Clozapine in community practice: a 3-year follow-up study in the Australian Capital Territory

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Use of clozapine in community-based patients with recorded diagnosis of schizophrenia or schizoaffective disorder. Compared with typical antipsychotics, clozapine involves additional mandatory blood monitoring and is complicated to prescribe due to the requirements of the Clozaril Patient Monitoring System (CPMS).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
Patients who had a recorded and appropriately documented diagnosis of schizophrenia or schizoaffective disorder, and whose psychiatric history was known, particularly for the 2 years before commencing clozapine.

Setting
Community and primary care. The economic analysis was carried out in Australia.

Dates to which data relate
Effectiveness and resource use data corresponded to patients who commenced clozapine in the Australian Capital Territory (ACT) before 1 July 1994. Clozapine has been used in the ACT since early in 1993, its use having been facilitated by a Commonwealth government-funded Clozapine Co-ordinator. The price year was 1996-1997.

Source of effectiveness data
The evidence for the final outcomes was based on a single study.

Link between effectiveness and cost data
Costing was performed retrospectively on the same patient sample as that used in the effectiveness analysis.

Study sample
Power calculations were not used to determine the sample size. A total of 42 patients met the requirements for entry to the study; five were excluded from consideration; one because of death, one because of being admitted to a nursing home during the study period for pre-existing senile dementia, and three being lost to follow-up after moving interstate with their families. The remaining cohort of 37 patients, with a mean (SD) age of 34.0 (8.39) years at first prescription of clozapine, constituted the study sample.
Study design
This was a before and after cohort study, carried out in community practice within the ACT (regional population about 400,000). Data were obtained from records maintained by the ACT hospital and community health system and health services in nearby areas of New South Wales, from other hospital sources when appropriate, and from health workers and the Clozaril Patient Monitoring System (CPMS). The duration of the follow-up was 3 years after the initiation of the use of clozapine, compared with 2 years before. The loss to follow-up was 3 patients. The study cohort was divided into two groups (continuers and discontinuers) on the a priori basis of whether or not they remained on clozapine until the end of the study period without having a total period off clozapine in excess of 3 months in any 1-year. Of the cohort of 37 patients, 25 (68%) were continuers with a mean (SD) age at first prescription of clozapine of 34.5 (8.46) years and 12 (32%), with a corresponding mean (SD) age of 32.9 (8.51), were discontinuers. The only significant difference between the preclozapine demographic and clinical characteristics of the continuers and discontinuers was that the latter had a history of fewer hospitalisations. The reasons for temporarily or permanently discontinuing clozapine were lack of therapeutic response and/or non-compliance (n=6) or intolerable side effects (n=6, 16.2% of the total sample). It was reported that prior to 1 July 1994 in Australia, all patients were required to be under 24-hour supervision (in a hospital or a hostel) when commencing clozapine.

Analysis of effectiveness
The principle used in the analysis of effectiveness was stated to be intention to treat. The clinical outcome measure was change in clinical status (as rated retrospectively for each patient by their treating psychiatrist) using a seven-point scale at the study’s end (3 years after commencing clozapine) compared with the period immediately prior to commencing clozapine. Baseline (preclozapine) and progress Brief Psychiatric Rating Scale (BRPS) scores (1-7 rating) were accessed for those patients to whom this scale had been administered. A side-effect checklist developed by the authors was used by the treating psychiatrist to assess retrospectively the side effects after 3 years on clozapine; the experience of epileptic seizures in the periods before or after the commencement of clozapine was also part of the information supplied by the psychiatrist. The living circumstances and employment status in the 6 months prior to the study’s end were documented from recorded information and/or from information supplied by relevant mental health workers. It was reported that data for years 1 and 2 preclozapine that did not differ significantly from each other were averaged.

Effectiveness results
The effectiveness results were as follows:

At 3 years postclozapine, there was a significant improvement in clinical status for both the cohort (p<0.0001) and the continuers (p<0.0001); 86.1% of the cohort showed moderate or marked improvement and all of the continuers (n=24) showed improvement (half moderate and half marked).

Five of nine patients who were not taking clozapine at the study’s end were unimproved or had deteriorated.

It was reported that there were too few progress (postclozapine) BRPS scores to permit an analysis of the effect of clozapine on BRPS.

Side effects present after 3 years on clozapine were weight gain (severe, 1; moderate, 3; mild, 7), increased sleep (moderate, 5; mild, 6), drowsiness (moderate, 2; mild, 7), increased salivation at night (moderate;1; mild, 6) and in the daytime (mild, 5), sweating (moderate, 1; mild, 5), constipation (mild, 5), dizziness (mild, 3), night-time incontinence (mild, 1), and nausea (mild, 1).

There were no deaths from suicide in the cohort over the postclozapine period of 3 years; 4 patients had at least one epileptic seizure (two had a prior history of convulsions).

There was no change in the number of patients who were institutionalised (in hospital or in a hostel) while on clozapine but there was a significant increase in the number of subjects who were employed or studying at study’s end compared with baseline (cohort 21:12, p=0.012; continuers 18:10, p=0.008).

Employment and accommodation status in the discontinuers did not change significantly over the study period.
The continuers were more likely to be employed or studying 3 years postclozapine (p=0.02).

**Clinical conclusions**
The reported improvement in clinical state following long-term clozapine treatment broadly confirms the previous findings. The absence of improvement in living circumstances in patients on clozapine is not surprising given the low level of institutionalisation at baseline. In contrast to the continuers, the discontinuers did not show a pattern of improvement in outcomes in the 3-year follow-up period.

