Do findings from new trials for schizophrenia fit with existing evidence: not duped ... just beguiled?

CLIVE E. ADAMS and MAHESH JAYARAM

Abstract. No treatment has caused a greater revolution in the treatment of people with schizophrenia than chlorpromazine. The new generation of drugs has been embraced by psychiatry with an enthusiasm fostered by the unmet needs of both patients and industry. Recent, independently funded trials have highlighted already existing data illustrating how the new antipsychotics drugs are an additional advance but not a revolution. In this story there are lessons for psychiatry - to opt for science rather than seduction.

Only 60 years ago there were almost no pharmacological managements for people with schizophrenia. ECT and other physical treatments were used but nothing was as successful as chlorpromazine. This drug did revolutionise the care of people with schizophrenia worldwide (Freeman, 1958) and assured chlorpromazine's place in medical history (Turner, 2007). Shortly after chlorpromazine came haloperidol and many other antipsychotics, often with the promise of being equally clinically effective but with different side effect profiles, and this, indeed, seemed to be the case (Joy *et al.*, 2006; Marques *et al.*, 2004). Depot formulations were a further advance in means of administration but they never replicated chlorpromazine's initial revolution.

The trial-based evidence of the 1960s and 1970s is of variable quality and limited perspective (Thorley & Adams, 1998). It is, however, easy to judge the past by standards of today. The first CONSORT statement, encouraging better reporting of trials, is only a decade old (Begg *et al.*, 1996). Nevertheless, recent objective summaries of all trial-based evidence of older antipsychotics highlights compelling evidence of the short term benefits as regards delusions, hallucinations and thought disorder, and variable adverse effects (Hartung *et al.*, 2005; Joy *et al.*, 2006; Matar & Almerie, 2007; Soares *et al.*, 2000; Thorley *et al.*, 2003). Long term data are remarkably few for an illness that is often life long. There is no persuasive evidence that these drugs really have any effect on the negative symptoms of schizophrenia.

The heady 1960s gave way to the more cynical 1970s. Drug patents were running out. The initial justified wave of enthusiasm for antipsychotic medication gave way to the recognition of partial response to medications and a rediscovery of the damaging nature of schizophrenia (Hafner, 2004). This was fertile ground for a pharmaceutical industry, coming of age, wishing to encourage hope of a new pharmacologically-based revolution of treatment of people with schizophrenia. Clozapine, first formulated in the 1960s, was the first in a new generation of drugs. In the 1970s, clozapine was withdrawn in most countries because of blood dyscrasias, but was safely reintroduced with haematological monitoring in the late 1980s (Kane *et al.*, 1988). Clozapine remains a compound with an intriguing effect profile (Tuunainen *et al.*, 2000; Wahlbeck *et al.*, 2000) but its reintroduction was soon followed by marketing of a swathe of new 'atypical' drugs. Initially atypicality was linked with the inability of these drugs to cause catalepsy in rats. However, it became clear that some older generation drugs were found not to cause the rodent effect and that some new ones did. 'Atypical' became synonymous with 'new' or expensive.

New generation drugs were often favourably compared to a toxic older drug (Kennedy *et al.*, 2000). This was considerably contributed to by trial design. All drugs have a dose-event curve. As doses increase positive events also increase, only to plateau. There is a dose beyond which only negative effects occur and more positive outcomes are unlikely (see Figure 1).

Address for correspondence: Dr. C.E. Adams, Co-ordinating Editor, Cochrane Schizophrenia Group, Division of Psychiatry, University of Nottingham, Duncan MacMillan House, Portchester Road, Nottingham NG3 6AA, (United Kingdom).
Fax: +(0)115 969 1300 x 48210
E-mail: ceadams@cochrane-sz.org
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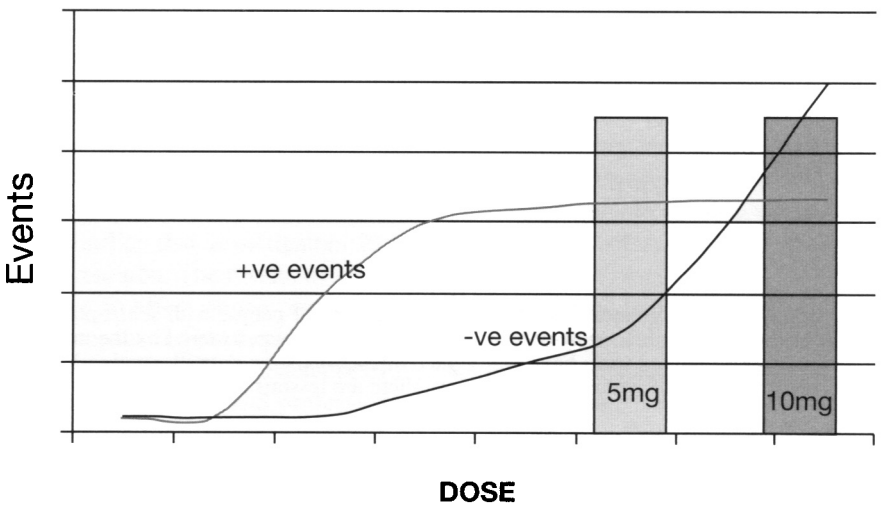

Figure 1. – *The dose vs event curve of a hypothetical old generation antipsychotic.*

It is perfectly feasible to simply halve or even quarter the dose of a familiar old drug with a wide positive effect plateau, compare it with a dose of known moderate toxicity, and find that the quarter dose is equally clinically effective with a different side effect profile. The new generation drugs were widely advertised as equally clinically effective [as older drugs] but with different adverse effect profiles.

