Preliminary Version

A review of clinical and economic evaluations applied to psychotropic therapies used in the treatment of schizophrenia in Argentina

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Abstract
Introduction: Schizophrenia is considered to be a serious mental disorder that affects over 21 million people all over the world, and is associated with disability that frequently affects the patient’s educational and working performance. In Argentina, two of the most widely used antipsychotics in the treatment of this disorder are Haloperidol and Risperidone. Both of them are provided for free to patients without health coverage in the public health care facilities.

Objective: In this paper we seek to evaluate the clinical and economic benefits of prescribing psychotropic therapies based on Haloperidol (a first-generation antipsychotic that is part of the group of the butyrophenone drugs) versus Risperidone (an atypical or second-generation antipsychotic-neuroleptic drug) on adult patients that have been diagnosed with schizophrenia.

Methodology: An exhaustive survey of relevant articles published since 2006 up to the present day was carried out.

Conclusions: Intermittent treatment usually fails to prevent relapses, due to irregular protection. That is why continuous treatment is more effective. Although the injectable formats of both drugs (Haloperidol DEPOT and long-term acting injectable Risperidone) have not proved to have significant differences regarding clinical effectiveness vis-à-vis the tablet formats, they show a higher cost-effectiveness ratio by reducing patients’ relapses. Moreover, long-term acting injectable Risperidone exhibits a higher ratio of clinical cost-benefits than Haloperidol DEPOT. Haloperidol is less expensive than Risperidone but shows a lower cost-effectiveness ratio; in comparison with Haloperidol, the treatment with Risperidone produces i) an improvement on the QALYs and iii) a significant reduction of the negative symptoms.

Discussion: In most cases antipsychotic treatments are effective to control the positive and negative symptoms associated to schizophrenia, allowing patients to live in their communities without any impairments. However, it is extremely important to combine pharmacological treatment with other measures that constitute what is called psychosocial therapy.

Introduction
Schizophrenia is defined as a mental illness that involves positive symptoms associated with excesses (alterations in the thoughts or delirium, alterations in perception or hallucinations, alterations of the behavior, incoherence, illogicality, distractibility, tachylalia, etc.) and negative
symptoms related to deficiencies (lack of energy and motivation, emotional disorders, social withdrawal, immutable facial expression, low visual contact, absence or deficit of vowels expressions when speaking, etc.).

People who suffer from schizophrenia have a life expectancy 15 to 30 years shorter than general population. Approximately 2 million new cases are recorded each year worldwide, and the prevalence rates do not show significant quantitative differences between ethnic groups and geographical regions. At least two thirds of the patients need to be hospitalized once in their lives because of this disease (WHO, 2016).

Schizophrenia is an extremely expensive disorder; psychotropic drugs’ expenses involve the biggest costs along with relapses and repeated hospitalization due to patient’s lack of commitment to treatments (Leucht et al., 2012). The loss of autonomy and reduced labor productivity that involves having schizophrenia does not exclusively affect the patients but also their family and loved ones, either through the need to deliver personal care services to the patients, as well as their own health deterioration because of these duties. Caring activities usually involves a group of quite heterogeneous actions aimed mainly at covering the patients’ lack of autonomy that this disorder carries along with (Moreno et al., 2012).

According to the clinical practice guides from the National Institute for Health and Care Excellence (2006), schizophrenia treatment must complement anti-psychotic medication along with therapeutic counseling. The treatment of Schizophrenia with antipsychotic medication might require a multidimensional approach that should take into account the efficacy (the ability of an intervention to get the desired result under ideal conditions), the effectiveness (the degree to which the intended effect is obtained under routine clinical practice conditions or settings) and the efficiency (value of the intervention as relative to its cost to the individual or society) (Crespo- Facorro et.al, 2017). The selection of the best drug available must be made by the professional alongside the patient, taking into account the results of an integral medical check-up. The WHO Model List of Essential Medicines details four injectable antipsychotics for the treatment of Schizophrenia and considers them as a part of the minimum set of medicines necessary for basic health care and as the most cost-effective and safe medicines for this purpose. These antipsychotics are: Chlorpromazine, Fluphenazine, Haloperidol and Risperidone (WHO, 2013).

