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A study of clozapine and long-term hospitalisation rates

AIMS AND METHOD

The aim of the study was to investigate the use of clozapine in treatment-resistant schizophrenia and its impact on hospitalisation rates when prescribed in accordance with National Institute for Clinical Excellence (NICE) guidelines. Case records were examined of patients admitted to the psychiatric unit of Glan Clwyd Hospital between 1996 and 2001.

RESULTS

Of 59 patients identified as having treatment-resistant schizophrenia, 83% had been considered for clozapine, 48% were taking clozapine, 20% had refused the drug and 15% had stopped taking it because of side-effects. The mean annual hospitalisation rate for patients receiving clozapine for a minimum of 3 years was 13.5 days, markedly lower than those not receiving this drug (34.0

days, $P=0.03$). Older patients were less likely to have been offered clozapine ($P=0.006$).

CLINICAL IMPLICATIONS

This study supports the NICE guidelines recommending clozapine for patients with treatment-resistant disease. Clozapine is offered less often to older patients; factors influencing this require investigation.

The guidelines for the treatment of schizophrenia published by the National Institute for Clinical Excellence (NICE) recommend the use of clozapine in treatment-resistant disease (National Institute for Clinical Excellence, 2002). Treatment resistance is defined by NICE as 'a lack of significant clinical improvement despite the sequential use of the recommended doses for 6 to 8 weeks of at least two antipsychotics, one of which must be an atypical antipsychotic' (National Institute for Clinical Excellence, 2002). Clozapine is reserved for treatment-resistant disease because of the risk of serious adverse reactions (Kilian *et al*, 1999).

Meta-analyses suggest that clozapine is more effective than other antipsychotics in treatment-resistant schizophrenia (Tuunainen *et al*, 2003; Wahlbeck *et al*, 2003). However, many patients either refuse clozapine or discontinue it because of current practice, which requires hospitalisation for the commencement of treatment and repeated venepuncture, as well as the risk of adverse effects. The greater efficacy of clozapine is thought to shorten or prevent psychiatric hospitalisation over the longer term, but evidence for this is limited (Aitchison & Kerwin, 1997). Most studies are of less than 1 year's duration, and usually measure relapse rate rather than the annual hospitalisation rate (Wahlbeck *et al*, 2003). We therefore decided to investigate if adherence to NICE guidelines confers benefits in terms of a sustained reduction in hospitalisation rates.

Method

Patients admitted to the psychiatric unit at Glan Clwyd Hospital from 1996 to 2001 inclusive were identified as having a schizophreniform disorder by their discharge ICD-10 coding (F20.0–20.9; World Health Organization, 1992). This hospital serves a population of 250 000 in Conwy and Denbighshire; considerable deprivation in the coastal towns contrasts with a more affluent hinterland.

Inclusion and exclusion criteria

Records were examined for inclusion according to the criteria listed in Table 1. This identified patients who were under the continuing care of a general adult psychiatrist and were therefore likely to have records with sufficient data to establish a diagnosis of treatment-resistant schizophrenia.

Data extraction and outcome measures

Case records were obtained, and in-patient notes and clinic correspondence examined. Data extracted included the patient's gender and age; which of the four consultant psychiatrists was responsible for care; current antipsychotic medication; and whether the patient fulfilled NICE criteria for treatment-resistant schizophrenia; if so, whether the patient was taking clozapine and when was it started; had the patient been offered clozapine but refused; had the patient discontinued clozapine; and had the patient not been offered clozapine (no documentation).

Annual hospitalisation rate

The annual hospitalisation rate (AHR) was calculated by summation of the number of days spent in hospital over a 7-year period (1996–2002 inclusive) or since first presentation, if this was later than 1996, and was expressed as the mean annual number of days each patient was hospitalised. Only patients known to the service for a minimum of 3 years were included in this calculation, and the effect of clozapine on the AHR was calculated only if the drug had been prescribed for at least 3 years. This was to determine the long-term effect on hospitalisation rates, and to allow determination of the annual rate without denominator bias.

