

## Active monitoring of 12 760 clozapine recipients in the UK and Ireland

### Beyond pharmacovigilance

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**Background** People prescribed clozapine for treatment-resistant schizophrenia have mandatory haematological monitoring through a case register for identifying reversible neutropenia.

**Aims** To quantify risk factors for agranulocytosis in subjects receiving clozapine.

**Method** Data from 12 760 subjects registered to receive clozapine from January 1990 to April 1997 were analysed. Risk factors for agranulocytosis were quantified using a Cox proportional-hazards regression analysis.

**Results** The risk for agranulocytosis in Asian subjects was 2.4 times that in Caucasians ( $P=0.03$ ). There was an age-related increase in risk of 53% per decade ( $P=0.0001$ ).

**Conclusions** The case register yielded valuable information for guiding research into the causes of the haematological reactions.

**Declaration of interest** The Clozaril Patient Monitoring Service is part of Novartis Pharmaceuticals. Three authors (D.O.S., C.A., A.A.) are employed by Novartis and three (J.M., A.M., R.K.) are in receipt of research grants from the company.

Pharmacovigilance monitors the safety of new drugs. Case registers are probably the most efficient method for surveillance, but are not widely used. Clozapine was the first drug in the UK to use a drug-based registry. Experience with this registry over eight years provides an opportunity to examine this tool for post-marketing surveillance. Surveillance in the UK is undertaken by the Clozaril Patient Monitoring Service (CPMS), a 'no blood no drug' computerised database.

### METHOD

#### The clozapine case register

Data from 12 760 subjects from the UK and Ireland were analysed. The purpose of the CPMS is to monitor white blood cell (WBC), neutrophil and platelet counts of people prescribed clozapine. Results are classified as follows: green - WBC more than  $3.5 \times 10^9/l$  and neutrophil concentration more than  $2.0 \times 10^9/l$ ; amber - WBC  $3.0-3.5 \times 10^9/l$  and/or neutrophils  $1.5-2.0 \times 10^9/l$ ; red - WBC less than  $3.0 \times 10^9/l$  and/or neutrophils less than  $1.5 \times 10^9/l$  and/or platelets less than  $50 \times 10^9/l$ . Neutropenia is defined as a neutrophil count of  $0.5-1.5 \times 10^9/l$ , agranulocytosis as a neutrophil count of less than  $0.5 \times 10^9/l$ . Until 1995, blood samples were required on a weekly basis for the first 18 weeks of treatment, and fortnightly thereafter. Data from Atkin *et al* (1996) revealed that the sampling frequency after one year could be reduced to once every four weeks in the majority of subjects exhibiting stable haematological profiles.

All subjects were reported by the registering psychiatrist to suffer from treatment-resistant schizophrenia. Withdrawals were classified as being for haematological or non-haematological reasons. Non-haematological withdrawals included subjects who never took clozapine after the first pre-treatment blood test, those failing to

comply with blood tests, or those withdrawing because of adverse effects or poor clinical response.

### Statistical methods

Cox proportional-hazards regression analysis was carried out, using the PHREG procedure in SAS/STAT (version 6.12; SAS Institute, 1996) software. Regression analyses analysed effects of potential covariates on the following end-points: time to agranulocytosis, time to neutropenia and time to non-haematological withdrawal. The stepwise model selection method constructed parsimonious models from the variables age, gender, race, clozapine dose and baseline haematology. Conditional hazard ratios were computed with 95% confidence intervals. Survival analysis was undertaken because subject accrual continued throughout the observation period with varying durations of follow-up. Wald tests confirmed hazard ratio significance. Contingency table analyses (Fisher's exact tests) and exact binomial confidence intervals were produced using StatXact-3 (Cytel Software, 1995). Vital statistics for the UK in 1995 (Office for National Statistics, 1995) were used to calculate expected UK cohort suicides. Standardised mortality ratios (SMRs) were calculated as 100 times the number of observed deaths divided by the number of expected deaths, with 95% confidence limits assuming a Poisson distribution (Breslow & Day, 1987).

### RESULTS

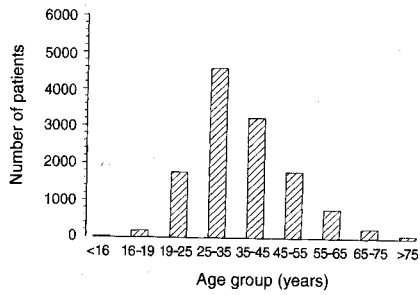
#### Baseline characteristics

##### Demographics

The cohort of 12 760 subjects comprised 8533 males (67%) and 4227 females (33%). Caucasian subjects numbered 11 300 (89%), and there were 689 (5%) of African-Caribbean origin, 506 Asian (4%), 212 mixed race (2%) and 53 Oriental (<1%). For analysis the mixed and Oriental subgroups were combined. Mean age at first blood test was higher in females (39.7 years, range 13.8-90.4) than in males (35.4 years, range 9.6-84.1). Age distribution is shown in Fig. 1. The modal age group was 25-35 years, with few subjects younger than 16 or older than 65.

