n = 22), 6 (8.22%) had thyroid disease and 16 (21.92%) did not. Of those who had thyroid pathology, 6 (8.22%) received atypical antipsychotics and 2 (2.74%) did not receive treatment with atypical antipsychotics. Based on the relative risk, patients receiving atypical antipsychotics have 9.19 less likely to have thyroid pathology (OR: 9.188; CI: 1.684 – 50.136).

There is a significant and small association between patients with pathology thyroid and those receiving combined antipsychotics ($\chi^2_{(df)} = 8.28_{(1)}$; $\varphi = .029$; $p = 0.04$). Table shows that from the total of patients receiving antipsychotic combined drugs (n = 75), 28 (29.79%) had thyroid pathology and 46 (48.94%) had no thyroid disease. Of those who had thyroid pathology 28 (29.79%) were treated with combined antipsychotics and 1 (1.06%) was not. Based on the relative risk patients receiving combined antipsychotics, present 11.98 less likely to have thyroid pathology (OR_ 11.978; CI: 1.521 – 94.347).

Table 6 - Patients treated with different types of antipsychotics and having thyroid disease

Variables	**Thyroid pathology**		
	No	**Yes**	
Classical antipsychotics (n; %)			$\chi^2_{(df)}$; p; φ
No	23 (29.11)	0 (0)	$5.249_{(1)}$; .022; .258
Yes	45 (56.96)	11 (13.92)	
Atypical antipsychotics (n; %)			$\chi^2_{(df)}$; p; φ
No	49 (67.12)	2 (2.74)	$8.589_{(1)}$; .003; .343
Yes	16 (21.92)	6 (8.22)	
Combined antipsychotics (n; %)			$\chi^2_{(df)}$; p; φ
No	19 (20.21)	1 (1.06)	$8.283_{(1)}$; .004; .295
Yes	46 (48.94)	28 (29.79)	

4.5.2. PATIENTS TREATED WITH DIFFERENT TYPE OF ANTIPSYCHOTICS WITH OVERWEIGHT

There was no significant association between overweight patients and those who received classical ($\chi^2_{(df)} = 0.57_{(1)}$; φ=-.092; $p = 0.45$), atypical, ($\chi^2_{(df)} = 1.204_{(1)}$; φ=-.136; $p = 0.27$) and combined antipsychotics, ($\chi^2_{(df)} = .55_{(1)}$; φ=.82; $p = 0.47$). .

Table 7 - Patients treated with different type of antipsychotics with overweight

Variables	**Overweight**		
	No	**Yes**	
Classical antipsychotics (n; %)			$\chi^2_{(df)}$; *p*; φ
No	13 (19.4)	10 (14.93)	$0.569_{(1)}$; .451; -.092
Yes	29 (43.28)	15 (22.39)	
Atypical antipsychotics (n; %)			$\chi^2_{(df)}$; *p*; φ
No	25 (38.46)	20 (30.77)	$1.204_{(1)}$; .273; -.136
Yes	14 (21.54)	6 (9.23)	
Combined antipsychotics (n; %)			$\chi^2_{(df)}$; *p*; φ
No	10 (12.99)	5 (6.49)	$0.549_{(1)}$; .471; .082
Yes	35 (45.45)	27 (35.06)	

4.5.3. PATIENTS TREATED WITH DIFFERENT TYPE OF ANTIPSYCHOTICS AND WITH OBESITY

There was no significant association between obese patients and those who received classical ($\chi^2_{(df)}$ = $.47_{(1)}$; φ=.84; p = 0.47), atypical ($\chi^2_{(df)}$ = $.020_{(1)}$; φ=-.18; p = 0.89) and with those receiving combined antipsychotics, ($\chi^2_{(df)}$ = $2.12_{(1)}$; φ=.17; p = 0.15).

