CATIE: welcome to the real world

E. Álvarez Martínez[1]
M. Bernardo Arroyo[2]
M. Roca Bennasar[3]

[1] Psychiatry Service
Hospital de Sant Pau
Universitat Autònoma
Barcelona (Spain)

[2] Psychiatry Service
Hospital Clinic
Institut d'Investigacions Biomèdiques Agustí Pi i Sunyer (IDIBAPS)
Universitat de Barcelona
Barcelona (Spain)

[3] Psychiatry Unit
Hospital Juan March
Institut Universitari d'Investigació en Ciències de la Salut (IUNICS)
Universitat de les Illes Balears
Palma de Mallorca (Spain)

Schizophrenia is probably the most complex mental disease that can be suffered by the human being and is a daily challenge for the clinician. The appearance of useful drugs for it in the beginning of the 1950's reversed the proportion of patients with sufficient personal independence to live in the community in relationship to those who required permanent care. Since then, the range of drugs has not stopped growing, with an outstanding inflection at the end of the eighties after the reappearance of clozapine on the market, with proven efficacy although it does not induce extrapyramidal adverse events. The existing possibilities of the choice of drug treatment have continued to increase, with drugs that demonstrate their utility in efficacy studies, as required by the regulatory authorities of the pharmaceutical companies for their marketing.

In the middle of the era of scientific medicine (evidence based), the choice of the best drug should be made, according to the Cochrane Collaboration, in a hierarchy of «values» constructed according to the methodological rigor following in the clinical trials[1]. This hierarchy begins in the trial conducted under strict experimental conditions (randomized, controlled, double blind, placebo controlled and/or with the best drug possible, etc.), goes through case-control studies and finishes up in the not very «advisable» experts committees. However, for the clinician, these sources of knowledge are more a reason for dissatisfaction[2,3]. In fact, the high response to placebo, exaggerated proportion of drop-outs, and enrolment conditions of the patients that drastically limit their representativeness in the daily visits, worry the psychiatrist and discourage him/her to base his/her decision on these trials. In fact, one of the utilities of these studies is rather perverse: the elaboration of therapeutic guidelines by the academic or theoretic professionals with limited clinical training, that possibly serves the regulatory authorities to «direct» the medical prescription.

Correspondence:
Miguel Roca Benassar
Universidad Illes Balears
Servicio de Psiquiatría
Ctra. Valldemossa, km. 7,4
07010 Palma de Mallorca
Correo electrónico: miguel.roca@telefonica.net

A few years ago, three important groups of the Cochrane Collaboration who work in schizophrenia published an extensive and thorough reflection on the utility of experimental design studies (clinical trials) in decision making of the psychiatrist[4]. To respond to their concerns, they conducted a systematic review of all the literature generated by clinical trials with antipsychotics, studying the critical variables for the psychiatrist in his/her daily practice. The results were devastating: most of the patients are men and repeat participants of clinical trials; in addition, their enrolment profile (collaborators, non-dependent, without risk of self or heteroaggressiveness, without comorbidity or consumption of other drugs or toxic abuse) distance them from the patient generally seen. The place where the trials are conducted (generally acute patient units) represents a minimum part of the facilities where the patients will be controlled. The study duration (weeks or months) is very short in relationship to the usual treatment duration of the schizophrenia. Evaluation tools are explanatory variables without possible translation to the clinical reality and the comparison drug is usually haloperidol (that is not exactly the best possible). The authors conclude the study stating that it is essential to conduct studies using pragmatic variables identifiable with the patient's reality, having a prolonged duration (more than one year), with real patients, in which one of the few enrolment criteria is that the subject wants to participate, patients with comorbid conditions, additional treatments and possible associated substance abuses. They should be done in all types of health care facilities and the best possible drug should be used as comparison. They even question the obligatoriness of «blinding» of the drug and they are only inflexible from the methodological point of view, as is obvious, in the need for randomization.

