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EFFECTIVENESS OF MODERN ANTIPSYCHOTIC DRUGS FOR THE TREATMENT OF SCHIZOPHRENIA AND OTHER PSYCHOTIC DISORDERS: THERAPEUTIC PROGRESS OR MORE OF THE SAME?

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Antipsychotic or neuroleptic drugs are the most effective known medications for the treatment of psychotic symptoms in schizophrenia and related mental disorders. Despite progress in pharmacological therapy for schizophrenia over the last twenty years, quality of life in most patients diagnosed with schizophrenia remains below normal levels. Recent clinical trials not sponsored by the pharmaceuticals industry on the effectiveness and cost-utility of different classes of antipsychotics indicate that there are no substantial differences between modern second-generation or atypical antipsychotics and older, conventional ones with regard to discontinuation rates, efficacy or quality of life. These results reflect our lack of knowledge on the physiopathology of schizophrenia, but also serve to stimulate research on new pharmacological targets, psychological treatments, and alternative psychosocial interventions.
Key Words: *Antipsychotic drugs, Schizophrenia, Effectiveness*

Los antipsicóticos o neurolépticos son los fármacos con la mayor eficacia conocida para tratar los síntomas psicóticos en la esquizofrenia y otros trastornos mentales relacionados. A pesar de los avances en la terapia farmacológica de la esquizofrenia durante las dos últimas décadas, la calidad de vida en la gran mayoría de pacientes con diagnóstico de esquizofrenia crónica se mantiene por debajo de la normalidad. Recientes ensayos clínicos no subvencionados por empresas farmacéuticas sobre la efectividad y la relación coste-beneficio de las distintas clases de fármacos antipsicóticos disponibles para el tratamiento de la esquizofrenia, indican que no existen grandes diferencias entre los modernos antipsicóticos atípicos o de segunda generación y los convencionales en cuanto a eficacia, tasa de abandono o calidad de vida. Estos resultados evidencian nuestro desconocimiento sobre la fisiopatología de la esquizofrenia, pero también estimulan la investigación de nuevas dianas farmacológicas, tratamientos psicológicos e intervenciones psicosociales alternativas.
Palabras clave: *Antipsicóticos, Esquizofrenia, Efectividad*

The clinical introduction in 1952 of the first neuroleptic drugs, such as chlorpromazine, for the treatment of manic agitation and schizophrenia, is traditionally considered to represent a crucial advance in the field of psychiatry. Despite the fact that the progressive decrease in the number of patients admitted to mental institutions is commonly attributed to the introduction of these drugs – mainly in the USA –, it was in fact a range of social, political and economic factors unrelated to the efficacy of neuroleptics that triggered the well-known phenomenon of "psychiatric deinstitutionalization" (González Pardo & Pérez Álvarez, 2007). Nevertheless, it is beyond doubt that neuroleptic drugs represented and continue to represent a significant therapeutic advance in the treatment of schizophrenic symptoms. The first neuroleptics were actually discovered by a kind of serendipity, via research and experience with antihistaminic drugs for the treatment of allergic reactions and the prevention of physiological stress reactions during major surgery (Healy, 2002).

The term neuroleptic, literally "that seizes the nerves", was coined by the French psychiatrists Delay and Deniker, to whom is attributed the introduction of chlorpromazine for the treatment of schizophrenia. Though now in disuse, this term reflects perfectly the neurological and psychic effect of these drugs, which cause a general reduction of spontaneous movements and a state of emotional indifference to environmental stimuli. This neuroleptic effect is commonly considered as therapeutic above all in agitated or aggressive patients, many of whom tend to present psychotic symptoms. The therapeutic potential of neuroleptics is evident in the treatment of the so-called

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positive symptoms of schizophrenia, since they tend to attenuate the psychic impact of delusions, auditory hallucinations, agitation and anxiety. Long-term treatment with antipsychotics in patients diagnosed with schizophrenia has also been seen to lead to improvement in other symptoms, such as disorganized thinking or inappropriate behaviour, and to a decrease in relapses in the form of psychotic episodes. Thus, there is currently a tendency to refer to these drugs as 'antipsychotics', since they reduce these psychotic symptoms without totally eliminating them. Even so, other, more devastating and lasting symptoms of schizophrenia, such as the reduction of emotivity, social isolation, lack of initiative or motivation, anhedonia, language deficiencies (the so-called negative symptoms), or cognitive and mood disorders, do not appreciably improve – or indeed even worsen – as a result of chronic treatment with antipsychotics (Miyamoto, Duncan, Marx & Lieberman, 2005).