Table 8 - Patients treated with different type of antipsychotics with obesity

Variables	**Obesity**		
	No	**Yes**	
Classical antipsychotics (n; %)			**$\chi^2_{(df)}$; p; φ**
No	18 (26.87)	5 (7.46)	$0.468_{(1)}$; .494; .084
Yes	31 (46.27)	13 (19.4)	
Atypical antipsychotics (n; %)			**$\chi^2_{(df)}$; p; φ**
No	33 (50.77)	12 (18.46)	$0.020_{(1)}$;888; -.018
Yes	15 (23.08)	5 (7.69)	
Combined antipsychotics (n; %)			**$\chi^2_{(df)}$; p; φ**
No	13 (16.88)	2 (2.6)	$2.120_{(1)}$; .145; .166
Yes	42 (54.55)	20 (25.97)	

4.5.4. PATIENTS TREATED WITH DIFFERENT TYPE OF ANTIPSYCHOTICS AND WITH HYPOTENSION

The total hypotensive patients (n = 15), 6 (7.59%) were treated with classic antipsychotics and 9 (11.39%) were not. Of those receiving treatment with classical antipsychotics 6 (7.59%) had hypotension and 50 (63.29%) did not present hypotension. Based on the relative risk, there was a decrease in the occurrence of hypotension in patients who did not receive classical antipsychotics in 81.3% and estimate of the variability was 38.6% 94.3% (OR: .187; CI: .057 - .614). Regarding to treatment with atypical antipsychotics, these were not associated with hypotension ($\chi^2_{(df)}$ = $2.12_{(1)}$; φ=.17; p = 0.15). .finally we can see that there is a significant and small association between

patients with hypotension and receiving combined antipsychotics, ($\chi^2_{(df)}$ = 4.018$_{(1)}$; φ= .21; p = 0.45). The total hypotensive patients (n = 20), 19 (20.21%) were treated with combined antipsychotics and 1 (1.06%) was not. Of those receiving treatment with combined antipsychotics 19 (20.21%) had hypotension and 55 (58.51%) did not present hypotension. Based on the relative risk, patients with hypotension, have 6.56 less likely to have received treatment with antipsychotic drugs combined (OR: 6.564; CI: .822 – 52.403).

Table 9 - Patients treated with different type of antipsychotics and with hypotension

Variables	**Hypotension**		
	No	**Yes**	
Classical antipsychotics (n; %)			**$\chi^2_{(df)}$; p; φ**
No	14 (17.72)	9 (11.39)	8.559$_{(1)}$; .003; -.329
Yes	50 (63.29)	6 (7.59)	
Atypical antipsychotics (n; %)			**$\chi^2_{(df)}$; p; φ**
No	39 (53.42)	12 (16.44)	0.116$_{(1)}$; .733; -.040
Yes	16 (21.92)	6 (8.22)	
Combined antipsychotics (n; %)			**$\chi^2_{(df)}$; p; φ**
No	19 (20.21)	1 (1.06)	4.018$_{(1)}$; .045; .207
Yes	55 (58.51)	19 (20.21)	

4.6. REGRESSION MODEL FOR THE NUMBER OF ADMISSIONS, COMORBIDITIES AND DIFFERENT TREATMENTS

A binary logistic model between the dependent variable (1-3 admission vs 4 or more admission) and the independents variables (hypotension,hyperthesion, normotension,normal weight, overweight, obesity and different type of antipsychotic's treatment).It was observed that this model was significant ($\chi^2_{(df)}$ = 19.73$_{(9)}$; R^2= .296; p = .02), and the use of classical antipsychotics until the third admission increases 4 times more the chance to have more admissions (Wald $_{(df)}$ = 5.095$_{(1)}$; OR: 4.046; CI: 1.202 – 13.616; p = .024). This model shows that only 29.6% ($R^2_{\text{Nagelkerke}}$ = 0.296) of readmission was explained by the use of classical antipsychotics until the third admission.

Table 10 - Binary logistic regression model between the different admission, comorbidities and different antipsychotic treatments