Statistical analysis

Data were collated using Microsoft Excel 2000 and analyses undertaken using unpaired *t*-tests and χ^2 tests

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papers**Table 1. Inclusion and exclusion criteria for the study sample**

Factor	Inclusion criteria	Exclusion criteria
Age	16–75 years; under general adult consultant psychiatrist care	Under care of old-age psychiatry or child and adolescent psychiatry services
Diagnosis	Schizophreniform disorder (ICD–10 F20.0–20.9) diagnosis remains valid	Revised diagnosis since discharge favours another disorder
Admission	Admission to acute general psychiatric unit between 1 Jan 1996 and 31 Dec 2001 (complete annual data compiled)	Not admitted to unit during study period
Service contact	Under review by consultant psychiatrist during 12 months to 31 Dec 2002	Moved out of area, or no longer under consultant psychiatrist review

Table 2. Differences in annual hospitalisation rate according to clozapine treatment status

	Number (% of total patients)	Age, years Mean (95% CI)	Gender, male n (% of patients)	AHR, days Mean (95% CI)
Treatment responsive patients	32 (35)	45.2 (40.3–50.1)	23 (72)	14.2 (9.8–18.6) ^b
Treatment-resistant patients	59 (65)	42.6 (39.6–45.6)	42 (71)	25.6 (16.8–34.4) ^b
Patients receiving clozapine therapy	28 (31)	38.0 (33.7–42.3) ^a	20 (71)	13.5 (8.6–18.4) ^c
Patients not receiving clozapine therapy	31 (34)	46.4 (42.3–50.5) ^a	22 (71)	34.0 (20.4–47.5) ^c
Not offered clozapine	10 (11)	51.5 (42.2–60.7)	8 (80)	50.4 (20.1–80.7) ^d
Refused clozapine	12 (13)	43.2 (36.5–49.9)	9 (75)	21.5 (10.8–32.1)
Discontinued clozapine	9 (10)	44.4 (37.3–51.4)	5 (56)	36.0 (1 patient)
Total sample	91 (100)	43.5 (s.d. 12.2)	65 (71)	21.5 (15.6–27.3)

AHR, annual hospitalisation rate.
Superscripts denote significant differences between means; a= $P < 0.005$; b, c, d= $P < 0.05$.

as appropriate. Data are presented as means with 95% confidence intervals.

Results

During the period 1996–2001, a total of 185 patients with a final diagnosis of a schizophreniform disorder were admitted to the hospital; for 11 of them (6%), records were unobtainable. Of the 174 records examined, 91 cases met the inclusion criteria. Of the 83 excluded patients, the majority ($n=61$, 35%) were no longer under local consultant psychiatrist review (the patient was either managed in primary care or had left the region); 14 patients (8%) had a revised (non-schizophreniform) diagnosis; 7 records (4%) listed the patient as deceased; and 5 patients (3%) were managed by old age psychiatric services.

Study sample

Sample demographics and fulfilment of NICE criteria for a diagnosis of treatment-resistant schizophrenia are summarised in Table 2. The sample varied in age (range 22–72 years); the majority (71%) were male, and most (65%) fulfilled the NICE criteria. Diagnosis of treatment-resistant schizophrenia (TRS) did not vary with age

($t=0.96$, d.f.=91, $P=0.34$), gender (proportion with TRS: male 65%, female 65%; $\chi^2=0.004$, d.f.=1, $P=1.00$) or consultant psychiatrist responsible for care (proportion with TRS with each consultant: 52%, 76%, 64% and 66%; $\chi^2=3.14$, d.f.=3, $P=0.37$).

Of patients who met the NICE criteria for treatment-resistant schizophrenia, 28 (48%) were received clozapine, 12 (20%) had been offered clozapine but refused, 9 (15%) discontinued clozapine owing to adverse reactions and 10 (17%) had not been offered clozapine. Hence, 83% of these patients had been offered clozapine in accordance with NICE guidelines. The 10 patients who had not been offered clozapine were significantly older than those who were taking, had refused or had discontinued clozapine (mean difference 10.7 years, 95% CI 3.3–18.1; $t=2.88$, d.f.=57, $P=0.006$).

