Generic clozapine: outcomes after switching formulations

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Summary Two generic preparations of clozapine have been licensed in the UK. The bioequivalence of these products compared with Clozaril® has not been unequivocally demonstrated. Clinical equivalence has also been questioned. The objective of this study was to determine clinical outcomes for all patients switched from Clozaril® to a generic formulation in one mental health service. We examined dosage data and Clinical Global Impression (CGI) of Severity of Illness scores for 337 patients before and after the switch and CGI change scores after the switch. There was no evidence of clinical deterioration or need to use higher dosages. Generic clozapine is not inferior to Clozaril®.

Declaration of interest None.

Clozapine is indicated in treatment-resistant schizophrenia, where it is uniquely effective (National Institute for Clinical Excellence, 2003). Clozapine has been available in the UK for 15 years under the brand name Clozaril®. Two branded generic products have recently been licensed. Standard bioequivalence studies are difficult to conduct for clozapine, where small doses can cause profound hypotension and tachycardia in healthy volunteers; bioequivalence across the dosage range has not been unequivocally demonstrated for the available products (Anon, 2001; Ereshefsky & Glazier, 2001).

Clinical equivalence has also been questioned (Anon, 2001). Five papers reporting on outcomes in a total of 131 patients have been published. One, a case series (Mofsen & Balter, 2001), reported a high relapse rate and one (Kluznik *et al*, 2001), which was sponsored by the patent holder, reported a trend towards deterioration. These papers have been widely cited as proof that switching patients to generic clozapine is a high-risk strategy. The work of Makela *et al* (2003) (no sponsorship declared), and also of Sajbel *et al* (2001) and Stoner *et al* (2003), both sponsored by a generic manufacturer, did not replicate these findings. This work is less well known.

We report on our experiences of switching all patients in a single mental health trust from Clozaril® (Novartis Pharmaceuticals, Surrey, UK) to generic clozapine.

METHOD

All patients (n=337) were switched from Clozaril® to generic clozapine (Zaponex®; IVAX Pharmaceuticals, London, UK). There were no exclusions.

The following data were collected for each patient:

(a) at baseline (1 month before the switch): name, gender, ethnicity, age, duration of treatment with Clozaril®, dose and Clinical Global Impression of Severity of Illness (CGI; Guy, 1976).

(b) at follow up (3 months after the switch): dose, CGIs and Clinical Global Impression of change over the past 3 months (CGIc). The CGIc score was chosen as the primary outcome measure, as it is simple to complete and detects change that is clinically meaningful.

Patients who remained on generic clozapine at the point of follow-up were compared with those who dropped out of treatment (independent t-test for continuous data and χ^2 for categorical data). Patients who remained on treatment were divided into 3 groups depending on the duration of clozapine treatment at the time of the switch (<18, 18–52, >52 weeks). The CGI severity scores and doses of clozapine before and after switching were compared using paired-samples t-tests. The CGIs score after switching was then subtracted from the baseline score to give an estimate of change. This calculated change score was compared with the clinician-completed CGIc score using Pearson's correlation, a test of internal validity.

RESULTS

Of the 337 patients switched from Clozaril® to generic clozapine, 304 (90.2%) remained on treatment 3 months later; 26 patients (7.7%) stopped treatment; 5 (1.5%) moved out of the area and 2 (0.6%) died. Completers had been on treatment for longer at the point of switch (mean 62.6 *v.* 23 months, t=3.778, P<0.001) and were receiving a higher dose (mean 443 mg/day *v.* 340 mg/day, t=2.559, P=0.011) than those who stopped treatment. There were no differences with respect to age or gender.

Mean CGIs scores before and after the switch were: patients treated for <18 weeks (3.74, 3.37, t=1.17, P=0.25); 18–52 weeks' treatment (3.86, 3.41, t=1.991, P=0.056); >52 weeks' treatment (3.42, 3.19, t=3.658, P<0.001); and for the whole group (3.49, 3.23, t=4.242, P<0.001).

Significant dose increases were seen in those who had been treated for <18 weeks (mean 327 mg before, 380 mg after, t=3.732, P=0.001). No significant dosage adjustments were seen in other patients.

