Editorial

CATIE and CUtLASS: can we handle the truth?

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Summary

Two large, non-commercial clinical trials comparing first- and second-generation antipsychotic drugs for people with chronic schizophrenia in the US and UK have shown unexpected results. In general, the newer drugs were no more effective or better tolerated than the older drugs. Clozapine outperformed other second-generation drugs. The implications are considered.

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When clozapine was licensed as an antipsychotic in the US and UK over 15 years ago, it seemed a revolutionary drug with improved efficacy over existing agents.[1] This triggered the development of a series of new drugs termed 'atypical' (or second-generation) on the basis of an apparently reduced risk of neurological side-effects. They were designed to mimic clozapine's pharmacology of lower dopamine D_2 receptor affinity and higher affinity for other neuroreceptors, in particular $5\text{-}HT_{2A}$. This new class of drugs was heralded as the first major advance in the therapeutics of schizophrenia for 40 years. The second-generation drugs appeared to have important advantages over their first-generation (typical or conventional) predecessors, including better efficacy for positive, negative and mood symptoms, and improved tolerability. In addition, it was reported that they had cognitive-enhancing effects.[2] It was also claimed that the higher cost of these drugs would be offset by savings resulting from decreased use of healthcare services. None the less, the global antipsychotic drug market has increased 30-fold since the late 1980s to more than US$15 billion per year.

Despite these claims, meta-analyses and systematic reviews have provided only limited support for the superiority of second-generation antipsychotics.[3–5] Much of the evidence about their efficacy relative to first-generation drugs comes from short-term, industry-funded trials where patients are highly selected, drop-out rates are high and outcomes are based mainly on statistical comparisons of symptom ratings.[6] As a result, healthcare policy makers on both sides of the Atlantic faced a dilemma with respect to the rising costs of mental healthcare and the lack of demonstrably improved outcomes of patients. In addition, many questions remained unanswered. Were the second-generation antipsychotics incontrovertibly superior to the first-generation drugs and where was the evidence showing that they represented a major advance in routine mental healthcare settings? Were some better than others? Was clozapine superior to other second-generation antipsychotics? To address these questions, the National Institute of Mental Health in the US and the NHS Health Technology Assessment R&D Office in the UK each separately funded a 'pragmatic', or practical, clinical trial

in the late 1990s, with no sponsorship from industry. Pragmatic trials characteristically have broad inclusion criteria and long follow-up, aiming to mimic routine clinical practice as far as is consistent with a rigorous randomised design.[7] Their purpose is to clarify the effects of an intervention in real-life clinical practice and patient populations.

Two trials

The US Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)[8] was a double-blind trial in which 1493 patients with chronic schizophrenia were randomised to one of the second-generation antipsychotics olanzapine, quetiapine, risperidone, ziprasidone (the last was added into the design after the study had begun), or the medium-potency first-generation drug perphenazine. The primary aim of the trial was to compare the effectiveness of perphenazine with several second-generation antipsychotics. The primary outcome for the trial, chosen to reflect real-world practice, was discontinuation of the drug and switching to another antipsychotic for any reason, be it lack of efficacy, too many side-effects or patient choice. This outcome was chosen, rather than symptom improvement, since it was felt to encapsulate all kinds of 'drug failure' in a simple categorical variable. The trial was run over 57 sites between 2001 and 2004 and the sample size had 76% power to detect 12% differences in discontinuation rates. The participants were in general largely stable outpatients with a mean illness duration and treatment history of 14 years. Clinicians prescribed medication to participants under double-blind conditions, with dose titrated against clinical response, and analyses later showed that drug dosage used was generally similar to US clinical practice with some variation.

The results showed, first, that all drugs had limitations, in that 74% of patients were discontinued from their randomised treatment over 18 months. Median time to discontinuation overall was 4.6 months. Olanzapine proved to be the most effective in terms of having the lowest discontinuation rate (64%), but had the highest side-effect burden overall. Surprisingly, the remaining second-generation drugs differed neither from each other, nor from the first-generation antipsychotic perphenazine, in terms of effectiveness or extrapyramidal side-effects. There was no evidence that second-generation drugs were better for negative symptoms or cognitive deficits.[9] Individual drugs differed in specific side-effects. Olanzapine caused most weight gain and dyslipidaemia, quetiapine caused most anticholinergic effects, risperidone the most hyperprolactinaemia and sexual side-effects.