In Argentina, around 400,000 people have schizophrenia (WHO, 2016), with adults and adolescents of low socioeconomic status (SES) showing an increased risk of developing this type of disorder (Ortiz, Lopez and Borges, 2007). In this country, Haloperidol and Risperidone are the two most widely used anti-psychotics in the treatment of the schizophrenic disorder (Gargoloff et al., 2009). Both of them are provided for free to patients without health coverage in the public health care facilities, although the population receiving Risperidone is 10% higher than that receiving Haloperidol (MSN, 2011). This situation raises the question whether there is evidence of clinical and economics benefits supporting the prescription of one drug over the other.

Objectives

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1 The WHO Model Lists of Essential Medicines has been updated every two years since 1977. The current versions are the 19th WHO Essential Medicines List and the 5th WHO Essential Medicines List for Children updated in April 2015.
The general objective of this paper consists in evaluating the clinical and economic benefits of psychotropic therapies based on Haloperidol and Risperidone applied in adult patients that have been diagnosed with schizophrenia following DSM-5 guidelines. Specific objectives include:

a) Identify the most commonly prescribed drugs for the treatment of each stage of the schizophrenic disorder in Argentina.

b) Inquire about the relative advantages of different psychotropic administration therapies, and in particular i) between continuous treatment vs. intermittent treatment (of the psychotic episode) and ii) long-acting injectable versions versus oral versions of daily intake.

c) Analyze the results of cost-effectiveness and clinical studies performed in relation to Haloperidol and Risperidone, and in particular those comparing both drugs.

Methodology

To accomplish the first particular objective, an interview with key informants of the Argentinean public health sector was performed. For objectives two and three, a comprehensive search of the electronic databases GOOGLE SCHOLAR, EBSCO, JSTOR, SAGE JOURNALS, BIOMED CENTRAL, COCHRANE, WILEY LIBRARY, SPRINGER LINK, PUB MED and SCOPUS for peer-reviewed articles published in English was conducted in the last week of September 2016 and updated in April 2017. Search terms were: Schizophrenia, Schizophrenic Disorders, Pharmacoeconomic Analysis, Drug Economic Evaluation, Haloperidol, Risperidone, Drug Therapy, and Pharmacotherapy. In addition, a hand-search of the reference lists of published articles was also conducted. All articles were assessed for their suitability assigning each of them a relevance punctuation (from 0 to 10) taking into account both the methodological quality and the response degree to each of the questions posed in the present revision. In order to define the scoring, the quality guide for economic studies developed by NICE (NICE, 2006) was used. Those items which had a relevance score of less than 5 were discarded. At the same time, only the scientific papers published from 2006 until the present were considered, so as to get updated sources.

Results

Objective 1

Schizophrenia is a mental disorder that has three phases. The acute phase or crisis is characterized by a psychotic outbreak that is an abrupt manifestation of the positive symptomatology of schizophrenia for a short period of time and involves a temporary rupture of reality; patients under this state have hallucinations or delirium with their consequent decompensation. When the psychotic outbreak occurs, the patient should be hospitalized.

2 The selected studies includes patients who do not present any other pathologies such as hypothyroidism, cardiac or pulmonary conditions, hypocaemia, cancer, Parkinson’s disease, epilepsy, diabetes, liver or kidney failure, etc. Studies that include pregnant patients or patients with drinking or smoking problems were also excluded.

3 The diagnostic and statistical Manual of mental disorders (DSM), edited by the American Psychiatry Association develops a classification of mental disorders that provides clear descriptions of the diagnostic categories, so as to allow physicians and health researchers to diagnose, study and exchange information and treat different mental disorders. The last updated edition is the fifth; known as DSM-5 and it was published on May 18, 2013.
In Argentina, the combined use of Haloperidol and Lorazepam is the most usual indication for emergency care in the acute phase of this disease, in the absence of a previous medication regimen. It is recommended to provide 2-10 mg PO⁴ or IM⁵ of Haloperidol, together with 2 mg of Lorazepam or IM if necessary every thirty minutes until stabilization and decreased agitation in the patient (MSN, 2013). Haloperidol has an excellent acute antipsychotic profile but is not very sedative, so it should be accompanied by an anxiolytic and hypnotic like Lorazepam (Espinoza, 2004).