	Independent variables	Model [1-3 admissions (0) *vs* 4 or more(1)]			
		B	**SE**	**Wald$_{(df)}$; *p***	**OR (CI 95%)**
Blood pressure	**Hypotension**	-0.319	1.434	$0.049_{(1)}$; 0.824	0.727 (0.044; 12.084)
(0-no; 1-yes)	**Hypertension**	-1,48	1.351	$1.2_{(1)}$; 0.273	0.228 (0.016; 3.217)
	Normotension	-0.937	1.363	$0.473_{(1)}$; 0.492	0.392 (0.027; 5.665)
BMI class	**Normal weight**	0.868	0.681	$1.627_{(1)}$; 0.202	2.382 (0.628; 9.04)
(0-no; 1-yes)	**Overweight**	-0.828	0.796	$1.084_{(1)}$; 0.298	0.437 (0.092; 2.077)
	Obesity	0.159	0.801	$0.039_{(1)}$; 0.843	1.172 (0.244; 5.636)
Treatment	**Classical antipsychotics**	1.398	0.619	$5.095_{(1)}$; 0.024	4.046 (1.202; 13.616)
(0-no; 1-yes)	**Atypical antipsychotics**	-0.523	0.687	$0.58_{(1)}$; 0.446	0.592 (0.154; 2.279)
	Combined antipsychotics	-0.227	0.653	$0.121_{(1)}$; 0.728	0.797 (0.222; 2.866)
Constant		0.036	1.584	$0.001_{(1)}$; 0.982	1.036
$\chi^2_{(df)}$; *p*; $R^2_{Nagelkerke}$				$19.729_{(9)}$; .020; .296	

5. DISCUSSION

5.1. SAMPLE

Most of the participants in this study were young adults with ages between 20-29 years old, which corresponds to the range of ages of schizophrenia onset described in literature (Piper et al., 2012; Stilo & Murray, 2010), although it has been found a more precocious age of its onset in women (25-35 years old) (Piper et al., 2012). The sample was made up by single women, despite men not being include in the sample as showed in a trial performed by Robinson et al.,(1999) where there was a higher percentage of schizophrenic single men.

5.2. RESIDENCE

The most patients in this sample lived in urban areas which is in agreement with studies that showed that the incidence of schizophrenia is higher in urban areas than in rural areas in developed countries (Piper et al., 2012) and is more common in men educated in cities than those who were educated in rural areas (Bloomfield et al., 2015)..

5.3. LEVEL OF EDUCATION

Patients in the trial presented only elementary education, which is in line with the trial performed by Robinson et al., (1999), which showed that these patients generally do not evolve to secondary education. Despite a more precocious onset for women and a low level of school education, which are factors associated to the worst diagnosis, in the case of the present sample we did not find the worst diagnosis, since 70% of the patients were employed (excluding students), and thus it can be stated that these patients showed higher levels of social functioning as described by Levine & Rabinowitz (2009).

5.4. PROFESSIONAL STATUS

Studies have shown that about 41-64% of patients who had their first psychotic episode were employed (Tandberg, 2012). In European studies, employment rates of schizophrenic patients

range from 8% to 35% (Kiejna et al., 2015) and only 10-20% of these patients present competitive job (Fleischhacker et al., 2014).

In our study the employment rates were 69.7% (excluding students), higher than those described by Kiejna et al., (2015.). This employment rates is perhaps due to the fact that schizophrenia had late onset in women as is referred by some works (Levine & Rabinowitz, 2009; Miron et al, 2014.) and therefore, the course of the disease is more favorable (Barkhof et al, 2013.). Women can acquire higher levels of social functioning than men (Levine et al., 2009) because they have negative and residual symptoms less severe (Barkhof et al., 2013) as it was found in our sample.

The unemployment rate in schizophrenic patients in the study of Tandberg et al. (2012) is 51%. Factors associated with this high rate unemployment in schizophrenics are various: the presence of negative symptoms, cognitive dysfunction (Kiejna et al, 2015; Tandberg et al, 2012.); the early onset of disease, the presence of the metabolic syndrome, the number and duration of hospital stay and the lack of insight regarding the disease (Kiejna et al., 2015).

In our study, the unemployment rate was 22.8%. This rate is well below the rates of unemployment described by Tandberg et al. (2012), which leads us to think that this group of patients are unlikely to have negative symptoms, cognitive dysfunction, and not many admissions (Tandberg et al., 2012; Kiejna et al., 2015)

