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COMMENTARY

First and second generation antipsychotics: translating the results from pragmatic trials into clinical practice

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Commentary on: F Cheng, PB Jones (2013). Drug treatments for schizophrenia: pragmatism in trial design shows lack of progress in drug design. *Epidemiology and Psychiatric Sciences* (doi:10.1017/S204579601200073X).

As Cheng and Jones document in this issue, pragmatic clinical trials have provided remarkably consistent results from comparisons of first and second generation antipsychotics in patients with schizophrenia. When clozapine is removed from consideration, we are left with a group of medications that have similar efficacy in treating psychotic symptoms and very different side effect profiles. Translating this information into selecting an antipsychotic is complicated, but there are some principles that can be derived from this review.

Before commenting on drug selection for certain types of patients, it is important to consider whether there are populations of patients where these pragmatic studies may not be very helpful. Patients who are strong and relatively rapid responders to an antipsychotic are probably underrepresented in these trials. These individuals seldom enter clinical trials because there is little or no incentive. Some of these patients are probably included in the EUFEST study (Kahn *et al.* 2008) since patients were excluded who had been on an antipsychotic for more than two consecutive weeks. In contrast, the CAFÉ trial (McEvoy *et al.* 2007) included patients who had been on an antipsychotic for an average of about 6 weeks. The subjects in CATIE (Lieberman *et al.* 2005) and CUtLASS (Jones *et al.* 2006) were individuals who had received antipsychotics for decades, on average, but still had persistent psychotic symptoms. This – and the open label design – probably explains why the number of discontinuations was lower in EUFEST. Clinicians and researchers who treat schizophrenia have been aware for a very long time (Garver *et al.* 1988) that there are certain patients who respond early and vigorously to an antipsychotic. A more recent study (Kinon *et al.* 2010) found that 28% of patients with acute schizophrenia showed at least a 20% improvement after 2 weeks of treatment. Many or most of these individuals are unlikely to be interested in enrolling in a clinical trial. The point is that there are some limitations in generalizing from trials which are probably biased towards patients who are not the best drug responders.

For the majority of patients the Cheng and Jones review suggests that drug decision-making – absent a consideration of clozapine – should be driven by side effects and not by efficacy. The treatment of early-onset schizophrenia spectrum disorders (TEOSS) study (Sikich *et al.* 2008) provides a good example. In this study of children and adolescents, the weight gain and metabolic changes associated with olanzapine were severe and led the NIMH Data Safety Board to terminate olanzapine as a condition. This and similar data led the 2009 Schizophrenia Patient Outcomes Team (PORT) (Buchanan *et al.* 2010) to designate olanzapine as a second line medication for young, first episode patients. Olanzapine, clozapine, quetiapine, risperidone and other first and second generation antipsychotics also have effects on weight and metabolic parameters in patients at all stages of treatment although olanzapine and clozapine seem to be particularly severe. This raises the question as to the place of an agent such as olanzapine, which may have a small efficacy advantage in large trials but also has a serious side effect liability. My view is that olanzapine should probably be viewed as an agent that should only be prescribed when the clinician is prepared to monitor its effects and where the patient is fully aware of its dangers. Weight should be monitored carefully and the medication should be changed when certain parameters are reached. The Mount Sinai guidelines (Marder *et al.* 2004) suggest

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that a weight gain of 1 BMI unit should lead to re-evaluation and perhaps a medication change. The clinician may also consider evaluating insulin resistance before and shortly after starting the drug. An elevation in triglycerides – with or without a weight increase may suggest changing strategies.

The management approach should be similar if the patient is prescribed an antipsychotic with a high likelihood of causing EPS. High potency first generation antipsychotics, risperidone, paliperidone and others will fit into this category. Under these circumstances, the clinician should be familiar with how to evaluate acute and tardive movement disorders. Patients should be warned about akathisia and the prescriber should perform a focused examination at every visit during the first few weeks of treatment.

The same approach should be applied to other side effects including prolactin elevation, sedation, hypotension, anticholinergic effects and others. Although there is not a single agent that stands out for having superior efficacy and fewer side effects, there are more choices that are available to clinicians. Most patients will need to live with an antipsychotic that is not completely effective and which has side effects. Matching the side effects to the patient is probably the best that can be done. Once the best tolerated antipsychotic is identified, the focus of treatment can turn to learning to live better despite symptoms and side effects that may persist.

It is notable that these approaches are not specific to first or second generation medications. Rather, it may be that designating an antipsychotic as a first or second generation agent provides very little information and it is unclear that there is a shared pharmacology in each group. The consistent results from this review may lead to a conclusion that there is no reason to do any more comparisons of first and second generation antipsychotics. The choice is among a relatively wide range of antipsychotics which makes prescribing more confusing but which leaves a much wider selection.

Declaration of interests

Consulting: Abbott, Astellas, Bristol Meyers Squibb, Otsuka, Lundbeck, Genetech, Roche, Targacept, EnVivo, Zogenix, Shire

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