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Antipsychotics for schizophrenia: the paradigm of psychiatric drugs

Antipsicóticos para la esquizofrenia: paradigma de los medicamentos psiquiátricos

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ABSTRACT Antipsychotic drugs do not appear to reverse the causes of schizophrenia, and although they can relieve symptoms in the short to medium term, in the long term they may not be beneficial and could even be counterproductive. Their use should be limited to acute situations in which agitation and tension is disabling. The drugs have significant adverse effects, and given the refusal of a person to continue taking them, a harm reduction strategy to support and monitor the withdrawal may be preferable to coercion. There are alternatives to neuroleptics. Prescribers should be more vigilant and consider the assessments of users regarding the drugs' effects. Adherence to treatment guidelines is low, probably because the guidelines are based on clinical trials of deficient quality which consequently should be improved and extended over a greater period of time. The root of the problem is likely the tautology on the etiology and biological nature of what is known as schizophrenia, which in fact does not seem to be more than a commercial and ideological construct.

KEY WORDS Schizophrenia; Antipsychotic Agents; Marketing; Effectiveness; Medication Adherence.

RESUMEN Los antipsicóticos no parecen revertir las causas de la esquizofrenia y, aunque son fármacos que pueden aliviar los síntomas a corto y mediano plazo, a largo plazo pueden no ser beneficiosos e incluso ser contraproducentes. Su empleo debería limitarse a situaciones agudas con agitación y tensión incapacitante. Presentan considerables efectos adversos y, ante la negativa de una persona a seguir tomándolos, adoptar una estrategia de reducción de daños apoyando y supervisando la retirada puede ser preferible a la coerción. Existen alternativas a los neurolépticos. Los prescriptores deberían estar más atentos y considerar las valoraciones que los usuarios hacen de sus efectos. El apego a las guías de tratamiento es escaso, seguramente por basarse en ensayos clinicos de calidad deficiente, que deben mejorar y prolongarse en el tiempo. La raíz del problema probablemente se encuentra en la tautología sobre la etiología y naturaleza biológica de lo que llaman esquizofrenia, que realmente no parece ser más que un constructo ideológico-comercial.

PALABRAS CLAVES Esquizofrenia; Antipsicóticos; Mercadeo; Efectividad; Cumplimiento de la Medicación.

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INTRODUCTION

> "A lot of medicines are blue-colored, including Haldol. I take Haldol to be under no illusions that I'll end up dying mad one day, in a dirty place, without any food. It's the way every madman ends." (*All Dogs Are Blue*, Rodrigo de Souza Leão)

Schizophrenia is characterized by the difficulty to differentiate/distinguish what is real and what is not, with the co-presence of anxiety and depression disorders and, occasionally, suicidal tendencies. Symptoms include tension, difficulty concentrating, insomnia, auditory or visual hallucinations, false beliefs, and alterations in thought and affect. Schizophrenia is also an important cause of long-term disabilities; it alters social and family relations and entails learning and occupational difficulties, loss of productivity, unemployment, physical illness, and early mortality. Dopaminergic hyperfunction resulting from specific genetic susceptibility and, in some cases, infectious, toxic or traumatic susceptibilities is suggested as the biological base. However, for this disorder to manifest itself, biographic factors and psychosocial difficulties are fundamental.[1]

The so-called antipsychotics are considered the key to treat schizophrenia.[2] This denomination indicates that these drugs act specifically on altered neurochemical processes that cause psychosis; however, less specific terminology is also used to refer to them: Major tranquillizers (which have calming effects), ataractic drugs (which induce imperturbability), or neuroleptics (that take hold of nerves).

Soon after neuroleptic drugs were first used in hospitals, it was noted that they acted as an antagonist on dopamine receptors. The clinical potency of this drug was related to the affinity for these receptors. The dopamine hypothesis of schizophrenia was formulated.[3] If dopaminergic antagonists improved schizophrenia, dopaminergic hyperactivity would be part of its physiopathology. It was already known that amphetamines increased the release of dopamine, induced schizophreniform psychoses, and could make preexisting psychoses more severe; these disorders could be treated with neuroleptics. *Post mortem* studies indicated an overexpression of dopaminergic receptors in the brain of schizophrenic individuals, although this could be explained by the previous use of neuroleptics. This overexpression was also observed with neuroimaging techniques *in vivo* on schizophrenic individuals who had not been exposed to neuroleptics, but these observations were inconsistent.[4] The dopaminergic nigrostriatal pathway was associated with motor control, the mesolimbic pathway with the control of complex behaviors and the motivational system, while the mesocortical pathway was associated with cognitive functions and the response to environmental pressure and difficulties, the tuberoinfundibular pathway intervenes with neuroendocrine regulation. These behavioral areas had traditionally been associated with schizophrenia. However, there was a temporal dissociation between the antidopaminergic therapeutic and adverse effects. Moreover, it was difficult to correlate dopaminergic hyperactivity with the psychopathology of schizophrenia. Thus, it was put forward that subcortical dopaminergic hyperactivity would explain the positive symptoms of schizophrenia (agitation, delirium and hallucinations), while frontal hypoactivity would explain the negative symptoms (apathy, abulia, lack of interest).

As the medical use of antipsychotic drugs is not limited to schizophrenia treatment, and these drugs have been used unspecifically for the treatment of very diverse disorders, a new dopamine hypothesis makes this neurotransmitter the final common pathway in the development of psychosis and other disorders, intervening in a game of counterweights between several neurotransmitters that, when destabilized, create a predisposition to mental disorders. This increase in dopaminergic activity can occur before psychosis, as a result of changes in the environment.[5]

Several brain anatomical abnormalities have been associated with schizophrenia, like ventricular enlargement, prefrontal atrophy, and others. However, these abnormalities lack the adequate sensitivity and specificity required to have diagnostic usefulness, as they are only present in 30% to 40% of the affected individuals, and in 10% to 30% of the examinations.[1] These abnormalities could also be caused by situations of pressure and marginalization in sensitive periods of development.[6]

As it is not possible to identify the biological markers of schizophrenia, diagnoses are based on

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complaints and behaviors of patients as well as their temporal evolution. This information is compared with the criteria for diagnosis, adopted by consensus of expert medical committees. Eighty three percent of the members who were part of the psychotic disorders panel of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) was being funded by the pharmaceutical industry.[7] Diagnosis categories for mental disorders are not objective realities, but mere conventions with a remarkable ideological weight. Although the current denomination of schizophrenia dates from the 19th century, and it had been described since ancient times, a satisfactory definition of this disorder has yet to be developed,[8] which gives room for data manipulation. The percentage of patients with schizophrenia who showed improvement was of 35.4% from 1895 to 1955, and of 48.5% from 1956 to 1985. This increase was believed to be the result of the discovery of chlorpromazine, but at the same time it was also due to the broadening of the diagnostic criteria. After the re-emergence of more narrow criteria during the 1970s and 1980s, favorable outcome rate was once again 36.4%.[9]