5.5. READMISSION

The admission rates were high up to the third admission (64%) and diminished to half on the fourth admission, despite being described in the literature that readmission numbers increase throughout time, reaching 86% in 7 years in schizophrenic patients (Dixon et al., 1997). In this trial, we did not find any association between the duration of the first readmission and the subsequent ones. The possible explanation could be that it is a group of young adult women that show a more favourable course of the disease and thus managed to reach higher social functioning levels (Barkhof et al.,2013). The latter describes that in young adults the risk of readmission is more precocious (in an interval inferior to 14 days), with a lower risk in an interval of 1-5 years and with a higher risk in the case of single patients in an interval of 1-7 years (Lin

et al., 2010). In this one, the interval between readmissions was 3 years (between the first and the fourth readmissions) which is in line with Lin et al., (2010). There are other factors associated with the increase of the probability of a patient being readmitted, such as the severity of the disease, low functioning level, lack of family support and reduction in the active population, and by each reduction of 1% in the active population the readmission rate increases by 2% (Kiejna et al., 2015), a lack of insight that contributes to the reduction of the adhesion to the treatment (Robinson et al., 1999). We observed in the studied sample that the higher the level of school education, the lower the risk of patients having a second or third readmission, as they had less negative symptoms, cognitive deficits, lack of insight regarding their disease (Kiejna et al., 2015; Tandberg et al., 2012) and better functioning levels. Since the majority of patients were employed, they had a better adhesion to the treatment and gave less importance to psychotic, negative and cognitive symptoms as described by (Robinson et al., 1999).

5.6. ASSESSMENT OF COMORBIDITIES

5.6.1. OBESITY

Weight gain has been described as a collateral effect when treating with antipsychotics, being very common in women treated with antipsychotics (Mitchell et al.,2013), and it seems to be a protective factor in preventing subsequent readmissions. This fact was observed in this trial on which obesity contributes to lower the probability of patients being readmitted, due to the fact of probable weight gain being associated to a better adhesion to the treatment with antipsychotics and improvement of the schizophrenia psychopathological symptomatology as already described by Hui et al., (2015), contributing so that these patients only had 3 admissions. But it is known that other factors contribute to weight gain, such as caloric ingestion increase, energy spending reduction, resistance to insulin (Scigliano & Ronchetti, 2013) and genetic factors (Fleischhacker et al., 2014). In factors associated to weight gain, it was only possible to explore the effects of the treatment. We can observe that from the third admission were used more atypical antipsychotics than classic antipsychotics, which corresponds to the time on which the patients gained weight. It is known that this treatment is responsible for increasing weight in women (Britvic et al., 2013; Schennach et al., 2012), as observed in our trial on which were prescribed high and medium risk atypical antipsychotics (clozapine and olanzapine) in weight gain (Sirota et al.,2015). Prescription of combined antipsychotics

(polytherapy) can also contribute to weight gain, as described in literature (Li et al., 2013). The antagonism 5HT2A/2C observed with clozapine and olanzapine is responsible for increasing appetite and food ingestion (Britvic et al., 2013) and posteriorly increasing weight (Mitchell et al., 2013). Despite not having been found an association between weight gain and the different treatments with antipsychotics, one might have considered that probably obesity in this group of patients could be a result of genetic factors. Still regarding atypical antipsychotics, it can be observed that this treatment contributes to lower the readmission risk in about 74%, and the average number of readmission days (except the fifth and the tenth admissions where it was observed a higher average number of admission days) that correspond to the number of days associated to clozapine and risperidone (70 to 40 days, respectively). In other admissions were used combined antipsychotics over classic ones that are responsible for increasing the number of readmissions, but not the average number of admission days; being the average number of admissions for haloperidol of 38 days similar to the average number of admission days found in the Paula et al. (2007) trial.

5.6.2. BLOOD PRESSURE (BP)

Blood pressure is defined as an increase of systolic blood pressure (SBP)> 140mmHg and diastolic blood pressure (DBP)> 90mmHg. It is considered normal-high if the (SBP) value is between 130-139 mmHg and (DBP) <85 mmHg; normal if (SBP) is ≤120 mmHg and (DBP) ≤ 80mmHg (Magrini & J., 2011). And finally, hypotension is classified as a reduction of (BP) < 100/60 mmHg.

Metabolic syndrome is very frequent in schizophrenic patients (Neelamekam et al., 2014) and it is characterized mainly by abdominal obesity (Chang & Lai, 2013) and general obesity that it is correlated with HTA, DM type II (Chang & Lai, 2013). Factors associated to this syndrome include: unhealthy habits, genetic predisposition (Nurjono & Lee, 2013), metabolic dysregulation and exposure to antipsychotics (Joshi, 2013; Nurjono & Lee, 2013).