Perphenazine had highest rates of discontinuation for extrapyramidal side-effects, even though direct measures of these effects did not differ significantly between drugs.

CATIE included a subsequent trial for those participants who discontinued the first phase because of a lack of efficacy.[10] They were invited to be re-randomised to a comparison of open-label clozapine *v*. other second-generation antipsychotics, with time to all-cause discontinuation again as the primary outcome. In the 99 participants entering CATIE phase 2, clozapine emerged as being significantly more effective than the other second-generation drugs, with a median time to discontinuation of 10 months, twice the length of the next best, olanzapine.

The UK Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS)[11,12] comprised a pair of smaller, open (i.e. not-masked to patients and clinicians) randomised trials comparing classes of drug as grouped in most clinical guidelines: first-generation *v*. second-generation drug other than clozapine (CUtLASS 1), and other second-generation drug *v*. clozapine. Primary outcome was quality of life at 1 year and symptoms were the main secondary outcome. Outcomes were assessed by assessors masked to treatment allocation. In CUtLASS 1, 227 people with schizophrenia, mostly out-patients, who were being assessed by their clinical team for medication review because of poor response or adverse effects were randomised to either a first-generation or a second-generation drug other than clozapine (amisulpride, olanzapine, quetiapine or risperidone). The choice of individual drug within each class was made by the managing clinician in advance of randomisation. The rate of follow-up interview was 81% at 1 year. The results showed no advantage of second-generation drugs in terms of quality of life or symptoms over 1 year. In fact, those participants receiving a first-generation antipsychotic did rather better. In addition, there were no significant differences in rates of objectively assessed extrapyramidal side-effects. Participants reported no clear preference for either class of drug. The CUtLASS 2 trial was of similar design and compared clozapine with other second-generation drugs in 136 patients who had not responded well to two or more previous drugs. Results showed that there was a significant advantage for clozapine in symptom improvements over 1 year; moreover, patients significantly preferred it.

How do these two trials compare? The rationale for each trial was the perceived need for relevant, real-life trial data to inform policy and routine clinical practice. The trials were designed wholly separately of each other and conducted in different healthcare systems. The investigators in both trials predicted that second-generation antipsychotics would outperform first-generation drugs, and that clozapine would be the most effective. Both trials were government funded and both were designed to reflect routine clinical practice as much as possible, with broad inclusion criteria intended to enroll representative patients. The participants were very similar clinically and demographically in the two trials. The main results were broadly the same in each trial and surprised both groups of investigators. In both trials, the primary hypotheses were not supported and second-generation antipsychotics were not found to be more effective (with the exception of olanzapine in CATIE). Moreover, they did not produce measurably fewer extrapyramidal side-effects overall. In both trials, clozapine was the most effective for treatment-resistant patients.

Are first-generation as good as second-generation drugs?

Why did both trials fail to find the expected clinical advantage for second-generation antipsychotic drugs? Could each have had design flaws? Sample size was not a problem in CATIE. CUtLASS had 75% power to find an effect and the results showed a trend for participants receiving first-generation drugs to do better, suggesting that a larger sample would not have changed the result. Another possible problem might be that both trials included mostly patients with long histories of treatment. This may have limited the scope for any medication to demonstrate improvements. None the less, both trials went on to show that clozapine had a significant advantage. A related issue is that, if patients were already taking a second-generation drug at baseline and this presumably was not fully effective, then this meant that the sample was biased to non-responders to second-generation antipsychotics. However, in CUtLASS 1 80% of patients were being treated with a first-generation drug when referred into the trial. Moreover, CATIE patients switched at study entry from a second-generation antipsychotic to perphenazine did no better (or worse) than those switched to another second-generation drug.[8,13]