The occasion of this article exceeded the authors' intensions. Faced with the appearance of new drugs with different varieties of action mechanisms, the need for information applicable to the daily clinical setting, that is to the real world, was increasingly pressing. In fact, the questions having the greatest relevance posed by the clinician were: What antipsychotic should be chosen? What clinical result will be the same when one or the other is chosen? Do they all have the same advantages regarding the classical antipsychotics.

A STUDY OF EFFECTIVENESS

This need to thoroughly evaluate effectiveness, that is, utility in the real world, of second generation antipsychotics (which are already 90 % of the antipsychotics prescribed in the United States) versus the oldest drugs has motivated the performance of Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)[5-7]. This study has been promoted by the National Institute of Mental Health (NIMH), independently from the pharmaceutical industry, with the well-defined purpose of conducting a comparison of the effectiveness of antipsychotic drugs. The protocol was designed and given advice by renowned experts in the field of schizophrenia, with the collaboration of health care managers and user representatives. It took place between January 2001 and December 2004 in 57 public and private sites of the United States.

The patients were randomly assigned to treatment with olanzapine, perphenazine, quetiapine and risperidone and followed-up for 18 months or until their discontinuation for any reason, when they were included in another treatment arm. In January 2002, after it was marketed in the United States, a fifth treatment option with ziprasidone was included. Participants were between 18 and 65 years of age, with a diagnosis of chronic schizophrenia according to DSM-IV criteria. The patients with tardive dyskinesis symptoms could be enrolled, although the randomization plan excluded them from treatment with perphenazine. The medication doses were flexible, according to medical criteria, up to 4 tablets daily of olanzapine (7.5 mg), perphenazine (8 mg), quetiapine (200 mg), risperidone (1.5 mg) and ziprasidone (40 mg).

Evaluation was based on a principal assessment criterion: discontinuation of treatment for any reason. The secondary criteria included specific reasons for discontinuation, whether they were lack of efficacy or tolerability problems (weight gain, extrapyramidal effects or excessive sedation). The patients were administered the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impression (CGI) scale and the evaluations were made at months 1, 3, 6, 9, 12, 15 and 18. The trial has an 85 % statistical power to identify absolute differences of 12 % in the discontinuation rates and Kaplan Meier survival curves were used to estimate time to discontinuation. The treatment groups were compared with the stratified Cox's proportional hazards regression models.

A total of 1493 patients were included in the randomization. The mean modal doses were: 20.1 mg of olanzapine, 20.8 mg of perphenazine, 543 mg of quetiapine, 3.9 mg of risperidone and 112.8 mg of ziprasidone. A total of 74 % of the patients in the analysis by intention to treat (1,061 of 1,432) discontinued treatment before 18 months. Significant differences were found between the different antipsychotics, both in efficacy and tolerability. The longest discontinuation period for any reason, including lack of efficacy as well as the duration of the satisfactory treatment, with lower hospitalization rate due to exacerbation was for olanzapine. In regards to treatment drop-out due to intolerable side effects, risperidone had the lowest rate (10 %) and olanzapine the highest (18 %). Olanzapine was associated with weight gain and greater increases of glycated hemoglobin, triglycerides and total cholesterol. There was no cataract formation with quetiapine. Risperidone was associated with hyperprolactinemia. No prolongation of the correct QT interval was found with ziprasidone. Perphenazine showed greater incidence of extrapyramidal symptoms.

CONCLUSIONS

The CATIE study, with its virtues and defects, has the advantage of returning psychiatry to the real world. For years, the clinicians have not tired of repeating that the patients of the daily practice differ in many aspects from the cases included in controlled clinical trials. Effectiveness and efficacy are no longer analogic concepts and the CATIE is a determined bet to analyze effectiveness, with pragmatic variables.