The idea of use of these expensive compounds was successfully sold to a receptive population of clinicians, policy makers and public. The new drugs were moderately effective for schizophrenia but few considered the new generation a welcome expansion of drug treatments rather than a revolution (Centre for Reviews and Dissemination, 2007). Even clinicians in low and middle-income countries were made to feel guilty for not being able to afford the expensive new drugs (Adams *et al.*, 2006).

Reviews undertaken in a systematic and financially disinterested way were rare. They, however, consistently showed the new drugs to have effects - both good and bad - but data to be limited (Duggan *et al.*, 2000), biased (Heres *et al.*, 2006; Kennedy *et al.*, 2000; Montgomery *et al.*, 2004) and often difficult to interpret (Srisurapanont *et al.*, 2004). In 2002 UK guidelines began to use words carefully when suggesting that atypicals should be '*a*' rather than '*the*' first choice for people with schizophrenia (NHS, 2007). Anything but full endorsement has, however, not been entirely welcomed by industry, clinicians, many academics or patients. Nevertheless, moderation of wholehearted acceptance of use of atypicals has recently gained further momentum by witnessing industry trying to offset law suits regarding prevalent and damaging adverse effects with large out of court settlements (Dyer, 2007).

There have been calls both for more pragmatic trials to clarify the issue of efficacy of psychotropic medications (Adams, 2002; Thornley & Adams, 1998; Hotopf *et al.*, 1999) and for studies with more independent funding (Heres *et al.*, 2006; Montgomery *et al.*, 2004). Two recent landmark independently funded semi-pragmatic trials, CATIE (Lieberman *et al.*, 2005) and CUtLASS (Jones *et al.*, 2006), addressed issues of antipsychotic discontinuation along with efficacy and adverse effects. We extracted data for CATIE's primary outcome (leaving the study early) from Cochrane reviews relevant to the comparison drugs (Duggan *et al.*, 2005; El-Sayeh & Morganti, 2006; Hartung *et al.*, 2005; Jayaram *et al.*, 2006; Mota *et al.*, 2002; Soares *et al.*, 2000; Srisuranapont *et al.*, 2004) in both CATIE and CUtLASS, and undertook a before and after comparison (Table I).

For every comparison, data from the new studies only increased precision. In no case did they materially change the impression already available from existing evidence. The increase in precision of the perphenazine result is particularly noticeable. The research community has largely ignored this old antipsychotic and addition of CATIE's data hugely influences the result (Hartung *et al.*, 2005). The other key finding of these important trials - not presented in this table - is that there is little to

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choose between the newer drugs and intelligent use of older antipsychotics. This applies to both positive and negative effects. The results of these two new independent trials highlight what has been apparent from less disinterested sources for years.

The most certain thing we know about new and old generation antipsychotic drugs is that most patients will choose to stop them within a matter of weeks. In terms of positive effects there is littlie to choose between these drugs and all have frequent negative effects that can be serious.

Table I. – *Data for CATIE's primary outcome taken from all relevant trials before and after CATIE and CUtLASS – the risperidone data.*

Risperidone vs		**Number of trials**	**Experiemntal n/N**	**Control n/N**	**RR**	**95% CI**
Olanzapine	Before	9	228/657	174/667	1.33	(1.14, 1.55)
	After	12	594/1178	498/1212	1.19	(1.10, 1.28)
Quetiapine	Before	1	59/175	176/553	1.06	(0.83, 1.35)
	After	3	321/538	465/913	0.92	(0.84, 1.00)
Perphenazine	Before	1	4/55	15/52	0.88	(0.47, 1.64)
	After	2	267/396	211/313	0.99	(0.90, 1.08)
Amisulpride	Before	1	32/113	37/115	0.88	(0.59, 1.31)
	After	2	41/135	40/128	1.02	(0.58, 1.80)
Sulpiride	only after	1	27/58	9/22	1.14	(0.64, 2.02)

When Professor Peter Jones, Chair of Psychiatry in Cambridge, UK and principle investigator on CUtLASS, was interviewed regarding the results of his study he suggested that the subspecialty of psychiatry - and perhaps policy makers and service users as well - had not been so much "duped"[1] by industry as much as "beguiled"[2] (Vedantam, 2007). This gentle and charming comment carries within it both warning and rebuke. Perhaps industry, with huge pecuniary interests at stake, would dupe clinicians, researchers, patients and opinion leaders if they had to. Perhaps industry does (Heres *et al.*, 2006; Montgomery *et al.*, 2004). However, every bit as concerning is the uncomfortable evidence convicting a speciality guilty of complacency; a speciality, perhaps wanting - for mixed motives - to be beguiled or seduced. The data were always there to be seen.

Part of intelligence is to learn from experience. Individually and collectively there is much to be learnt from the experience of the new generation antipsychotics. Psychiatric treatments should be scientifically evaluated and these evaluations critically appraised with patient care in mind. No one, no institution and no subspecialty is above seduction and it is important to remain wary of being beguiled by good intentions, false hope, fashion and mammon.

[1] Dupe – to fool or hoax

[2] Beguile – to influence by slyness; to attract; cause to be enamoured (www.websters-online-dictionary.org)

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