THE RESOUNDING SUCCESS OF NEUROLEPTICS

The use of neuroleptics in Spain increased by 540% between 1985 and 2006.[10] In Australia, it increased by 217.7% between 2000 and 2011.[11] In the United States, several neuroleptics have been among the top-selling drugs throughout the years.[12] In Manitoba, Canada, the sale of neuroleptics increased by 227% and of neuroleptic users by 62% between 1996 and 2006.[13]

The increase of neuroleptic drug sales reflects several simultaneous promotion strategies: increasing of the authorized indications; broadening the diagnostic limits through the artifice of "disorders within the spectrum of...," or defining as pathological what in reality is normal; promoting a non-specific use for behavioral disorders, and expanding the use to populations such as the elderly, intellectually disabled persons, children, and teenagers. Another strategy is to promote the use of doses that exceed the officially recommended maximum limits, a more serious problem in polypharmacy cases.

Towards the mid-20th century, there was a wave of therapeutic optimism associated with the introduction of chlorpromazine, which could not be attributed to decisive tests of its efficacy. At that time, psychodynamic treatments were no longer used, and the physical psychiatric treatments available were cruel. Tranquilizers commercialized at that time (barbiturates, carbamates, bromides) presented different management difficulties: paradoxical excitement prior to sedation; lethal dose too close to therapeutic dose; possibility of causing toxic psychosis, confusion, and a high risk of dependency; abuse and withdrawal reactions. These difficulties did not occur in chlorpromazine treatments and, when its sedative effect was tested with favorable outcome, it soon substituted its predecessors.[14]

The arrival of chlorpromazine to the pharmaceutical market in the US was highly successful; in 1955, the company SmithKline&French had a turnover of 75 million USD.[15] That same year, three out of ten prescriptions dispensed were for tranquilizers, and in the State of New York, one out of two.[16] The bibliography distributed by the pharmaceutical industry among the medical-pharmaceutical professionals was misleading in two aspects. First, it described the drug in a way that led to indiscriminate use for almost any problem, emotional state or life stage, profession and/or circumstance. Second, it made little to no mention of the drug's adverse effects, contraindications or long-term use; at most, the bibliography would indicate that research was still ongoing, inducing a false sense of security. The professional and general press gave the impression that a "psychiatric aspirin" had been discovered, a "happiness pill" that eased mental and emotional pain and was a cure for the psychopathology symptoms.

In 1957, the article written by Brill and Patton[17] reported an expansion of the use of tranquilizers (chlorpromazine, mainly) of 250% during 1955 and 1956 at psychiatric hospitals in the State of New York. Meanwhile, there was a decrease of 500 patients in the residential population and a further similar number between 1956 and 1957, as compared to an average annual increase of 2,000 in the prior decade. Moreover, a reduction in the practices of isolation and mechanic

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restraints was observed in these institutions. These changes mainly affected schizophrenic individuals and occurred in an abrupt manner. This was attributed to the use of neuroleptics.

This conclusion was criticized as a cause-and-effect relation could not be established between these events. To establish this relation, it was at least necessary to do a cohort analysis comparing results between neuroleptic-exposed and non-exposed subjects. Epstein et al.[18] analyzed the discharge rates at psychiatric hospitals of California, the analysis criteria being whether or not the patients had received ataractic drugs, and whether or not the hospital made intensive use of these drugs. The research focused on white males of 24-44 years of age who had been admitted for the first time in 1956 and 1957. In 1956, 673 subjects were admitted; 36% received ataractic drugs during the first 6 months, of which 63% was discharged after six months and 74% after 18 months, as compared to 67% and 88% of non-drug treated patients, respectively. In 1957, 740 subjects were admitted; 48% received ataractic drugs, out of which 64% was discharged after six months, as compared to 71% of non-drug treated users. When a comparison was made between the three hospitals that treated the largest proportion of their patients with ataraxic drugs and the three that treated the smallest proportion, the total hospital retention rates were the same in 1956, and in 1957 the retention rates of the first group were slightly higher. In the high drug usage hospitals, 49% of the patients were drug treated in 1956, and 63% in 1957; in the low usage hospitals, the corresponding numbers were 26% in 1956, and 34% in 1957.

The first non-controlled chlorpromazine trials resulted in very positive assessments, but it was soon recognized that the enthusiasm had to be curbed. The "psychiatric penicillin" had not been discovered by then. After the first placebo-controlled and crossed design clinical trials, it was clear that chlorpromazine was strictly indicated for states of increased tension and excitation. It was effective against any serious state of hypermotility and increased abnormal initiative, but had no effect on delirium and hallucinations. Neuroleptics were called chemical "straitjackets" and "lobotomies."[14]

In the first comparative studies, neuroleptics were superior to their barbituric predecessors. A 12-week-long research study[19] conducted on 641 male schizophrenic patients upon first admittance, double blind and randomized, compared five branches of neuroleptic treatment (chlorpromazine, triflupromazine, mepazine, prochlorperazine, perphenazine) against each other and against phenobarbital. Treatments were initiated with equivalent doses of each drug, which were gradually increased in a predetermined manner and were then adjusted with clinical criteria. Twenty-four different clinical criteria of change were employed. Average daily doses of chlorpromazine were of 635 mg and 50 mg of perphenazine. The trial was completed by 74% of the subjects. Only 21 patients were discontinued from treatment because of adverse reactions. The five different types of neuroleptics were more effective than phenobarbital, and all five of them were equally effective, except for mepazine, which was less effective. Clinical criteria of change that showed most improvement were: resistiveness, belligerence, thinking disturbance, and degree of illness.

Is there no treatment without neuroleptics?

Cole et al.[20] compared the effect of three neuroleptics (chlorpromazine, fluphenazine, and thioridazine) against placebo in a randomized, parallel clinical trial of six weeks, on 463 acute schizophrenia patients of recent hospitalization. Doses were adjusted according to flexible clinical criteria resulting on an average daily dose equivalent to 650 mg of chlorpromazine. The assessments were carried out by psychiatrists and nurses. The study was completed by 74% of the subjects, and most of the premature dropouts as a result of lack of efficacy were from the placebo group. The condition of no drug-treated subject worsened, 5% remained stable, 20% showed minimal improvement, and the remaining 75% showed "significant or very significant improvement." Of the placebo group, 40% showed "significant or very significant improvement." Out of 21 factors, the 13 that greatly improved were: social participation, confusion, self-care, hebephrenic symptoms, agitation and tension, slow conversation, incoherent conversation, irritability, environment indifference, hostility, hearing hallucinations, persecutory ideas, and disorientation. Neuroleptic effect transcended mere tranquilization.