Although estimates of the clinical efficacy of classic or conventional antipsychotics vary widely depending on the clinical criterion employed, in general it is estimated that just a third of schizophrenic patients respond favourably to these drugs, achieving both social and employment integration; another third respond partially, improving their symptoms but suffering relapses that sometimes require their hospitalization and in need of social assistance (Lewander, 1992); finally, the remaining third do not respond at all, or only minimally, to antipsychotics (Meyer & Quenzer, 2005; Kane, 1996). For example, some meta-analyses show a relapse rate of 55% in schizophrenic patients who receive a placebo, while the rate falls to 21% in those treated chronically with antipsychotics, indicating a net efficacy of antipsychotics of 34% against placebo from this perspective (Davis et al., 1993). Despite their limited efficacy, however, multiple studies have shown chlorpromazine and other classic neuroleptics to be more effective than placebo or psychotherapy alone in the treatment and prophylaxis of psychotic episodes in patients with schizophrenia (Davis et al., 1993; May et al., 1981; Prien & Cole, 1968).

Unfortunately, the discontinuation rate for neuroleptic treatment is very high, due not only to the fact that it is only moderately effective for the treatment of psychoses, but also, and indeed mainly, to the high incidence of adverse side-effects (van Putten, 1974). Notable among many other such effects are those known as extrapyramidal symptoms (EPS), observed in almost 75% of patients with schizophrenia receiving long-term treatment with antipsychotics, in the form of movement disorders such as tardive dyskinesia, dystonia or akinesia/Parkinsonian bradykinesia, as well as akathisia, a subjective sensation of motor restlessness.

ATYPICAL ANTIPSYCHOTICS

At the end of the 1980s, the pharmacological treatment of schizophrenia appeared to take a new turn with the reintroduction of clozapine in Europe for treating schizophrenia resistant to conventional neuroleptics. Diverse randomized clinical trials succeeded in demonstrating that clozapine had unique pharmacological characteristics, in that it was more effective for the treatment of resistant schizophrenia and had fewer EPSs (Kurz, Hummer, Oberbauer & Fleischhacker, 1995; Kane, Honigfeld, Singer & Meltzer, 1988). However, clozapine is associated with the risk of potentially fatal agranulocytosis, sedation, hypotension and weight gain. Therefore, diverse antipsychotic drugs have been developed in attempts to imitate the pharmacological and therapeutic properties of clozapine, agents generally referred to as second-generation or "atypical" antipsychotics: risperidone, quetiapine, olanzapine, amisulpride, ziprasidone, and so on.

There is currently no consensus among specialists on the criterion of atypicality, with respect to conventional neuroleptics or antipsychotics. For some, atypicality would be based on their distinctive pharmacological properties, given that they tend to be antagonists (with a blocking effect) of not only dopamine receptors (especially type D2), but also of different serotonin receptors, with even greater affinity (type 5HT-2). However, this criterion is not met, for example, by amisulpride, since it does not have such affinity for serotonin, but rather for different dopamine receptors (types D2 and D3). For others, though, atypicality would be based on the lower tendency of these drugs to cause EPSs, compared to conventional neuroleptics such as haloperidol (like chlorpromazine, a prototypical high-potency neuroleptic). With the possible exception of clozapine, these EPSs appear only as a result of moderately high therapeutic doses of risperidone or other atypical antipsychotics. Finally, other specialists highlight the supposed greater efficacy of the atypical agents for

treating the negative symptoms of schizophrenia, by comparison with conventional neuroleptics (Davis, Chen & Glick, 2003). In any case, the lower risk of EPSs with atypical antipsychotics has greatly popularized their use as first-choice therapeutic agents for the treatment of schizophrenia and other psychotic disorders in clinical practice, so that, despite their high cost, they have largely supplanted conventional antipsychotics.

Due in part to the enormous cost to health systems, the issue of the efficacy of atypical antipsychotics has given rise to extensive debate, especially amid revelations of new adverse effects, such as obesity, hyperlipidemia, diabetes, resistance to the action of insulin and hypercholesterolemia (a set of symptoms known as "metabolic syndrome"), and a greater associated risk of cardiovascular or cerebrovascular disorders in general (Lieberman, 2004). Furthermore, the supposed greater therapeutic efficacy of atypical antipsychotics in general for the treatment of schizophrenia, as against conventional neuroleptics, has been called into question by various meta-analyses and systematic reviews over a number of years (Bagnall et al., 2003; Leucht, Wahlbeck, Hamann & Kissling, 2003; Geddes, Freemantle, Harrison & Bebbington, 2000). It would seem that the majority of studies comparing therapeutic efficacy and tolerance for atypical and conventional antipsychotics produced highly inconsistent and even contradictory results, depending on the type of conventional antipsychotic of reference – which is usually haloperidol, a potent neuroleptic with high risk of EPSs – and the dose, which tends to be very high.

