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Triangulating views on antipsychotics

The article by David Cunningham Owens (2008) is one of the most thoughtful, stimulating, witty and clinically relevant that *APT* has published. It urges us to reconsider our views on what we call atypical antipsychotics. As an authority on extrapyramidal symptoms, he describes how the absence of parkinsonian side-effects may endow an antipsychotic with other advantages, including lower risks of depression and cognitive impairment, and of worsening negative and perhaps also positive symptoms of schizophrenia. There is no doubt that haloperidol (widely used in clinical trials as a comparator) can be made to appear very inferior, by prescribing it without prophylactic anticholinergic medication, and 'efficacy trials' in which this is done carry a bias against the classical antipsychotic. Owens is not surprised that 'effectiveness studies' such as CATIE fail to show consistent advantages for newer (atypical) antipsychotics in maintenance treatment for schizophrenia.

It would be a mistake to interpret his article as undermining the conclusion that the atypicals represent a therapeutic advance, or to support a conspiratorial view of the pharmaceutical industry. Advances in the treatment of psychosis and severely disturbed behaviour have come very slowly over 150 years, from the use of bromide salts (1857) and sedatives (chloral in 1869, barbiturates from 1905, antihistamines in the 1940s and benzodiazepines from 1961). It was the fortuitous discoveries of the properties of lithium from 1948 and chlorpromazine (a product of the antihistamine industry) from 1952 that represent the beginnings of modern psychotherapeutics. Naturally, drug innovators such as Paul Janssen (1926–2003), who discovered haloperidol (1958), wanted to produce an antipsychotic that would have fewer extrapyramidal side-effects and greater efficacy than haloperidol and the other older drugs. They saw the opportunity to do this, first by selective blockade of subtypes of dopamine receptors (the benzamide drugs), and later by modifying the structure of clozapine (e.g. olanzapine and quetiapine) and by attempting to mimic its pharmacological actions, especially blockade of serotonin (5-HT) receptors (e.g. risperidone). Thus, the atypicals represent the application of neuroscientific knowledge and logic to drug development. What this has produced for clinicians (treating some of the most devastating human disorders) is a range of therapeutic options with a variety of different side-effects and possibly some differences in efficacy.

The effectiveness studies discussed by Owens involved randomisation of patients to receive one of several possible drugs. This is an unnatural procedure that avoids the crucial step in which a clinician discusses the available drugs with the patient and then decides which might best suit their needs.

The findings of CATIE (funded independently of industry) do suggest that some atypicals are more likely than other drugs to be continued, for reasons of both efficacy and individual side-effects, although the differences are relatively small.

A third angle from which to view treatments is that of the 'observational study', in which a large cohort of patients is allocated a treatment, chosen by the clinician. These studies tend to confirm that the individual properties of different drugs (sedation, weight gain and metabolic effects, endocrine and sexual side-effects, and extrapyramidal side-effects) do occur in the real-world setting as predicted by the efficacy trials. Such studies tend to be sponsored by the industry and therefore to attract more scepticism. However, the findings should be included in a 'triangulated' view of the role of atypical antipsychotics. This combined information is the basis on which the clinician can make the individualised risk/benefit appraisal recommended by Owens and illustrated in his Fig. 2.

The industry has been richly rewarded for its investment in research in neuroscience and psychosis, and it will need this success to make the further investments that are required to explore the wealth of information that is arising from the basic neurosciences. For example, the exploration of glutamate (and the phencyclidine – PCP – model of psychosis) and endocannabinoids and their interaction with dopamine are tantalising subjects for therapeutic research and development. Moreover, the function and pharmacology of dopamine pathways has probably much more to tell us about psychosis, mood disorders and addictions.

Declaration of interest

J.C. has provided advice and lectures at meetings sponsored by the manufacturers of several atypical antipsychotics, including those mentioned here. He has met Paul Janssen and reviewed his biography.

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