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The project mentioned above had a second part,[21] which focused on the community adjustment of the patients who had been discharged. Out of 344 subjects that completed the previous study, 299 (87%) were discharged, 176 (59%) of which did not require rehospitalization the following year, and 78 out of the 123 who have been rehospitalized were discharged once more; as a result, one year after the original study was conducted, 254 subjects were living as part of the community. Sixty-eight percent of this group showed minimal or no psychopathology. Only 11% could be described as functioning as well as the average person in the community, although most (68%) had returned to their prior functional level, and 57% was considered active or moderately active. Among actual or potential wage-earner patients, 12% had not been employed during that year, 58% had been employed at the end of the follow-up period, 68% of which had a job in accordance with their level of education and 54% was economically self-sufficient. Sixty-four percent of the housewives were carrying out their activities adequately. When attempting to determine the influence of the diverse, personal, and premorbid factors and of the treatment on social adjustment, it was found that the subjects in the placebo group had the least probability of rehospitalization. There was a positive correlation between improvement upon discharge and absence of psychopathology one year after discharge in subjects that received neuroleptics. Eighty percent of the non-drug treated group and the group that used them continuously after discharge attended their jobs regularly; but this happened in only 56% of the patients who received drugs only sporadically.

In another research study,[22] 80 schizophrenics of 16-40 years of age, most of which had one or no previous hospitalization, were randomly assigned double blindly to either placebo or chlorpromazine medication (up to 900 mg per day). Upon discharge, patients who received chlorpromazine were significantly better than the subjects who received placebo. Patients were followed for three years after discharge. Outpatient treatment was not supervised by the research team, so patients were divided in four categories in the final outcome analysis, based on the randomly assigned medications and on the use of neuroleptics during follow-up: 24 subjects in the PL-Off group (placebo condition in the hospital and off neuroleptics during follow up), 17 in the PL-On group (placebo condition in the hospital but neuroleptic condition during follow up), 22 in the CPZ-On group (chlorpromazine condition randomly assigned and continued receiving neuroleptics during follow-up) and 17 in the CPZ-Off group (chlorpromazine condition randomly assigned but off neuroleptics after discharge). At the last follow up, 39 subjects were taking neuroleptics and received the medication regularly at least two-thirds of the time; 41 subjects were off neuroleptics and had not taken this medication at least two-thirds of the time. PL-Off group showed a significant improvement superior to the other three groups, and there were no differences between PL-On and CPZ-On. Eight percent of the subjects in group PL-Off required rehospitalization, 73% of the CPZ-On group, 53% of the PL-On group, and 47% of the CPZ-Off group.

Subsequently, a randomized research study compared five different treatments: milieu therapy alone, milieu therapy plus psychoanalytical psychotherapy, milieu therapy plus neuroleptics, milieu therapy plus psychotherapy and neuroleptics, or milieu therapy plus electroconvulsive therapy.[23] Follow-up extended for up to five years. The groups that received neuroleptics or electroconvulsive therapy showed better results initially, but this difference in results dissipated after three years.

The above mentioned research studies show a short-term superiority of neuroleptics against placebo when treating acute schizophrenia episodes. This superiority has been confirmed by meta-analysis.[24]

The duration of untreated psychosis has a negative effect on the subsequent response to neuroleptics and it was decided that, as routine, all cases should be treated immediately, as it was considered that a delay in the beginning of the treatment to allow time for spontaneous remissions to occur (schizophreniform disorders) would be detrimental for the patient and, thus, the ethical decision was to initiate the treatment without delay, when the first symptoms appeared. A meta-analysis[25] was performed, which included comparative, quasi-experimental, and random assignment studies on first or second episode schizophrenia spectrum subjects, with at least one unmedicated control group and a minimum follow up of one year.

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Research studies in which subjects were withdrawn from prior antipsychotic treatment were excluded. Six research studies were found, with a total of 623 subjects. There was no evidence of damage related to non-neuroleptic therapies, even when randomized research studies were the only ones analyzed.

Schizophrenia normally presents a prodromal period of one to three years, with non-specific behaviors and psychological symptoms, functional deterioration, and brief sporadic mitigated psychotic manifestations. Between 22% and 40% of individuals with these characteristics develop a frank psychotic episode before a year and are in ultra-elevated risk of transition to psychosis. To prevent or delay this episode could prove useful. A recent revision[26] included randomized research studies, which evaluated the effect of any intervention to prevent the transition to psychosis in persons with prodromal symptoms but with no prior episodes. Out of 11 studies included, in five of them, neuroleptics were used (risperidone, olanzapine and amisulpride). It was concluded that neuroleptics have not shown effects in preventing the beginning of psychosis, although some complex psychological therapies do achieve this prevention.

Do neuroleptics prevent relapses?

An indefinitely continued neuroleptic treatment is recommended to avoid schizophrenic relapses.[2] A recent meta-analysis[27] that included 65 clinical trials, a total of 6,493 subjects, supports this use. After a period of stability, groups that had continued the neuroleptic treatment were compared to others who had this drug replaced by placebos. Relapses after one year were of 27% in the neuroleptic groups, as compared to 69% of the placebo groups; rehospitalizations were of 10% and 26% respectively. Drug-treated groups presented more adverse effects than the placebo groups. The average duration and mode of the clinical trials were of 26 weeks, and very few had a duration of one year, and only one of two years. A meta-regression found that the longer the follow-up, the smaller the difference of relapses between placebo and antipsychotic drug groups, to the point where there was no longer a difference after two years. In all of the research studies included, the withdrawal of stabilizing neuroleptics to be substituted by placebo, in general, was abrupt, and although in 11 studies it was described as gradual, with an average of 28 days, it is considered a fast withdrawal. In placebo groups, there was a higher incidence of dyskinesia, a symptom of neuroleptic withdrawal. After four to six weeks since the withdrawal of chronically used neuroleptics, some patients experienced a worsening of positive symptoms, with agitation and akathisia, as well as vegetative manifestations and, generally, preceded by dyskinesias.[28] Therefore, rather than proving the usefulness of continuous drug use in relapse prevention, what is shown is an increase of the psychosis risk as a result of withdrawal, in other words, not a therapeutic effect, but a toxic result.