Precipitated conclusions cannot and should not be drawn from the CATIE study, a tendency to do so sometimes being shown by some health care managers. It would be a gross mistake if the clinicians consider the results of this study with the maximum of care and, on the contrary, the managers interpret the initial results as they want: for example deciding if a group of antipsychotic drugs, the classical ones, is more effective than another or applying cost-effectiveness criteria to some data that have only begun to open a way of study considered up to recently, erroneously, as a second line scenario. The CATIE does not show superiority of perphenazine as a representative of a type of drugs, for the previously mentioned reasons. Acting based on this premise would be to be completely mistaken. The investigators of CATIE considered that it was not ethical to randomize 15% of patients with tardive dyskinesis to the perphenazine group. It is not acceptable to restrict access to the drug group based on these data.

A second relevant question is to know if these results are applicable to the Spanish population. Some authors have criticized CATIE due to the excessive enrolment of men (75 %), that 40 % were married at some time of their lives, that 30 % of the patients enrolled did not take any medication when they entered into the study and finally, that the mean age of antipsychotic treatment onset was 26 years. Equally, the doses used in some of the drug, that would have favored their better tolerability and worsened their effectiveness or vice versa, have been criticized. In any case, the design supports, with the methodological problems that are impossible to evade in an effectiveness study, the possibility of generalizing results in other populations outside the United States. The imperfection and divergences of the real world, of the usual psychiatric patients, will never find a «perfect» design, without fissure or possible criticism, to evaluate effectiveness. Identifying the primary measure-

ment variables in a study of these characteristics is complex and the choice of the time to discontinuation seems to be a solution adjusted to the aims of CATIE.

Schizophrenia is a chronic disease, with very complex management, in which the patients flagrantly lack treatment compliance, they frequently change medications. At present, one cannot speak of a «best» treatment given the large variability of individual characteristics and responses within the framework of the disease history and course. In this sense, the CATIE results may be interpreted as disheartening[8]. But the opposite interpretation also has firm arguments: the disease has different treatments, some more effective, others better tolerated, and in fact, the availability of all of them, with equality of conditions for the physician and patient, is the only guarantee for a clinical practice adapted to the present resources. This is the real world of the treatment of schizophrenia that CATIE brings us nearer to, perhaps the same as the so-called «gold standards», in form of controlled efficacy studies. Strictly analyzing effectiveness will not be a gold standard of the scientific practice but it merits consideration as silver; sterling silver.

In Spain, even in Europe, economic and health care problems clearly hinder or prevent the conduction of an effectiveness study having similar characteristics to that promoted by the National Institute of Mental Health. Not only this: effectiveness study projects under pragmatic conditions have, as we understand it, erroneously limited possibilities of receiving support in the public notifications of research in our country. A long-term effectiveness study, including pragmatic variables that refer to the cognitive evaluation and performance and personal independence of the patients, for example, would be absolutely necessary. If such a design does not find an echo in these public bodies that finance the research, perhaps it is time for other scientific institutions to propose the convenience of planning them in a more or less near future.

REFERENCES

1. Gray GE. Evidence-based medicine: an introduction for psychiatrists. J Psychiatr Pract 2002;8:5-13.
2. Freemantle N, Blonde L, Bolinger B, Gerber RA, Hobbs FD. Real-world trials to answer real-world questions. Pharmacoeconomics 2005;23:747-54.
3. Seeman MV. Clinical trials in psychiatry: do results apply to practice? Can J Psychiatry 2001;46:352-5.
4. Gilbody S, Wahlbeck K, Adams C. Randomized controlled trials in schizophrenia: a critical perspective on the literature. Acta Psychiatr Scand 2002;105:243-51.
5. Swartz MS, Perkins DO, Stroup TS, McEvoy JP, Nieri JM, Haak DC. Assessing Clinical and Functional Outcomes in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Schizophrenia Trial. Schizophr Bull 2003;29:33-43.
6. Stroup TS, McEvoy JP, Swart M, Byerly MJ, Glick ID, Canive JM, et al. The National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Project: Schizophrenia Trial Design and Protocol Development. Schizophr Bull 2003;29:15-31.
7. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005;353:1209-23.
8. Freedman R. The choice of antipsychotic drugs for schizophrenia. N Engl J Med 2005;353:1286-8.