One possible contributor to the unexpected findings is in choice of first-generation comparator. In CUtLASS, clinicians chose sulpiride in 49% of cases and in contrast to most industry-sponsored trials, haloperidol was chosen in just 8%. Sulpiride has been viewed anecdotally as having some atypical properties, but a recent Cochrane review[14] finds no evidence to support this. The avoidance by clinicians of high-potency first-generation drugs and the use of moderate doses in both trials probably explains the failure to find excess rates of extrapyramidal effects. A further factor in explaining the results was the way the data were analysed, using more advanced methods than has been usual in the past. For example, in dealing with the problem of missing data, both trials chose to avoid the usual practice of using 'last observation carried forward' for patients who drop out during the trial, where the last available ratings are counted as if they are real end-point data. There is now evidence that this produces bias in the final results.

There are caveats. One is that neither trial was powered to look at the issue of tardive dyskinesia, the bête noir of first-generation antipsychotics. Although there is emerging evidence that second-generation drugs may not be as free of risk for tardive dyskinesia as once thought, this is still a potential limitation of first-generation antipsychotics.[15] This needs to be set against the risk of serious metabolic consequences of some second-generation drugs.

Into the future

In the end, we think that the convergence in the results of these two trials is compelling. The finding of clinical equivalence between second- and first-generation antipsychotics derives further support from a third trial with a similar pragmatic design,[16] which found no advantage for olanzapine in comparison with haloperidol given in lower doses than has been traditional. One issue is the differences in design between the CATIE/CUtLASS trials and most previous trials. CATIE and CUtLASS aspired to go beyond efficacy comparisons (can drug A work better than drug B under ideal conditions?) and compare the effectiveness of drug treatments (does drug A work better than drug B as really used in clinical practice?). We would argue that such practical trials are more relevant to policy makers, mental healthcare administrators and practitioners, since the results they produce are more generalisable to routine clinical practice.

A final aim of both CATIE and CUtLASS was to look at the economics of prescribing. In CUtLASS, the detailed costs of direct healthcare over 1 year varied greatly between patients, with a mean of £18 800 for those in the first-generation arm and £20 100 in the

second-generation arm. Of these costs, just 2.1% and 3.8% were costs of the drugs themselves. For clozapine it was a similarly low proportion, at 4%. Schizophrenia is an expensive disorder to manage but not because of the prices of drug treatments. The cost-effectiveness data from the CATIE trial indicated that perphenazine was significantly less costly and not less effective than the second-generation antipsychotics as a group,[17] a result replicated for the first-generation antipsychotics in CUtLASS.[18]

Where does this leave prescribers? Our conclusion must be that first-generation drugs, if carefully prescribed, are as good as most second-generation drugs in many if not most patients with established schizophrenia. This is good news as it increases the range of choices of antipsychotic drugs. Careful prescribing of first-generation antipsychotics means using lower doses than was often done in the past and avoiding high-potency drugs. Clozapine clearly remains an important drug where others have failed. Choosing which drug to switch to may depend on the reasons for switching in the first place: lack of efficacy might suggest a switch to olanzapine or clozapine, whereas lack of tolerability might suggest another choice. Note that the findings may not be the same for first-line treatments[19,20] and that the role of long-acting medications has yet to be made clear.

It is worth reflecting on how crudely we often use antipsychotic drugs. Polypharmacy, the prescribing of two or more antipsychotics in parallel, is widespread despite the lack of evidence to support it and the knowledge that it doubles costs and multiplies safety risks. Off-label prescribing is common. It is perhaps not surprising that, in the context of a severe, chronic illness, clinicians are tempted to resort to untested measures. It is the same sense of frustration that allowed us to be 'beguiled', as Peter Jones described it (Washington Post article 3 October 2006, http://www.washingtonpost.com/wp-dyn/content/article/2006/10/02/AR2006100201378.html), by the promise of a new class of drugs. These trials emphasise again the urgent need for discovering new, safe, effective medications, as well as knowing how to best use our existing treatments.

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