A two-year research study,[29] with first-episode subjects aged 18-45 years, attempted to determine how the reduction or early discontinuation of neuroleptics, as compared to the conventional maintenance treatment, affected the relapse risk and social and vocational functioning. A total of 131 subjects were recruited who, after six months of symptom remission, were randomized, then observed in an open follow-up of 18 months. One hundred and twenty-eight subjects completed the study, 43% of the reduction-withdrawal group relapsed, and 21% of the maintenance group relapsed. There were no differences in functional outcomes. All the subjects who completed the research study were invited to continue follow-up for up to seven years.[30] During this prolonged follow-up, treatment was established by the clinical team and not by the researchers. The primary outcome was the rate of recovery, defined by symptomatic and functional criteria, according to the group they had been assigned to in the initial research study. After seven years, 103 subjects were located, including 51 of the maintenance group and 52 of the reduction-discontinuation group. Subjects who were not located showed no differences when compared to subjects who were located. Recovery rate at the seven-year follow-up was 17.6% in the maintenance group, and 40.4% in the reduction-discontinuation group. The highest recovery rate in the reduction-withdrawal group was a result of an improved functional state, while the symptomatic states were similar in both groups. There were no differences in acute

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fare-ups. Survival curves in both groups became closer until the third year, where they crossed. Overall, 67 subjects had at least one relapse episode during the seven-year follow up. Thirty-five of them were in the maintenance group, and 32 were in the reduction-discontinuation group. Thirty-six subjects suffered no relapses, 20 of which were in the reduction-discontinuation group and 16 in the maintenance group.

A twenty-year follow-up study[31] attempted to estimate the frequency and severity of psychosis experienced by schizophrenic patients with maintained neuroleptic treatment, and whether it is less severe when neuroleptics are not used. For this purpose, a cohort of 139 subjects was recruited (70 schizophrenic patients and 69 mood-disordered patients for the control group) who were assessed prospectively during hospitalization as a result of their worsened condition at the beginning of disorder, and two, four-and-a-half, seven-and-a-half, ten, fifteen, and twenty years later. These subjects came from successive admissions to two hospitals. Interviewers did not know the diagnosis of the subjects, the results of prior assessments, or the objective of the study. Inter-rater reliability was satisfactory. When assessed, between 62% and 67% of the subjects in the schizophrenia group received neuroleptics, between 3% and 14% received other non-neuroleptic psychoactive drugs, and between 23% and 31% received no drugs. The median antipsychotic dose at ten and fifteen-year follow-ups was equivalent to 575 mg and 500 mg of chlorpromazine, respectively. When all the assessments were performed, 25 subjects were receiving neuroleptics (group one); 24 received neuroleptics only in a percentage of the assessments (group two); and 15 did not receive neuroleptics in any assessment (group three). For six subjects, there was data of less than four assessments. When assessed, between 56% and 78% of the subjects on neuroleptics presented psychotic activity, as compared to between 17% and 27% of the subjects that were non-drug treated. Moreover, while in group one, 68% to 86% presented psychotic activity, in group three, the percentage was between 7% and 60%. Psychotic symptoms caused social life and instrumental capacity alterations, from moderate to severe, to between 35% and 73% of the subjects in group one, and between 0% and 30% in group three. The differences between drug treated groups and non-drug treated groups reached statistical significance after the four-and-a-half-year assessment. Seventy-two percent, 46% and 7% of groups one, two and three respectively presented psychotic symptoms in at least four assessments. Only twelve schizophrenic subjects presented no psychosis in all follow-up assessments; seven of them were in group three and the other five were in group two. Complete recovery was defined as the absence of positive and negative symptoms as well as no rehospitalization, the existence of social contacts, and having a job for at least half of the year prior to the assessment. Two subjects of group three were in complete recovery in all assessments. Half of the subjects in group one suffered no psychotic symptoms in at least one of the follow-up assessments, indicating potential for recovery.

Among the affective psychosis controls, similar results were observed. In the last assessment, 28% was receiving neuroleptics and 37% non-neuroleptic drugs. Only 12% presented psychotic activity in more than three assessments, and the rate of subjects with psychotic activity at the seven-and-a-half and ten-year follow ups was higher in neuroleptic users.

At least a fraction of schizophrenic patients can manage without long term continuous neuroleptic use. Lack of interest and emotional indifference state, while beneficial during an acute episode, might be detrimental to long-term personal, social, and instrumental recovery of the individual.

Are neuroleptics tolerated and safe?

It is frequent that clinical trials with neuroleptics inform only of the adverse effects that appear with a frequency of ≥5%, and even ≥10%. Non frequent but severe effects can go unnoticed. It is not certain that reports of clinical trials always inform, as is mandatory, the frequency of the "death" result. The result "losses as a result of adverse events," tends to mix adverse effects and lack of response as well as worsening of psychosis; thus, it is not a good indicator of tolerability-security, but a mixed one of tolerability and efficacy. An important number of individuals treated with neuroleptics suffer from adverse effects,[24,27] which affect their lives' quality.

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In the course of a year, 37% to 44% of patients develop pseudoparkinsonism, 26% to 35% develop akathisia, 1.1% to 4.5% develop tardive dyskinesia[32]; dyskinesia prevalence increases with the continuous use of narcoleptics. Anticholinergic adverse effects are also very frequent: in clinical trials, 10% to 20% suffered from blurred vision, the same amount suffered constipation, dry mouth 5% to 33%, micturition difficulties 10%, 4% to 42% from hypersalivation and drooling; centrally, they interfere with cognitive capacities.[33] Thirty-three percent of hospitalized patients on neuroleptics were obese, 68% presented dyslipidemia, 64% presented hypercholesterolemia, and 30%, hypertriglyceridemia.[34] Hyperprolactinemia was detected on up to 42% of male patients and on 75% of female patients using neuroleptics, which leads to gynecomastia, galactorrhea, menstrual irregularities, infertility, sexual dysfunction, gonadal atrophy, acne, and female hirsutism; long-term wise, it can cause osteoporosis, bone fractures, and breast cancer.[35] Six percent to 20% of neuroleptic users suffer from enuresis.[36] Of the subjects on clozapine, 2.7%suffer from seizures, and 0.8% of the cases suffer from agranulocytosis. Thirty nine percent of the subjects on olanzapine suffer from somnolence, and subjects treated with other neuroleptics suffer from somnolence more frequently.[37] Eight percent of the subjects show lengthening of the rate-corrected QTc on the electrocardiogram (predictive marker of sudden death).[38] Pulmonary thromboembolism has also been associated with the use of neuroleptics.[39]