The stabilization or post-crisis phase covers the six (up to twelve) months after the acute episode, where the patient is recovering its functionality. In this phase is recommended to maintain antipsychotic medication, reducing the dose in shape for several weeks. Continuous psycho-social care should also be provided. In Argentina, this instance is not contemplated, so that patients move directly from the acute to the maintenance phase.

Finally, the stable or maintenance phase is where patients may not present symptoms, or present symptoms such as: tension, irritability, depression, negative symptoms and cognitive impairment. Positive symptoms (hallucinations, delusions, behavioral disturbances) of the acute phase may persist in some patients, but to a lesser extent (AATRMC, 2009). During this phase the main objectives are promoting the social and work reintegration of the patient and minimizing the risk of relapses, without the drug causing severe adverse effects that alter the patients’ quality of life. In that sense, a maintenance dose can be used (reaching 20% of the effective dose through a slow and gradual decrease) (Alvano, 2000). In Argentina patients who go through this phase are mainly treated with Risperidone or, in a lesser proportion, with Haloperidol. Both drugs are used to treat positive and negative symptoms, and have a similar active principle.

**Objective 2**

Some professionals consider that intermittent pharmacological treatment, which refers to the use of medication during periods close to the relapse of the symptoms of schizophrenia, has a superior efficacy with respect to the continuous administration of psychoactive drugs. Intermittent pharmacological treatment includes: intervention based on prodrome (which evaluates the risk of the initial stage of relapse); the intervention in times of crisis during an acute episode or deterioration of mental health and the gradual increase of periods without drugs. The objective is to reduce exposure to drugs and reduce side effects. However, Sampson et al. (2013) show that i) intermittent antipsychotic treatment is not as effective as continuous treatment and ii) although costs are reduced for patients when they do not consume drugs on a daily basis, on the other hand they are increased by the higher rates of hospitalization suffered by these individuals.

Continuous treatment for schizophrenic disorder can be done orally (by taking daily tablets) or by injections (with applications every fifteen days approximately). Treatment with long-acting injections has demonstrated to reduce hospital admissions and patients’ relapses; and despite being more expensive than oral treatments, it has a better cost-effectiveness ratio (Olivares et al., 2008).

The treatment’s final result is affected by the patient’s cultural and social surroundings, education level, as well as his personality traits and age. Some patients do not comply with the treatment due to the belief that they have not been treated or diagnosed accurately or that the drugs they are taking are not effective, or because they do not fully understand the explanations given by their doctor. Other times, the cause of the ineffectiveness of the treatment lies in simple forgetfulness or having difficulty obtaining the medication they need. Because of the above mentioned reasons, the best way to avoid all the problems related to keeping up with the treatment is to use injectable long-term

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⁴ By mouth, orally.

⁵ Intramuscular
acting medication, in order to circumvent all the hassle that implies the daily taking of oral tablets for schizophrenic patients (Kirson et al., 2013).

**Objective 3**

According to the Vademecum (2016), Haloperidol is a classical or first generation antipsychotic drug (AT), and is part of the group of the Butyrophenones. It is one of the first antipsychotics to be used in the XXth century for the treatment of mental illnesses. It can be administered orally, through an intramuscular injection or an intravenous line. This psychotropic is a potent antagonist of cerebral dopaminergic receptors and, therefore, is included among high-potency neuroleptics. Haloperidol features neither antihistamine nor anticholinergic activity. Risperidone, on the other hand, belongs to the group of atypical or second generation (AA) antipsychotics-neuroleptics, which show a similar clinical effectiveness in comparison to first generation antipsychotics. The Risperidone’s action mechanism is unknown, though it is thought that its activity takes place due to a combined blocking of the dopaminergic receptors D2 and the serotonergic receptors S2 (dopaminergic serotonergic antagonist). Other effects Risperidone produces might be explained by the blocking of adrenergic-histaminergic alfa-2 receptors. This psychotropic is well absorbed by the gastrointestinal mucous membrane and is also fully metabolized by the liver.

Every antipsychotic has a common action mechanism: the antidopaminergic effect. First generation antipsychotics are the oldest, their action is mainly antidopaminergic and they are characterized by their effectiveness on the control of positive and little effective psychotic symptoms over negative ones. Second generation psychotropics are characterized by simultaneously blocking the dopaminergic and serotonergic receptors, and they also display a high degree of effectiveness both regarding positive as well as negative symptoms.

