International Journal of Neuropsychopharmacology (2010), **13**, 971–973. Copyright © CINP 2010
doi:10.1017/S1461145709991271

TRENDS AND PERSPECTIVES

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Designing outcome studies to determine efficacy and safety of antipsychotics for 'real world' treatment of schizophrenia

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Abstract

Over the last 5 years, some studies have questioned the efficacy of second-generation antipsychotics over first-generation neuroleptics in the treatment of schizophrenia. At the same time, these study results have led to re-examination of their design – particularly CATIE and CUtLASS – which essentially measured relatively short-/mid-term outcome and did not always take into account real-world clinical practice and outcome measures (e.g. prevalence of positive acute symptoms, exclusion of comorbidity with substance abuse, predominance of chronic patients, lack of quality of life/wellbeing measures, etc.). In fact, one of the greatest challenges to treatment of schizophrenia is its life-long, multifaceted, functional disability associated with progressive cognitive deterioration after each acute episode. As such, the most important goal of the treatment is not just to deal with acute episodes, but rather to improve long-term outcome. Specifically, we aim for modest improvement and then stabilization of the different clinical dimensions involved in the overall symptomatology (i.e. negative/anergic, impulsive, positive, mood and cognitive impairments), and to achieve 'clinical stabilization' after obtaining a partial or full remission of acute symptoms, thus reducing the risk of a progressive cognitive deterioration. All these aspects need to be properly evaluated in a long-run perspective.

Received 21 April 2009; Reviewed 9 June 2009; Revised 26 November 2009; Accepted 22 December 2009; First published online 4 February 2010

Key words: Antipsychotics, outcome studies, schizophrenia.

Over the past two decades, since the introduction of second-generation antipsychotics, there has been a major shift of the focus of treatment – from acute in-patient symptom control in the hospital to maintenance and improved quality of life in the community. In part, this is because regardless of which antipsychotic is used, most schizophrenia patients show a good response to medications during the first weeks – especially in positive, psychotic symptoms. Although this is a good first step, the bigger problem inherent in the disease is the life-long, waxing and waning, multifaceted, functional disabilities associated with progressive cognitive deterioration after each acute episode.

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Therefore, we argue that the most important goal of the treatment of schizophrenia is not just to deal with acute episodes (which are often phenomenologically similar of other psychotic disorders, e.g. acute drug toxicity), but rather to improve long-term outcome. Specifically, we aim for modest improvement and then stabilization of the different clinical dimensions involved in the overall symptomatology (i.e. negative/anergic, impulsive, positive, mood and cognitive impairments). In other words, the main objective of antipsychotic treatment should be to achieve 'clinical stabilization' after achieving a partial (or optimal) remission of symptoms in the acute phase; thus reducing the risk of a progressive cognitive deterioration (Altamura, 1996; Altamura *et al*. 2007).

Most data comparing first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs) (including CATIE, CUtLASS and EUFEST; Jones *et al*. 2006; Kahn *et al*. 2008; Lieberman *et al*. 2005) come from relatively short-/mid-term trials. Although each

antipsychotic is unique – they do not differ greatly on efficacy – the bigger difference is on side-effects especially extrapyramidal ones (EPS) and tardive dyskinesia (TD). Unfortunately, meta-analytical data – most of which is short-term, and focused on acute issues – have been extrapolated to the long-term global efficacy of using these compounds in continuation and maintenance phases of the disorder. On this basis, many clinicians believe that there are few differences between typical and atypical compounds and, moreover, their use is not supported by significant cost–benefit ratio studies (Altamura *et al*. 2008). In fact, critical revisions on major multicentre effectiveness trials and meta-analyses have been increasingly published (Davis *et al*. 2009; Glick, 2006; Leucht *et al*. 2009; Lewis & Lieberman, 2008; Meltzer & Bobo, 2006).