Most of the adverse effects are doses depending and are more pronounced in polytherapy cases. Neuroleptic polypharmacy and mega-doses are frequent, due to the use of other psychotropic drugs for psychiatric comorbidity, and of other prescribed drugs for physical health problems, or to treat adverse effects. Polypharmacy entails more risks of drug interactions and adversities. Physicians tend to understimate, when compared to user perception, the frequency and severity of the adverse effects of neuroleptics in almost all areas: psychic, neurologic, autonomic, and others.[40]

Brain anatomical anomalies identified in schizophrenia and its progression in time can be a cause (they make the patient susceptible) or consequence of the disorder (they become more severe with psychological pressure and isolation), or an effect of treatment (toxic effect of neuroleptics). Two hundred eleven subjects were prospectively followed since their first psychotic episode for fourteen years (mean period 7.2 years), and between two and five MRI brain scans were collected. It was aimed at determining the contribution of four potential predictors of brain volume loss: illness duration, antipsychotic treatment, illness severity, and substance abuse. General and specific brain tissue volume decrement was associated with the intensity of the neuroleptic treatment after controlling the effect of the other three predictors. The more a patient was treated with neuroleptic drugs, the bigger the gray matter loss. Illness severity had a modest effect, and substance abuse did not present an important association, after controlling for effects the other predictors.[41] Subsequently, the importance of the intensity of the antipsychotic treatment was ratified, and the duration of relapses was added as another variable that significantly predicts brain tissue loss,[42] although "relapse" was defined after data collection. A meta-analysis associated the longitudinal reduction of gray matter in schizophrenic patients with the accumulated exposure to neuroleptics throughout time, but not with the changes in the symptomatology, nor with the duration of the disorder.[43]

Schizophrenic patients have excess mortality.[44] During the period of time between 1999 and 2008, the mortality rate for schizophrenic patients was 20% and 9.37% for individuals who had not been diagnosed. This excess affected younger individuals, lessening with age, to the point of not affecting people over 90 years old. This difference was present in all causes of death, except cancer. However, mortality due to pulmonary cancer was higher among schizophrenic individuals. Excess mortality was kept after performing adjustments. This has been attributed to the mental disorder, the difficulties of self-care, sedentarism, smoking, substance abuse, and adverse effects of neuroleptics.

Researchers[45] have found that the risk of death in schizophrenic individuals was lower for patients who used neuroleptics until their demise, compared to patients who were not using them at that moment. It was also found that the risk of death was significantly lower in subjects with continuous use of neuroleptics than in subjects who had not taken this drug outside of hospital care. There was an inverse relation between mortality and accumulated

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duration of neuroleptic use. However, the mortality rate was especially low for individuals whose accumulated duration of neuroleptic use was of less than six months, but in-hospital deaths were not recorded, neuroleptics treatment tends to be halted in patients who are severely ill, and subjects who do not comply with treatment can present worse health for other reasons.

DISCREPANCIES BETWEEN EVIDENCE AND PRACTICE

Recommendations and guidelines to help with the process of making therapeutic decisions in schizophrenic cases have been developed[2] based on the best evidence available. The use of neuroleptic drugs as instructed by these guidelines has been associated with a higher reduction of psychopathology and less adverse effects.[46] However, the application of these guidelines seems to be more the exemption than the rule.[47] Clinical trials are likely to have a defective design, or there maybe is a publication or patient selection bias.

Out of 2000 clinical trials for schizophrenia published between 1948 and 1997, 64% were low quality, and only 1% reached the maximum score. Only 4% described adequately the assignation method for control and experimental groups. Only 22% described the blinding method used, and only 42% described what had happened with the study dropouts. Only one discussed adequately the problem of statistical power, and only three had big enough samples to detect a difference of 20%, with a signification of 5% and a potency of 80%. Fifty percent had less than 50 subjects. Fifty percent lasted ≤ 6 weeks, and only 19% lasted > 6 months. Eighty-six percent assessed drugs used; 63% assessed changes in symptoms as their main outcome, employing 640 different scales; 20% assessed the global symptomatology. Variables with direct clinical meaning such as "daily life activities" or "global performance" were assessed in 4% and 6%, respectively. Only 22% assessed adverse effects. Ninety-one percent of these clinical trials were developed in the US or Europe.[48]

A decade later there were 10,000 clinical trials on schizophrenia,[49] but their accessibility was reduced; only 28% was available at PubMed. The subjects' median increased to 60 per clinical trial, but the number of duplicated publications was also higher. Currently, 25% of the clinical trials are from China. No other changes have occurred.

Information regarding commercialization application of eight neuroleptics was used to identify 24 premarketing clinical trials, 20 of which had been published; the effect sizes published were, on average, 8% higher than what the approval documents stated. Out of the remaining four, three showed no superiority when compared with the placebo and the remaining one showed no superiority when compared to the active comparator.[50]

Clinical trials of neuroleptics for schizophrenia tend to exclude subjects with suicidal tendencies or with a substance abuse problem, which could have a negative effect on the external validity of the outcomes as a result of selecting a type of subject different from the ones treated during routine assistance. The same can be said about participation disposition. However, when the results of a 12-month-long research study that did not contemplate these exclusion criteria were compared the presence of these comorbidities, no differences were found in treatment discontinuation, study dropouts, psychopathology, or social functioning. Although, the firsts did show more depressive tendencies and were rehospitalized after a shorter period of time; these differences were associated with substance abuse and not with suicidal tendencies.[51] When the characteristics of the subjects who participated in a clinical trial with neuroleptics were compared to the non-participants that fitted the inclusion/non-exclusion criteria, no differences were found, except for the fact that the latter were more likely to have been hospitalized for physical reasons the year prior to the research.[52] These differences imply a more careful use of neuroleptics.

Over time, there has been a progressive reduction of the difference between the efficacy of placebo and neuroleptics in clinical trials performed between the years 1991 and 2006, as a result of an increase in the placebo effect and the reduction on the effect of the neuroleptic, even as active controllers. This has taken place despite the rise in subject numbers, the reduction of study dropouts, maintenance of the baseline symptom severity, and the improved quality of the studies.[53] In this context, conducting clinical trials controlled by placebo is

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ethically imperative, against the proposal of only using an active control in clinical trials on the use of neuroleptics to treat schizophrenia.

What do neuroleptic users experience?