Long-acting injections of first generation antipsychotics were the first to be developed, in particular those of Haloperidol. Haloperidol DEPOT (injectable version) has not shown any significant differences regarding medical effectiveness, side effects and behavioral responses in relation to Haloperidol in tablets (Quraishi et al., 2011). Dold et al., (2015) have demonstrated that, in comparison to other first generation high-potency antipsychotics, Haloperidol produces fewer side effects and reduces the positive symptoms of the disease more effectively. Nevertheless, studies performed so far do not show Haloperidol’s superiority in comparison to low-potency antipsychotics (Tardy et al., 2014).

Haloperidol is usually prescribed alongside Benzodiazepines (such as Diazepam, Lorazepam, Clonazepam, etc.) since these drugs have a sedative effect on patients that increases the neuroleptic sedative action of Haloperidol. However, the treatment carried out only with benzodiazepines is neither effective nor safe for patients (Dold et al., 2012).

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6 The positive symptoms of the schizophrenic disorder are related to the Mesolimbic pathway which is overactive (too much Dopamine), and the negative effects are related to the Mesocortical pathway, which is underactive (too little Dopamine). The same neurotransmitter (Dopamine) affects a part of the nervous system by excess and others by default, whereby antipsychotics perform the dopaminergic blocking function.

7 Currently, it is believed that the dopamine hypothesis is excessively simplistic, which has taken some researchers to pose the serotonergic hypothesis of the schizophrenic disorder, in which it is presumed that this neurotransmitter also plays an important role in this disorder.

8 Traditional antipsychotics (first generation) are classified into two groups, high potency and low potency, depending on the amount of necessary doses in order to achieve a certain result.
In comparison to other typical antipsychotics like Chlorpromazine, Haloperidol has produced better results in terms of patient adherence to treatment, but also a higher incidence rate of movement disorders as a result of their continued use (Leucht et al., 2008).

Risperidone was the first second-generation antipsychotic available in long-acting formulation (Chue and Chue, 2012). The Long- term acting injectable Risperidone (LTAIR) presents, in general, the same effectiveness as Risperidone in tablets, and although it contributes to reduce treatment dropout, it is much more expensive (Sampson et al., 2016).

Nielsen et al., (2014) made a retrospective inception cohort study of adults with schizophrenia using nationwide Danish registers from 1995 to 2009, comparing outcomes between patients receiving first-generation antipsychotic long-acting injections (FGA-LAIs) or Risperidone Long-acting injection (LTAIR). Among 4532 patients who initiated a treatment with long acting injectables, 2078 received LTAIR and 2454 received FGA-LAIs (zuclopenthixol decanoate = 52.2%, perphenazine decanoate = 37.2%, haloperidol decanoate = 5.0%, flupenthixol decanoate = 4.4%, fluphenazine decanoate = 1.3%). LTAIR was not superior to FGA-LAIs regarding time to psychiatric hospitalization, all-cause discontinuation, and duration of hospitalization.

Chee, Bin Abidin and Verma (2016), after carrying out a study on 77 patients diagnosed with schizophrenia that belonged to the Early Intervention Program on Psychosis of the Mental Health Institute of Singapore, concluded that Risperidone effectively reduces most of the negative symptoms of this disorder in comparison to Haloperidol, besides being tolerated better by patients. Tamrakar et al., (2006) discovered that, specifically after a week of treatment, patients who were treated with Risperidone did much better than those who were taking Haloperidol in terms of i) total score of positive and negative syndrome scale (PANSS), ii) negative symptoms’ scale and iii) general psychopathology scale.

Boettger, Jenewein and Breitbart (2015) have shown that Haloperidol and Risperidone are equally efficient in the managing of delirium, but they differ in their side effects since the most frequent extrapyramidal symptoms\(^9\) associated to the use of Haloperidol are akathisia (the inability to stay still), tardive dyskinesia (abnormal and involuntary movements of the orofacial region), hyperreflexia (excessive response to stimulation), muscular rigidness, opistothonos (rigidity and severe arching of the back, with the head thrown backwards) and occasional oculogyric crises (involuntary upward deviation of the eyes). Likewise, headaches, vertigo and seizures were observed on some patients who were administered this medication (Ahmed et al., 2007).