Annual hospitalisation rates

Patients with schizophrenia who did not fulfil the NICE criteria for treatment-resistant schizophrenia ($n=32$) had an annual hospitalisation rate of 14.2 days (Table 2). Patients with treatment-resistant disease who refused to take, could not tolerate or had not been offered clozapine ($n=22$) had a rate of 34.0 days, whereas those who tolerated and continued clozapine ($n=12$)

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had a rate of 13.5 days. Thus, long-term treatment with clozapine was associated with a mean reduction in hospitalisation of 20.5 days (95% CI 2.1–39.0; $t=2.26$, d.f.=32, $P=0.03$). This represents a reduction in AHR of 60%. Because the patients receiving clozapine were significantly younger than those not taking it, age was examined as an independent variable; however, there was no significant correlation between age and AHR in the treatment-resistant group ($r=0.22$, $t=1.30$, d.f.=32, $P=0.20$) or among those taking clozapine ($r=0.45$, $t=1.68$, d.f.=11, $P=0.12$).

Discussion

Clinical implications

Approximately a third of patients with schizophrenia meet the NICE criteria for treatment-resistant disease; this proportion increases in those requiring hospital admission. In our study, almost two-thirds of patients with schizophrenia were diagnosed as having treatment-resistant disease, reflecting the concentration of secondary care resources on serious mental illness. Most of these patients were considered for clozapine therapy (83%); a smaller proportion (48%) actually received it long-term. Of those offered clozapine, nearly a quarter refused and almost a fifth experienced adverse effects, terminating therapy. Older patients were significantly less likely to be offered clozapine. Age-related comorbidity might have contraindicated clozapine prescription, or there might have been concerns about likely adverse reactions. However, age alone should not determine whether such patients are offered clozapine (Alvir *et al*, 1993); our results suggest that the reduction in hospitalisation rates associated with clozapine is independent of age.

Long-term clozapine therapy was associated with a reduction of 21 days per year in bed occupancy. Moreover, this study did not include patients receiving clozapine prior to 1996 who were not admitted between 1996 and 2001; thus, the actual effect of clozapine in reducing hospitalisation rates is likely to have been underestimated.

The benefits of clozapine include quality-of-life gains as a result of reduced hospitalisation, given the preference of most patients for community living. This benefit must be balanced against the inconvenience of venepuncture, concerns over adverse effects and the increased burden on community teams required to monitor clozapine therapy. One UK study estimated a reduction in AHR from 49 days to 39 days with clozapine, based on retrospective interviews of 26 patients, their keyworkers or both (Aitchison & Kerwin, 1997). Theoretical modelling of the effect of clozapine (Duggan *et al*, 2003) suggests AHR would be reduced by 21 days from 130 days for all patients with schizophrenia; our data indicate similar reductions for patients with treatment-resistant disease (Table 2).

Limitations

To determine the long-term effect of clozapine on annual hospitalisation rates, we needed to study patients receiving clozapine or known to services for at least 3 years. This limited our sample size considerably, which must be taken into consideration when interpreting the data. There was also significant loss to follow-up (35%); patients out of area subsequently requiring hospitalisation are not included. Since a cohort study cannot establish causality, the observed association between reduced hospitalisation and clozapine therapy may have other explanations. Patients receiving clozapine long-term are generally compliant with oral medication regimens; those requiring depot antipsychotics might benefit from clozapine but are not prescribed it because of poor oral compliance. Thus, the reduction in hospital admission for patients taking clozapine may reflect a patient group more likely to comply with treatment and who may receive more psychosocial support, as they are reviewed more frequently by community mental health teams (because of the need for venepuncture).

Further research

This study demonstrates an association between long-term clozapine therapy and reduced hospitalisation; more studies are required to confirm reproducibility across regions. Our results accord with the finding that clozapine therapy reduces in-patient costs, while increasing out-patient and laboratory costs (Aitchison & Kerwin, 1997). Further work is required to establish procedures for starting clozapine therapy in the community; initial results are promising (O'Brien & Firn, 2002). This approach might increase patient acceptance, as some are reluctant to enter hospital for the purpose of commencing clozapine therapy.

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Declaration of interest

None.

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