Half of neuroleptic users have experienced withdrawal symptoms,[54] which appear after treatment discontinuation; some of these symptoms are similar to the symptoms that motivated the prescription; others are new, with a variable intensity and moment of origin depending on certain pharmacological characteristics, the type of use, and the individual under treatment. Frequently, these symptoms are construed as evidence of the persistence of the initial disorder and the need to continue treatment. Afterwards, patients and physicians are reluctant to new withdrawals, as they fear a "relapse." Other patients insist on neuroleptic discontinuation, in general, as they perceive that the benefits do not compensate the adverse effects.[55]

In neuroleptic clinical trials, global quitting rates range from 33% to 42%.[24,27] In medical routine conditions, approximately 40% of the patients fail to carry out the neuroleptic treatment before a year, and 75% before two years. It is considered as lack of therapeutic adherence when the subject takes less than 80% of the prescribed dose, but only 17% of the subjects take one-fifth or less of the prescribed neuroleptic doses.[56] Long-term injectable neuroleptic prescription is the strategy that is most used to improve fulfillment. Its use is based on the results of "mirrored" studies which compare relapses before and after its use, being each patient its own control,[57] a design with a high risk of bias. In randomized clinical trials with parallel control, they have not showed to be more effective or safe than oral neuroleptics.[58]

Mandatory outpatient treatment, administered by judicial order against the subject's will, does not seem to solve the problem either; it is also supported on "mirrored" studies", while randomized studies with parallel control show no additional benefits.[59]

As a result of the coercive answers to the complaints about treatment and the attempts of neuroleptic abandonment, the subject makes changes in the treatment that allows them to exercise their autonomy but which they hide, resulting in the therapist having false data. When this happens, it is considered that there is a lack of consciousness of the disorder. If symptoms appear, these are considered refractory, and "mega-doses," polytherapy, and coaction are used, which form an ascending spiral of unpleasant effects and destabilize the patient. Eventually, a rupture of the therapeutic relation, or a more tragic outcome, "legitimizes" the environment to force treatments up to irrational and immoral limits. Conversely, the participation of the subject in their treatment, listening with attention to the difficulties they are experiencing, and looking for an agreement between objectives with the patient would be an adequate response. Even when dealing with a subject who wants to completely discontinue neuroleptic use, implementing a damage reduction policy would prevent the abrupt discontinuation of treatment with patient follow-up loss, and it would also allow the possibility of offering new alternatives.[60]

Neuroleptics are, above all, psychoactive drugs and produce an altered and unpredictable physical and mental state, which interacts with the experience of upsetting feelings and disability, which had led the subject to ask for help. It can be useful if it entails the suppression of some of their afflictions. This unspecific effect can be reflected in the scales of symptom evaluation. Clinical trials are focused on a limited group of complains and results, and they relegate the rest to a collateral effect category, which makes it difficult to identify the complete range of long-term psychoactive and physical effects of neuroleptics. There also is a lack of information on their long-term effects, including the withdrawal effects.

Some scholars describe the effect of neuroleptics as "a petrification of emotions, blocking a person's initiative," "their curiosity and intellectual initiative transform in phlegmatic and robotic attitudes," "emotional neutrality without consciousness disorders", and "psychic straitjackets."[61] Upon asking young individuals who had been prescribed neuroleptics, but who had yet to experience the effect of this drug, about their expectations, their answers were: "a lot of help to eliminate my thoughts and to make the symptoms not bother me;" however, when asked after six weeks of continuous use, the patients said that the neuroleptics had caused a state of "indifference

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and detachment over symptoms."[62] At an open access internet database, where neuroleptic users shared their experiences, the predominant subjective effects described were sedation, cognitive impairment, and emotional flattening or indifference.[63] This information is consistent with the role of dopamine in processes associated with the ability to experience pleasure and motivation.

How are therapeutic decisions taken?

A second relapse schizophrenia case was presented to all individuals attending a psychiatry congress, and they were asked if they would prescribe a depot neuroleptic treatment or if they would continue oral treatment. Most of the participants recommended the first option. Afterwards, when presented the same case and options, patients asked them "what would you do if you were me?", and the answer was the same. Lastly, they were told to imagine that they were the protagonists of the case; then the answer changed, most of them chose to continue oral treatment.[64]

At another occasion, two case-scenarios were presented. In the first case-scenario, a patient had to be treated with one of two new neuroleptic drugs, of which they are given information in a 12-item list (six benefits and six risks), and they were asked to request more information. In the second case-scenario, schizophrenic patients were about to initiate a depot antipsychotic treatment, of which a 10-item list is provided (five benefits and five risks), and the psychiatrists were asked about which items they would talk about with the patients. In the first case, the psychiatrists asked about significantly more information regarding risks to inform themselves, but when informing the patients, the situation was inverted, and they put more emphasis on the benefits.[65]

CONCLUSIONS

Based on the information presented, we can conclude as follows:

1. The data used to recommend continuous use of neuroleptics to treat schizophrenia is far from adequate to maintain it. The quality of research done on this subject must be improved in transparency, sample size, and follow-up duration.
2. During assistance, the improvement of therapeutic compliance should go hand-in-hand with medical training and active participation of subjects in their own treatment. Coercive methods to impose treatment are not acceptable, regardless of other ethical considerations, on account of their ineffectiveness.

REFERENCES

1. van Os J, Kapur S. Schizophrenia. Lancet. 2009;374(9690):635-645.

2. Barnes TR, Schizophrenia Consensus Group of British Association for Psychopharmacology. Evidence-based guidelines for the pharmacological treatment of schizophrenia: recommendations from the British Association for Psychopharmacology. Journal of Psychopharmacology. 2011;25(5):567-620.

3. Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: version III – the final common pathway. Schizophrenia Bulletin. 2009;35(3):549-562.

4. Andreasen NC, Carson R, Diksic M, Evans A, Farde L, Gjedde A, Hakim A, Lal S, Nair N, Sedvall G, Tune L, Wong D. Workshop on schizophrenia, PET, and dopamine D2 receptors in the human nestriatum. Schizophrenia Bulletin. 1988;14:471-484.

5. Seeman P. All roads to schizophrenia lead to dopamine supersensitivity and elevated dopamine D2(high) receptors. CNS Neuroscience & Therapeutics. 2011;17(2):118-132.

6. Krabbendam L, Hooker CL, Aleman A. Neural effects of the social environment. Schizophrenia Bulletin. 2014;40(2):248-251.

7. Cosgrove L, Krimsky S. A comparison of DSM-IV and DSM-5 panel members' financial associations with industry: a pernicious problem persists. Plos Medicine. 2012;9(3):e1001190.

8. Álvarez JM, Colina F. Origen histórico de la esquizofrenia e historia de la subjetividad. Frenia,

SALUD COLECTIVA.2015;11(1):115-128. doi: 10.18294/sc.2015.410

Revista de Historia de la Psiquiatría. 2011;11(1):7-26.