Most patients in the trial were normotensive and we observed that they showed an inverse reason regarding hypertensive patients. Blood pressure (BP) increase is more common in women than in men (T., 2011). The discordance comes from other trials as the one that was performed in the Spanish population and showed that HTA prevalence was higher in men

(61,3%) when compared to women (Bobes et al., 2012). Possible explanations for this prevalence of normotensive patients on our sample can be the fact that HTA is more prevalent in men (Bobes et al., 2012) and in the entire women's population. Other reason is the fact that these patients have gone under treatment with combined antipsychotics, and with more classic over atypical ones.

Antipsychotics are also responsible for orthostatic hypotension in 75% of schizophrenic patients, which is more common in patients treated with combined antipsychotics (Mackin, 2008) and atypical antipsychotics (Khasawneh & Shankar, 2014). Atypical antipsychotics that cause hypertension include clozapine, olanzapine and ziprasidone (Khasawneh & Shankar, 2014), and risperidone and quetiapine present a lower risk of HTA (Khasawneh & Shankar, 2014). Despite not having been prescribed atypical antipsychotics that showed a risk of increasing HTA (olanzapine, ziprasidone and clozapine), as well as the ones with lower risk (risperidone and quetiapine), the effects of increasing BP can be attenuated by the atypical antipsychotics' hypotensive properties, since these act as a adrenergic antagonist (Mitchell et al., 2013). We also notice that the most prescribed classic antipsychotics were haloperidol, chlorpromazine and levomepromazine, and it is described that highly efficient classic antipsychotics (haloperidol, fluphenazine) present a low risk of orthostatic hypotension and tachycardia, since these drugs present a greater affinity for dopamine receptors (Lehman et al., 2010). Low efficiency classic antipsychotics (chlorpromazine, thioridazine) present a higher risk of sedation (Lehman et al., 2010) and orthostatic hypotension (Lehman et al., 2010; Mackin, 2008). This can be another explanation for not having been observed an increase of hypertensive patients. Trial patients that have undergone treatment with classic antipsychotics showed a reduced risk of hypotension (81,3 %) which is in line with a trial that compared the risk of hypotension between classic and atypical antipsychotics and concluded that risperidone was responsible for causing 2 times more hypotension when compared to perphenazine (Umbricht & Kane, 1996).

5.6.3. THYROID DISEASE

The prevalence of clinic hypothyroidism in patients with psychiatric diseases varies between 0,5-8% (Santos et al., 2012), but the prevalence of thyroid diseases in schizophrenic patients remains inconclusive. These patients present a greater frequency of thyroid autoimmune diseases and about 29% of schizophrenic patients show changes in thyroid hormones

(Radhakrishnan et al., 2013). In reality are described which changes of the thyroid function (severe hypothyroidism and hyperthyroidism) in schizophrenia can be associated to psychotic symptoms (Santos et al., 2012), and possible positive correlation between the increase of thyroid hormones and the severity of the schizophrenia (Thanoon et al., 2011).

The most frequently found comorbidity was the thyroid's pathology clinically described which increased from the first to the fifth admission and observed in just 35.8% of the patients. But it was not possible to specify which type of thyroid disease (hypothyroidism/hyperthyroidism) was associated to schizophrenia (Santos et al., 2012) and its severity (Radhakrishnan et al., 2013) since it was not possible to access laboratory data relative to TSH (thyroid stimulating hormone), T3 (triiodothyronine) and T4 (thyroxine). But we can observe that those patients were more readmitted up to the third admission and half were readmitted up to the fourth admission. Not all trials support the changing of thyroid hormones in schizophrenia as described in the (Akiibinu et al., 2012) trial which showed that in the acute stage of schizophrenia there is an increase of free T3/T4 and (Ichioka et al., 2012) that there was only an increase of T4 in the serum and the levels of T3 and TSH remained normal. On the other hand, the increase of basal TSH observed in hypothyroidism is associated to a poor response to treatment with antipsychotics and the increase of T3 will be an indicative of a better response to the treatment and an improvement of cognitive symptoms (Ichioka et al., 2012). In this trial were used combined antipsychotics (classic and atypical) over classic ones, since the atypical ones only increased from the third admission. The use of combined antipsychotics presents a synergic effect when blocking the dopaminergic transmission and it is responsible for increasing TSH (except quetiapine) which leads to sub-clinical hypothyroidism (Radhakrishnan et al., 2013; Santos et al., 2012). This state increases the sensitivity to the dopamine receptors and is responsible for increasing dopamine and reducing TSH in the serum. Thus, we might consider that the lower percentage of patients with thyroid disease found in this trial means that these patients were undergoing treatment and so have not yet presented visible thyroid disease as described in the trial by Santos et al. (2012). Treatment with combined antipsychotics in this trial reduces the chance of the patient developing thyroid disease, followed by atypical antipsychotics, since the pharmacological treatment is associated to subclinical hypothyroidism as described above. Therefore, we also observed that there was a reduction in the risk of readmission of patients treated with antipsychotics and that showed thyroid disease between 68.2% and 85.7%, since the levels of TSH diminish with treatment with antipsychotics.