**Measure of benefits used in the economic analysis**
No summary benefit measure was identified in the economic analysis, and only separate clinical outcomes were used, as reported in the effectiveness results.

**Direct costs**
Costs were not discounted despite a time frame of more than 1 year for the cost analysis. Some quantities were reported separately from the costs. Some cost items were reported separately. The cost analysis covered the costs of treatment attributable to bed use (hospital or hostel), clozapine tablets, blood monitoring, and the employment of a Clozapine Co-ordinator (this latter item was estimated to be 0.75 in year 1, 0.50 in year 2 and 0.33 in year 3 postclozapine, representing the proportion of time given to the study cohort). Within the study cohort the number of pathology tests was used as the basis for attributing individual costs of the Clozapine Co-ordinator. The perspective adopted in the cost analysis was not explicitly specified. The source of the cost data was the ACT Health Department. The cost for a bed-day in a psychiatry ward consisted of cost items such as nursing, pathology, imaging, medical, allied health, pharmacy, supplies, on costs and other costs, and overhead costs. The price year was 1996-97. The cost analysis did not cover the costs associated with community services utilised by the patients, either before or after the use of clozapine.

**Statistical analysis of costs**
The effect of clozapine on time spent in hospitals and hostels, and treatment costs, was examined using Friedman analyses followed by Wilcoxon tests where the former were statistically significant.

**Indirect Costs**
Despite the fact that employment status was evaluated in the study, no attempt was made to place any value on it.

**Currency**
Australian dollars (Aus$).

**Sensitivity analysis**
No sensitivity analysis was carried out.

**Estimated benefits used in the economic analysis**
See effectiveness results above.

**Cost results**
The total costs for the preclozapine period were not significantly different from the costs in any year postclozapine for either the cohort or the continuers.

The costs in years 2 and 3 postclozapine were significantly lower than in year 1 postclozapine for both the cohort (year 2, p=0.003; year 3, p=0.02) and the continuers (year 2, p=0.002; year 3, p=0.001).
Bed costs (hospital) for the discontinuing group did not change significantly over time.

There was no significant difference between the continuers and discontinuers in the total costs of hostel and hospital admissions.

Overall, there was no substantive evidence that clozapine use was associated either with an increase or with a decrease in the treatment costs.

**Synthesis of costs and benefits**

Costs and benefits were not combined since the use of clozapine appears to have been the weakly dominant strategy (with better clinical outcomes and equivalent costs).

**Authors' conclusions**

The findings of significant clinical improvement without evidence of increased cost lend support for the selective use of clozapine in community practice.

**CRD COMMENTARY - Selection of comparators**

The strategy of not using clozapine was regarded as the comparator. It allowed the active value of the intervention to be evaluated.

**Validity of estimate of measure of effectiveness**

The internal validity of the effectiveness results may be compromised due to the retrospective nature of the study design, the use of mirror-image comparisons, the lack of blinding procedures and the absence of a control group, as acknowledged by the authors. Furthermore, the claim that the effectiveness analysis being based on intention to treat principle does not appear to be justified given that a complete set of data on clinical outcomes was not presented. No power analysis was conducted to justify the sample size adopted in the study. It was noted that caution would be appropriate concerning the clinical judgements of psychiatrists, which in the context of an open trial may have been influenced by the views of the first author, who was known to be an enthusiast for clozapine (however the fact that two-thirds of all of the cohort were still on clozapine after 3 years was taken as evidence of perceived ongoing clinical benefit of the study drug independently of the study). It was further pointed out that the course of schizophrenia is variable, even in the late stages, and improvements/reduced hospital use could have occurred without any specific interventions. The study sample appears to have been representative of the study population (community-based patients who had refractory psychosis but who had not experienced extensive hospitalisation.

**Validity of estimate of measure of benefit**

The authors did not derive a summary measure of health benefit. The analysis was therefore one of cost-consequences design.

**Validity of estimate of costs**

The validity of the cost results was enhanced by the following features of the cost analysis: some quantities were reported separately from the costs; adequate details of cost estimation were given; the price year was specified; and statistical analysis was performed on resource use and cost data. However, the following features may have adversely affected the validity: it is not entirely clear whether the cost data were based on true costs or charges; the perspective adopted in the cost analysis was not explicitly specified; no discounting was applied; the costs associated with resources used in community practice were not included in the analysis (which the authors perceived as a serious limitation of the study); the effects of the study drug on indirect costs (productivity loss) were not fully addressed by converting the employment status to monetary terms; the cost results may not be generalisable outside the study setting.
Other issues
Given the inherent limitations of the study design and the lack of sensitivity analysis addressing uncertainties surrounding the costs and clinical outcomes, some degree of caution should be exercised in interpreting the study results. The issue of generalisability to other settings or countries was not addressed, although appropriate comparisons were made with other studies. As the authors implicitly acknowledge, a cost-utility approach may have been a more appropriate framework in the context in question. This could have incorporated the subjective assessment of the patients regarding the trade-off between the improved clinical outcomes and inconveniences caused due to side effects of the study drug. The issue of whether the study sample was representative of the study population was addressed by pointing out that the study community sample was similar to other samples in studies of clozapine. They were similar in terms of age, sex distribution and age of onset of illness, with the exception that the study sample had less time in hospital preclozapine, and had a shorter index period of hospitalisation and (in most cases) a lower preclozapine BRPS score.

Implications of the study
The authors suggest that there is a pressing need for long-term prospective studies (which include measures of change in quality of life) of the use of clozapine, notwithstanding the considerable problems to be encountered in conducting such a study and in the long-term follow-up of patients.

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