9. Hegarty JD, Baldessarini RJ, Tohen M, Waternaux C, Oepen G. One hundred years of schizophrenia: a meta-analysis of the outcome literature. American Journal of Psychiatry. 1994;151(10):1409-1416.

10. Simó Miñana J. Utilización de medicamentos en España y en Europa. Atención Primaria. 2012;44(6):335-347.

11. Stephenson CP, Karanges E, McGregor IS. Trends in the utilisation of psychotropic medications in Australia from 2000 to 2011. The Australian and New Zealand Journal of Psychiatry. 2013;47(1):74-87.

12. Lindsley CV. The top prescription drugs of 2011 in the United States: antipsychotics and antidepressants once again lead CNS therapeutics. ACS Chemical Neuroscience. 2012;3(8):630-631.

13. Alessi-Saverini S, Biscontri RD, Collins DM, Kazyrskyi A, Sareen J, Enns MW. Utilization and costs of antipsychotic agents: a Canadian population-based study, 1996-2006. Psychiatric Services. 2008;59(5):547-553.

14. Lehmann HE, Ban TA. The history of the psychopharmacology of schizophrenia. Canadian Journal of Psychiatry. 1997;42(2):152-162.

15. Diéguez A, Campos R, Huertas R. Breve historia de la psiquiatría. In: López-Muñoz F, Álamo González C. Historia de la psicofarmacología. Buenos Aires: Panamericana; 2005.

16. Committee on Public Health of the New York Academy of Medicine. Report on tranquilizing drugs. Bulletin of the New York Academy of Medicine. 1957;33(4):282-289.

17. Brill H, Patton RE. Analysis of 1955-1956 population fall in New York State mental hospitals in first year of large-scale use of tranquilizing drugs. American Journal of Psychiatry. 1957;114(6):509-517.

18. Epstein LJ, Morgan RD, Reynolds L. An approach to the effect of ataraxic drugs on hospital release rates. American Journal of Psychiatry. 1962;119:36-47.

19. Casey JF, Lasky JJ, Klett J, Hollister LE. Treatment of schizophrenic reactions with phenothiazine derivatives: a comparative study of chlorpromazine, trifluprom azine, mepazine, prochlorperazine, perphenazine, and phenobarbital. American Journal of Psychiatry. 1960;117:97-105.

20. The National Institute of Mental Health Psychopharmacology Service Center Collaborative Study Group. Phenothiazine treatment in acute schizophrenia: Effectiveness. Archive of General Psychiatry. 1964;10(3):246-261.

21. Schooler NR, Goldberg SC, Boothe H, Cole JO. One year after discharge: community adjustment of schizophrenic patients. American Journal of Psychiatry. 1967;123(8):986-995.

22. Rappaport M, Hopkins H, Hall K, Belleza T, Silverman J. Are there schizophrenics for whom drugs may be unnecessary or contraindicated? International Pharmacopsychiatry. 1978;13(2):100-111.

23. May PR, Tuma AH, Dixon WJ, Yale C, Thiele DA, Kraude WH. Schizophrenia. A follow-up study of results of five forms of treatment. Archives of General Psychiatry. 1981;38(7):776-784.

24. Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, Samara M, Barbui C, Engel RR, Geddes JR, Kissling W, Stapf MP, Lässig B, Salanti G, Davis JM. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet. 2013;382(9896):951-962.

25. Bola JR. Medication-free research in early episode schizophrenia: evidence of long-term harm? Schizophrenia Bulletin. 2006;32(2):288-296.

26. Stafford MR, Jackson H, Mayo-Wilson E, Morrison AP, Kendall T. Early interventions to prevent psychosis: systematic review and meta-analysis. BMJ. 2013;346:f185.

27. Leucht S, Tardy M, Kamossa K, Heres S, Kissling W, Salanti G, Davis JM. Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. Lancet. 2012;379(9831):2063-2071.

28. Gardos G, Cole JO. Maintenance antipsychotic therapy: is the cure worse than the disease? American Journal of Psychiatry. 1976;133(1):32-36.

29. Wunderink L, Nienhuis FJ, Sytema S, Slooff CJ, Knegtering R, Wiersma D. Guided discontinuation versus maintenance treatment in remitted first-episode psychosis: relapse rates and functional outcome. Journal of Clinical Psychiatry. 2007;68(5):654-661.

30. Wunderink L, Nieboer RM, Wiersma D, Sytema S, Nienhuis FJ. Recovery in remitted first-episode psychosis at 7 years of follow-up of an early dose reduction/discontinuation or maintenance treatment strategy: Long-term follow up of a

SALUD COLECTIVA.2015;11(1):115-128. doi: 10.18294/sc.2015.410

2-year randomized clinical trial. JAMA Psychiatry. 2013;70(9):913-920.

31. Harrow M, Jobe TH, Faul RN. Does treatment of schizophrenia with antipsychotic medications eliminate or reduce psychosis?: A 20-year multi-follow-up study. Psychological Medicine. 2014;44(14):3007-3016.

32. Miller DD, Caroff SN, Davis SM, Rosenheck RA, McEvoy JP, Saltz BL, Riggio S, Chakos MH, Swartz MS, Keefe RSE, Stroup TS, Lieberman JA, Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Extrapiramidal side-effects of antipsychotics in a randomised trial. British Journal of Psychiatry. 2008;193(4):279-288.

33. Ozbilem M, Adams CE. Systematic overview of Cochrane reviews for anticholinergic effects of antipsychotic drugs. Journal of Clinical Psychopharmacology. 2009;29(2):141-146.

34. Newcomer JW, Haupt DW. The metabolic effects of antipsychotic medications. Canadian Journal of Psychiatry. 2006;51(8):480-491.

35. Carvalho MM, Góis C. Hiperprolactinémia em doentes psiquiátricos. Acta Médica Portuguesa. 2011;24:1005-1012.

36. Harrison-Worlrych M, Skegg K, Ashton J, Herbison P, Skegg DCG. Nocturnal enuresis in patients taking clozapine, risperidone, olanzapine and quetiapine: comparative cohort study. British Journal of Psychiatry. 2011;199(2):140-144.

37. Collaborative Working Group on Clinical Trial Evaluations. Adverse effects of the atypical antipsychotics. Journal Clinical Psychiatry. 1998;59(Suppl 12):S17-S22.

38. Reilly JG, Ayis SA, Ferrier IN, Jones SJ, Thomas SHL. QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients. Lancet. 2000;355(9209):1048-1052.