6. CONCLUSION

The sample of this trial was made up by young adult women (n=107) with ages between 20-29 years old, single, residing in urban areas, with elementary school education and a high functional level, that despite the low level of school education allows to conclude that they did not show significant cognitive symptoms due to the fact that this population was actively employed. The duration of the first admission was not associated to posterior readmissions, since there were young adult patients with a more favourable course of the disease, despite this age group being more associated to the increase in the number of readmissions. It was also possible to observe that the interval between readmissions was 3 years to all admissions, suggesting that they were patients that adhered to the treatment and did not show severe cognitive deficits. Associated factors in reducing the readmission in this trial was weight gain, as it can be associated to adhesion to treatment. Weight gain was most noticeable when the patients started receiving treatment with atypical antipsychotics. Despite this trial not having found any significant associations between the treatment with atypical antipsychotics and weight gain, it can be stated that genetic factors could be contributing to obesity in this group of patients and pharmacological treatment aggravated weight gain by increasing food ingestion. This treatment was also responsible for reducing the number of readmissions and not increasing the number of admission days. We can also observe that most patients were normotensive and classic antipsychotics were associated to a lower risk of causing blood hypotension, whereas atypical antipsychotics were not associated to it, despite literature describing this possible association. Finally, the other comorbidity present in this trial was thyroid pathology that increased from the first to the fifth admission. This clinically described comorbidity can be the result of the synergic effect of the combined antipsychotics in the blockage of dopamine receptors and is responsible for increasing TSH (except quetiapine), leading to subclinical hypothyroidism. This state increases the dopamine receptors' sensitivity and is responsible for increasing dopamine and reducing TSH in the serum. Thus, we can consider that the lower percentage of patients with thyroid disease found in this trial means that these patients were undergoing treatment and so did not yet show visible thyroid disease as described in literature. Treatment with combined antipsychotics in this trial reduces the chance of patients developing thyroid disease. We also observed that there was a reduction in the risk of readmission of patients treated with antipsychotics and that showed thyroid disease between 68.2% and 85.7%, since the levels of TSH diminish with treatment with antipsychotics.

6.1. LIMITATIONS AND FUTURE PERPECTIVES

The first limitation of this study is the fact that it is a retrospective study that included only female patients not thereby allowing comparisons with the male patients and therefore not being able to generalize their results. The second limitation is related to the sample, which was selected for convenience because the collected data from all study patients with schizophrenia admitted to the study period. The third limitation was the lack of data from some laboratory parameters such as blood glucose, HDL, TSH values T3 and T4 that were present in some cases of patients, but most cases did not have this data and therefore was not possible to evaluate other co-morbidities and specify what were the most common thyroid diseases in these patients either by gender or age group. A fourth limitation was the lack of registration in the process data related to smoking, it would be an important factor since the majority of patients with schizophrenia have smoking habits marked. The fifth limitation was due to the fact of not being able to explore all described factors responsible for weight gain in this group of patients, only being able to explore the effect of antipsychotics, for lack of registration of other important parameters for assessing obesity such as, food intake, physical activity, insulin resistance, among others. The sixth limitation was also a lack of data on family support outside the hospital, these data could help assess adherence.

Future work should address these limitations by analyzing these associations in a larger population that includes male patients, with more extensive access to medical records that include laboratory parameters and psychometric and biometric data. Furthermore, a prospective design in future studies with an extensive characterization of a cohort of patients with schizophrenia would allow a valuable evaluation of the association between the different treatments and the most common psychiatric and medical comorbidities.

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