According to Escamilla (2001), it is very frequent that individuals that have been affected by schizophrenic disorder for more than one year develop some kind of affective disorder like mania or depression. In such cases, pharmacological treatment poses a real challenge, since it is not recommendable to add antidepressants to a patient who is already doing antipsychotics (Emsley & Jones, 2001). Second generation antipsychotics (like Risperidone) have shown to be more effective when treating this kind of patients in comparison to first generation antipsychotics (like Haloperidol) (Furtado et al., 2008).

A Belgian cost-effectiveness analysis made by De Graeve et. al, (2012) found that long-acting Risperidone is more effective and less costly than depot Haloperidol. LTAIR appears to represent a favorable frontline strategy for patients with schizophrenia requiring long-term maintenance treatment. A study performed in Taiwan by Yang et.al (2005) using the Kaplan-Meier method also showed that long-term action injectable Risperidone is more cost-effective than Haloperidol administered via DEPOT intramuscular injections. On the other hand, a scientific study performed by Hensen et al. (2010) in Sweden, found out that treatment with LTAIR produces an improvement

\(^9\)Extrapyramidal symptoms (EPS) are side effects of antipsychotic medication. EPS can cause involuntary movement and muscle control problems all over the body.
in QUALYs alongside a long term saving in relation to Haloperidol DEPOT. Risperidone is one of the most used second generation antipsychotics in the United Kingdom, together with Olanzapine, and it has proven to be the most cost-effective; it is expected that this tendency becomes worldwide in the following years (Jayaram et al., 2006).

Conclusions
In Argentina, the most usual indication for emergency care in the acute phase of schizophrenia is the combined use of Haloperidol and Lorazepam. Meanwhile during the maintenance phase patients are treated with Risperidone or, in a lesser proportion, with Haloperidol.

Intermittent treatment usually fails to prevent relapses, due to irregular protection. That is why continuous treatment is more effective and in particular the injectable modality is the most recommended since it facilitates the compliance of the treatment by the patient in a simple way and with little interference in his life, reducing the discomfort of the treatment with daily oral tablets.

Based on the revision carried out, we can conclude that: i) Risperidone features fewer side effects than Haloperidol ii) Treatment with Risperidone produces an improvement in QUALYs, iii) Risperidone reduces negative symptoms significantly in relation to Haloperidol, iv) LTAIR is more effective in the treatment of patients with schizophrenia who later develop depression or mania, v) LTAIR is not superior to Haloperidol regarding time to psychiatric hospitalization, all-cause discontinuation, and duration of hospitalization and vi) Haloperidol is less expensive than Risperidone but features a worse cost-effectiveness rate.

Discussion
The four main objectives of the treatment of schizophrenia are: controlling symptoms, reducing the frequency and severity of psychotic episodes, improving the quality of life and facilitating the socio-labor and family integration of the schizophrenic patient. An early diagnosis and adhesion to treatment are key elements to improve the prognosis of patients with schizophrenia. The challenge faced by health practitioners is the creation of an empathic therapeutic relationship with the patient and his family. Once created, an individualized therapeutic plan taking into account the biological, psychological, familiar and social aspects should be developed.

Although in most cases antipsychotic treatments have allowed the patients with schizophrenia to live in their communities without any impairments, it is extremely important to combine pharmacological treatment with other types of care that constitute what is called psychosocial therapy, which needs assistance mechanisms such as: counseling services, occupational workshops, day centers and self-help groups.

Argentina passed in 2010 the National Law of Mental Health (Law 26,657) which promotes the social insertion of patients with mental health disorders. The law establish the closure of specialized mental hospitals by the year 2020, and the integration of mental health care in general hospitals. The law also contemplated the creation of assistance mechanisms to provide the specific therapies required by patients with mental health disorders, but seven years after its approval more than half of the mental health budget is spent in specialized mental hospitals, and in some regions of Argentina assistance mechanisms do not exist, or are scarce in relation to the need (Tisera et. al, 2013).

Schizophrenic patients in Argentina are guaranteed the access to pharmacological treatment irrespective of his or her socioeconomic status. However, psychosocial therapy is not assured in most cases. This calls for a coordinated effort of all actors involved (patients, families, health care...
staff, health care institutions, health insurance organizations and the government) to revert this situation.

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