This very simplistic argument lacks the feedback from clinicians about their 'real world' experience seen in the outpatient clinics in Europe and America (Meyer, 2007; Tiihonen *et al*. 2006). In particular this may be a 'reductionistic' view of the value of at least some of the atypicals based on the following (arguably wrong) premises:

(*a*) Characterization of the acute episode mostly by the psychotic symptoms.
(*b*) Regarding the prognosis and treatment of schizophrenia as the sum of single acute episodes. Rather, what should be taken into account is the quality of life and the symptoms in the time-frame between episodes. That is the periods when the patients can be depressed, anhedonic/anergic, excited, hostile, anxious, etc., contributing to lack of stabilization (hospitalized or not).

In other words, we need to consider all the clinical parameters in order to asses the impact of different pharmacological treatments on the outcome, including the fact that schizophrenia consists of multiple dimensions (and not just the psychotic dimension, as erroneously emphasized by the use of D_2 antagonists). The specific action on all these domains should be carefully evaluated, for example on affective/emotional, cognitive, impulsive/aggressive patterns which affect clinical stability and outcome.

For these reasons, the best evaluation of the effect of any compound should include an assessment especially over a much longer observational period, at least 6–18 months. It is of paramount importance to look in particular to medium- and long-term results when trying to demonstrate clinically meaningful impact on the disorder as well as to determine the efficacy and difference among drugs. We lack such data at the moment, but what we do have suggests a trend for superiority of some atypicals *vs*. typical compounds, particularly for rehabilitation purposes (Csernansky *et al*. 2002; Percudani *et al*. 1999). Nevertheless, when designing long-term studies in schizophrenia, methodological difficulties related to costs and funding, in particular, should be taken into account.

A common perception of investigators working in the field is that atypicals better stabilize patients, mostly because patients adhere better to the new than older antipsychotics (Davis *et al*. 2003, 2009). Compliance seems better in the long term despite patients' poor insight about their disorder. The crucial issue is that having either a lack of efficacy for a particular drug or getting EPS/TD will cause patients to discontinue their medications (Carpenter & Buchanan, 2008).

Other considerations are the following: patient selection should avoid using patients with a long history of the disorder (i.e. there may be a 'ceiling effect' for treatment response); schizophrenia, being in part a neurodegenerative disorder, makes it difficult *per se* to detect differences after many years from the age of onset (Cahn *et al*. 2009). Differences are more likely to be detected in a sample of patients with a relatively short history compared to samples with a longer history. In this regard, the use of neuroimaging techniques may be particularly helpful in order to appreciate neurodegeneration signs due to the progression of the illness.

Other open questions – which clinical trials and the meta-analytical data have not definitely answered – include (and the answer might be interpreted as positive for the first two questions on the basis of available data; Garver *et al*. 2005; van Haren *et al*. 2007):

- Is an early start (short duration of untreated illness) of an atypical more likely to improve outcome compared to early use of a typical?
- Have the atypicals the capacity to better halt the ongoing neurodegenerative process of schizophrenia?
- Does the type of a prevalent dimension matter in terms of early use of an atypical (negative *vs*. positive symptoms) significantly influence course and outcome of the disorders? (differently from typical compounds?)

Finally, outcome variables over the long run should include (*a*) the hospitalization rate, (*b*) the degree of disability, (*c*) the quality of life, (*d*) the number of medical interventions, (*e*) the patient and doctor judgement about the value of the treatment (double-blinded) and (*f*) risk and cost–benefit ratio. Taken as a whole, these aspects should in turn effect other important aspects of the patient's ability to function in

the community, socially and vocationally which are crucial in order to obtain functional recovery (Andreasen *et al*. 2005; Harvey & Bellack, 2009).

Acknowledgements

The authors thank Dr Bernardo Dell'Osso (Fondazione IRCCS Policlinico, University of Milan, Milano, Italy) for his kind assistance in preparation of the manuscript.

Statement of Interest

None.

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