EFFECTIVENESS VERSUS EFFICACY

If the above is true, how are we to explain the generally accepted view that atypical or second-generation antipsychotics are more effective for treating not only the negative symptoms of schizophrenia, but also the associated mood and cognitive disorders, though not for improving quality of life? Recently, various researchers and clinical professionals have offered a possible solution to this paradox on employing measures of effectiveness, rather than simply of efficacy, for establishing the true therapeutic value of antipsychotics. Effectiveness refers to a drug's efficacy in conditions of regular use and in non-selected patients with a certain disorder or illness. However, in randomized clinical trials (RCT), which are the most widely used experimental procedures for determining the efficacy and safety of pharmacological or therapeutic treatments in human beings, effectiveness is not taken into account. In contrast to effectiveness (or "efficacy in the real world"), efficacy in RCTs is established at best in highly limited samples of no more than a thousand patients studiously selected so as to present a minimum of associated pathologies, with well-defined or prototypical clinical conditions, and who are, moreover, assessed in a short-term context in controlled environments such as hospitals or clinics. Therefore, it is reasonable to suppose that the results in effectiveness will be inferior to those of therapeutic efficacy, given the large number of factors that negatively affect the efficacy of drugs in real life.

UNEXPECTED RESULTS OF THE LATEST STUDIES ON THE EFFECTIVENESS OF ANTIPSYCHOTICS

In late 2006, the initial results were published of two large-scale multicentre studies analyzing for the first time the effectiveness of antipsychotics in the treatment of schizophrenia, and which, exceptionally, were not funded by pharmaceutical companies, but rather from public sources (Lieberman, 2006). These were the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), carried out under the auspices of the US National Institute of Mental Health, and the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1).

Table 1 provides a summary of the characteristics of the experimental design of the two studies. The CATIE trials showed originality in their attempts to establish the common conditions of use and prescription of antipsychotics, and were subdivided in three consecutive phases. The first had a randomized double-blind design as regards the assignment of treatments, in which patients with schizophrenia were assigned to treatment with either a conventional or first-generation antipsychotic (perphenazine) or a second-generation drug (olanzapine, quetiapine, risperidone or ziprasidone). Patients who discontinued the treatment in the first phase were allowed to participate in a study comparing clozapine with other atypical antipsychotics – the so-called efficacy pathway – or in another study comparing atypical antipsychotics other than clozapine with one another – the so-called tolerability pathway. This study has the additional peculiarity that the principal variable of

analysis is the discontinuation rate, which was used a general index of treatment effectiveness. Through a series of questionnaires, the discontinuation rate could be associated with lack of therapeutic efficacy, or with intolerance to side-effects.

In contradiction of the authors' initial hypothesis, the results of these first two phases of the CATIE trials (Table 2) showed high discontinuation rates in general for all types of antipsychotics, with large individual variations. Moreover, no great differences were appreciated with regard to the effectiveness of any of the antipsychotics utilized. Thus, although olanzapine was slightly more efficacious than the rest of the antipsychotics (except clozapine), it had a high discontinuation rate due to its adverse side-effects, such as weight gain and other endocrine disorders (Nasrallah, 2006; McEvoy et al., 2006; Lieberman et al., 2005). Atypical antipsychotics such as clozapine confirm their greater efficacy only in those patients who show resistance to treatment with other antipsychotics.

Furthermore, all the antipsychotic drugs produced a modest improvement in psychosocial function measured with quality of life scales, with no significant differences between first and second-generation antipsychotics (Swartz et al., 2007). Phase 3 of CATIE is currently under way. This final phase includes patients who dropped out of Phase 2, who will be treated in an open design with one or two of the conventional and atypical antipsychotics

TABLE 1
EXPERIMENTAL DESIGN OF THE FIRST TRIALS ON THE EFFECTIVENESS OF ANTIPSYCHOTICS

Country	CATIE USA	CUtLASS 1 United Kingdom
Public sponsor	*National Institute of Mental Health*	*National Health Service*
Primary clinical variable	Discontinuation of the assessed	Quality of life medication
Diagnosis	100% schizophrenia	75% schizophrenia, 25% other psychoses
Duration	18 months	12 months
Number of subjects	1460	227
Masking procedure	Double-blind	Open for patients and doctors, but blind for evaluators
Nº of participating institutions	57	14
Inclusion of patients with first psychotic episode	No	Yes (13%)
Antipsychotics utilized	4 SGA, 1 FGA (20% subjects, perphenazine)	4 SGA, 15 FGA (50% subjects)
Percentage of patients with previous antipsychotics treatment	74%	99%
Mean duration of the disorder	16 years	14 years