39. Kamijo Y, Soma K, Nagai T, Kurihara K, Ohwada T. Acute massive pulmonary thromboembolism associated with risperidone and conventional phenothiazines. Circulation Journal. 2003;67(1):46-48.

40. Lindström E, Lewander T, Malm U, Malt UF, Lublin H, Ahlfors UG. Patient-rated versus clinician-rated side effects of drug treatment in schizophrenia. Clinical validation of a self-rating version of the UKU side effect rating scale (UKU-SERS-pat). Nordic Journal of Psychiatry. 2001;55(Suppl 44):5-69.

41. Ho BC, Andreasen NC, Ziebell S, Pierson R, Magnotta V. Long-term antipsychotic treatment and brain volumes: a longitudinal study of first-episode schizophrenia. Archive of General Psychiatry. 2011;68(2):128-137.

42. Andreasen NC, Liu D, Ziebell BA, Vora A, Ho BC. Relapse duration, treatment intensity, and brain tissue loss in schizophrenia: a prospective longitudinal MRI study. American Journal of Psychiatry. 2013;170(6):609-615.

43. Fusar-Poli P, Smieskova R, Kempton MJ, Ho BC, Andreasen NC, Borgwardt S. Progressive brain changes in schizophrenia related to antipsychotic treatment?: A meta-analysis of longitudinal MRI studies. Neuroscience and Biobehavioral Reviews. 2013;37(8):1680-1691.

44. Kredentser MS, Martens PJ, Chochinov HM, Prior HJ. Cause and rate of death in people with schizophrenia across the lifespan: a population-based study in Manitoba, Canada. Journal of Clinical Psychiatry. 2014;75(2):154-161.

45. Tiihonen J, Lönnqvist J, Wahlbeck K, Klaukka T, Niskanen L, Tanskanen A, Haukka J. 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). Lancet. 2009;374(9690):620-627.

46. Weinmann S, Hoerger S, Erath M, Kilian R, Gaebel W, Becket T. Implementation of a schizophrenia practice guideline: clinical results. Journal of Clinical Psychiatry. 2008; 69(8):1299-1306.

47. Busch AB, Leheman AF, Goldman H, Frank RG. Changes over time and disparities in schizophrenia treatment quality. Medical Care. 2009;47(2):194-207.

48. Thorley B, Adams C. Content and quality of 2000 controlled trials in schizophrenia over 50 years. BMJ. 1998;317:1181-1184.

49. Miyar J, Adams CE. Content and quality of 10000 controlled trials in schizophrenia over 60 years. Schizophrenia Bulletin. 2013;39(1):226-229.

50. Turner EH, Knoepflmacher D, Shapley L. Publication bias in antipsychotic trials: an analysis of efficacy comparing the published literature to the US Food and Drug Administration Database. Plos Medicine. 2012;9(3):e1001189.

51. Boter H, Derks EM, Fleischhacker WW, Davidson M, Kahn RS, EUFEST Study Group. Generalizability of results of efficacy trials in first-episode schizophrenia: comparisons between subgroups of participants of the European First Episode

SALUD COLECTIVA.2015;11(1):115-128. doi: 10.18294/sc.2015.410

Schizophrenia Trial (EUFEST). Journal of Clinical Psychiatry. 2010;71(1):58-65.

52. Barnett PG, Scott JY, Rosenheck RA. How do clinical trial participants compare to other patients with schizophrenia? Schizophrenia Research. 2011;130(1-3):34-39.

53. Agid O, Siu CO, Potkin SG, Kapur S, Watsky E, Vanderburg D, Zipursky RB, Remington G. Meta-regression analysis of placebo response in antipsychotic trials, 1970-2010. American Journal of Psychiatry. 2013;170(11):1335-1344.

54. Salomon C, Hamilton B. "All roads lead to medication?": Qualitative responses from an Australian first-person survey of antipsychotic discontinuation. Psychiatric Rehabilitation Journal. 2013;36(3):160-165.

55. Dibonaventura M, Gabriel S, Dupclay L, Gupta S, Kim E. A patient perspective of the impact of medication side effects on adherence: results of a cross-sectional nationwide survey of patients with schizophrenia. BMC Psychiatry. 2012;12:20.

56. Remington G, Teo C, Mann M, Hahn M, Fonssias G, Aqid Q. Examining levels of antipsychotic adherence to better understand non-adherence. Journal of Clinical Psychopharmacology. 2013;33(2):261-263.

57. Kishimoto T, Nitta M, Borenstein M, Kane JM, Correll CU. Long-acting injectable versus oral antipsychotics in schizophrenia: a systematic review and meta-analysis of mirror-image studies. Journal of Clinical Psychiatry. 2013;74(10):957-965.

58. Kishimoto T, Robenzadeh A, Leucht C, Leucht S, Wanatabe K, Mimura M, Borenstein M, Kane JM, Correll CU. Long-acting injectable vs oral antipsychotics for relapse prevention in schizophrenia: a meta-analysis of randomized trials. Schizophrenia Bulletin. 2014;40(1):192-213.

59. Kisely SR, Campbell LA, Preston NJ. Compulsory community and involuntary outpatient treatment for people with severe mental disorders review. The Cochrane Database of Systematic Reviews. 2011;(2):CD004408.

60. Aldridge MA. Addressing non-adherence to antipsychotic medication: a harm-reduction approach. Journal of Psychiatric and Mental Health Nursing. 2012;19(1):85-96.

61. Rementerí I. La función de utilidad del uso de las drogas y las culturas de su consumo. Cuadernos Médico Sociales (Chile). 2014;54(1):35-41.

62. Mizrahi R, Bagby RM, Zipursky RB, Kapur S. How antipsychotics work: the patients' perspective. Progress in Neuro-Psychopharmacology & Biological Psychiatry. 2005;29(5):859-864.

63. Moncrieff J, Cohen D, Mason JP. The subjective experience of taking antipsychotic medication: a content analysis of Internet data. Acta Psychiatrica Scandinavica. 2009;120(2):102-111.

64. Mendel R, Hamann J, Traut-Mattausch E, Bühner M, Kissling W, Frey D. 'What would you do if you were me, doctor?': Randomised trial of psychiatrists personal versus professional perspectives on treatment recommendations. British Journal of Psychiatry. 2010;197(6):441-447.

65. Mendel R, Hamann J, Traut-Mattausch E, Jonas E, Heres S, Frey D, Kissling W. How psychiatrists inform themselves and their patients about risks and benefits of antipsychotic treatment. Acta Psychiatrica Scandinavica. 2009;120(2):112-119.

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