The CGIc scores after switching are shown in Fig. 1. The CGIc score was correlated with the calculated change score (Pearson's correlation=0.341, P<0.01). Using a 1-point difference from the anchor point of 4 (no change) as a measure of clinically significant change in mental state, overall 19 patients deteriorated, 193 stayed the same and 92 improved.

DISCUSSION

We found no evidence of dosage escalation or clinical deterioration in patients switched from branded Clozaril® to generic clozapine. This is consistent with the findings of Sajbel *et al* (2003), Stoner *et al* (2003) and Makela *et al* (2003), but in contrast to those of Kluznik *et al* (2001) and Mofsen & Balter (2001). Collectively, these studies report on outcomes in a total of 131 patients, less than half the number in our cohort. Individually, they lack the power to detect even large treatment effects. Their

different findings can easily be explained by combinations of small sample size, heterogeneous patient groups, the use of different outcome measures and patient selection, sponsorship and publication bias.

Almost 8% of patients discontinued clozapine after switching but before the 3-month follow-up period was complete. Although this attrition rate seems high, it is consistent with the meta-analysis of Wahlbeck *et al* (1999); 14.8% of patients in short-term randomised controlled trials and 39% of patients randomised to treatment with clozapine in long-term randomised controlled trials 'left the study early'.

Patients who were still taking clozapine 3 months after switching to the generic preparation tended to improve. This improvement was highly statistically significant but clinically small. Our results do not constitute proof that the generic preparation is superior to Clozaril®, simply that it is not inferior.

By using a CGIc score of much or very much worse as a proxy for relapse, three patients could be considered to have relapsed. In addition, 16 patients were rated as minimally worse. Wahlbeck *et al* (1999) found that 7.5% of patients in long-term studies relapsed. Our findings are consistent with this.

As expected, there was upwards dosage drift in the group of patients who had been treated for <18 weeks at baseline. Such patients are being initiated and stabilised on treatment. There was no dosage drift in those who had been treated for >18 weeks at baseline.

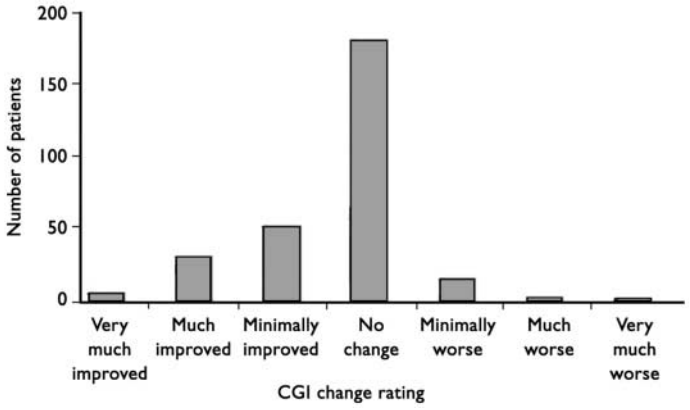

Fig. 1 Clinical Global Impression (CGI) change scores 3 months after switching from Clozaril® to generic clozapine. Overall, 16 patients were rated as minimally worse and 3 as much worse. Of the 3 patients rated to be much worse, 2 were known to be partially or non-compliant and 1 was chronically physically unwell; 8 of the 16 patients rated as minimally worse had 'spontaneous explanations' recorded on their rating form, such as family bereavement, compliance in doubt, acutely physically unwell and lost mental health review tribunal.

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Implications for clinical practice

Large numbers of patients around the world have been switched to generic preparations of clozapine (Ereshefsky & Glazer, 2001). The number of publications reporting on outcome is very small. Our study alone triples the number of patients for whom data are available. It may be true that generic preparations are not proven exactly bioequivalent to branded Clozaril® (Lam *et al*, 2001; Mofsen & Balter, 2001) but it is not clear that any differences that do exist are clinically important. The studies of Kluznik *et al* (2001) and Mofsen & Balter (2001) were widely cited by the original patent holders in a campaign aimed at protecting their monopoly. The selective use of studies reporting on the efficacy and safety of drugs makes evidence-based decision-making impossible. The methods used by the pharmaceutical industry must be challenged.

Limitations

The CGIc scores might not detect small changes in psychopathology, thus underestimating the number of patients whose mental state changed after the switch. Patients were followed-up for only 3 months after switching; nothing is known about outcomes beyond this point. Changes in other prescribed medicines or life events that may have affected outcome were not controlled for.

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