Based on Constantine and Tandon (2007).
CATIE: *Clinical Antipsychotic Trials of Intervention Effectiveness*
CUtLASS: *Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study*
SGA: Second-generation or atypical antipsychotic
FGA: First-generation or conventional antipsychotic

TABLE 2
SUMMARY OF PRINCIPAL RESULTS OBTAINED IN THE *CATIE* TRIALS

- ✔ After Phase I, a high percentage of patients discontinued the medication (74%) due to their own decision to abandon it (24%), due to lack of efficacy (24%), due to intolerance to adverse side-effects (15%) and for other reasons (6%).
- ✔ Highest percentage gives up olanzapine (19%), followed by perphenazine (16%), quetiapine and ziprasidone (15% each) and risperidone (10%).
- ✔ Reasons for discontinuation: metabolic syndrome-weight gain (olanzapine), EPSs (perphenazine).
- ✔ Mean time to discontinuation: maximum in olanzapine (9.2 months) as compared to the other drugs (between 3.5 and 5.6 months).
- ✔ Duration of successful treatment: greater in olanzapine (3 months) than the rest (0.5 to 1.5 months).
- ✔ Phase II, greater efficacy with clozapine (56% discontinue), as against olanzapine (72%), risperidone (86%) and quetiapine (93%).
- ✔ Phase II, similar tolerance, though better in risperidone (64% discontinue) than in olanzapine (67%), ziprasidone (77%) and quetiapine (84%).

TABLE 3
SUMMARY OF RESULTS OBTAINED IN THE *CUTLASS 1* TRIALS

Branch I

- ✔ 1-year study comparing the cost-utility relationship in FGAs and SGAs for the treatment of schizophrenia.
- ✔ FGA and SGA equal in general effectiveness and quality of life, with no differences in relation to side-effects.

Branch II

- ✔ 1-year study comparing clozapine with other SGAs in the treatment of treatment-resistant schizophrenia.
- ✔ Clozapine significantly more effective than other SGAs ($P<0.02$), but not in relation to improvement of quality of life ($P = 0.08$).

employed (including the newcomer aripiprazole). It is to be expected that, in accordance with meta-analyses in the field, the "third-generation" aripiprazole will not bring advantages with regard to tolerability or efficacy compared to the other classic or atypical antipsychotics (El-Sayeh & Morganti, 2006).

The second recent cost-effectiveness study (CUtLASS 1), carried out in the United Kingdom, confirms the results of the CATIE trials from the US (Table 3). Once again in contradiction of the researchers' initial hypothesis, as far as effectiveness and quality of life are concerned, the atypical or second-generation antipsychotics are similar to the classic neuroleptics (Jones et al., 2006). This study was quite exhaustive with regard to the assessment of effectiveness, rated on six different scales completed by the patient or evaluator, together with a quality of life scale. Not even clozapine was significantly better than the rest of the atypical antipsychotics in terms of quality of life, though it did stand out in its general efficacy for reducing psychotic symptoms. The results of these two clinical trials and of previous meta-analyses indicate that the difference in efficacy and tolerability between different classes of antipsychotics has been exaggerated, and they do not provide justification on cost-benefit grounds for the prescription of atypical antipsychotics as first-choice drug in the treatment of schizophrenia.

Furthermore, other results from CATIE and recent meta-analyses advise against the use of atypical antipsychotics for the treatment of the psychotic symptoms or agitation associated with dementias such as Alzheimer's disease, due to their lack of efficacy and the risk of death from cardiovascular disorders (Ballard & Waite, 2007; Schneider et al., 2006)

In conclusion, these new studies highlight the importance of individualizing treatment with antipsychotics, due to the high variability of response and discontinuation rate found. Likewise, they confirm the benefits of changing the antipsychotic drug in certain patients with schizophrenia resistant to treatment with drugs. They also indicate, except in patients with greater risk or the presence of EPSs, the justification of making conventional antipsychotics the first-choice class of drug, given their similar effectiveness and low cost. Finally, the unexpected results on the modest effectiveness of the pharmacological treatment of schizophrenia should lead to a reappraisal of current pharmacological approaches to this disorder. The key in terms of therapy would actually not necessarily seem to reside in the well-trodden path of direct or indirect modulation of the systems of dopaminergic neurotransmission in the brain, which is the action mechanism common to all antipsychotics developed up to now. Moreover, the extremely high discontinuation rate for antipsychotic medication, together with its minimal beneficial effect on the low quality of life of patients with schizophrenia, suggest an urgent need for the introduction of new and more effective drugs or therapies. We hope and trust that effectiveness studies can be extended to other psychoactive drugs, and that they will stimulate research on the etiopathology of schizophrenia and other serious mental disorders.

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