##### Racial baseline haematological differences

Compared with Caucasians, African-Caribbeans had significantly lower baseline WBC



**Fig. 1** Age distribution of complete population of 12760 subjects treated with clozapine.

( $6.58 \times 10^9/l$  (95% CI 6.42–6.75) *v.*  $7.68 \times 10^9/l$  (95% CI 7.63–7.72)), neutrophils  $3.84 \times 10^9/l$  (95% CI 3.71–3.97) *v.*  $5.05 \times 10^9/l$  (95% CI 5.01–5.09) and monocyte count ( $0.45 \times 10^9/l$  (95% CI 0.43–0.46) *v.*  $0.52 \times 10^9/l$  (95% CI 0.52–0.57)).

**Clozapine treatment characteristics**

Mean clozapine dose after 12 weeks of treatment was 388 mg/day (95% CI 384–391), and the mean maximum dose was 462 mg/day (95% CI 458–466). Forty-one per cent of subjects had a peak dose of more than 500 mg/day, and 5% exceeded the recommended maximum of 900 mg/day.

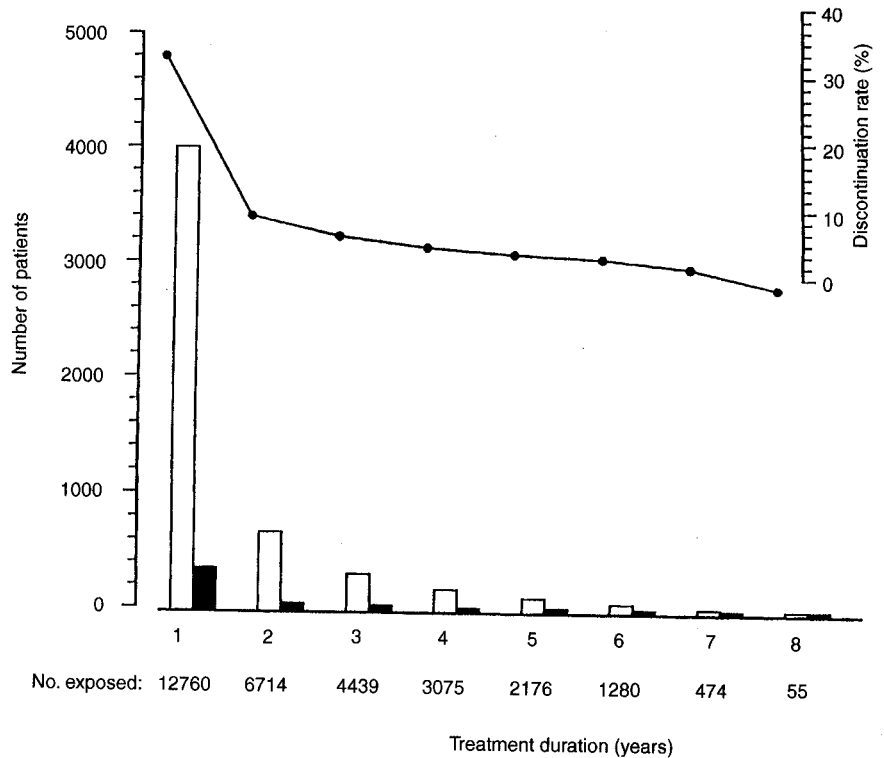
**Compliance with safety monitoring in the first year**

Treatment durations ranged from one day to 7.6 years. The highest discontinuation rate was seen in the first seven days after registration (5.4% of patients per week). This rate dropped to 1.1–2.3% per week during weeks 2–12. The discontinuation rate declined from 34% in the first year to 10% in the second, and to 3% by year 7 (Fig. 2).

**Predictors for non-haematological discontinuations within the first year**

**Race**

Compared with Caucasians, the hazard of withdrawal was increased by 65% in African-Caribbeans ( $P=0.0001$ ; hazard ratio 1.645, 95% CI 1.444–1.873) and by 38% in Oriental/mixed-race subjects ( $P=0.0034$ ), but was not increased in Asians ( $P=0.3578$ ).



**Fig. 2** Left axis: Bar graph showing numbers of non-haematological (□) and haematological (■) discontinuations by year of treatment. The number of subjects exposed is shown under the horizontal axis. Right axis: Overall annual discontinuation rate (%) (haematological and non-haematological combined).

**Age**

For each ten-year increase in subject age on starting clozapine, the risk of withdrawal in the first year increased by 33% ( $P=0.0001$ ; hazard ratio 1.329, 95% CI 1.297–1.363).

**Factors determining haematological discontinuations**

**Incidence of agranulocytosis**

The cumulative incidence of agranulocytosis in clozapine-treated subjects was 0.73% (93 patients). Peak risk occurred at 6–18 weeks with an incidence of 0.7% (76 subjects or 82%, discontinued during this interval). The earliest time to onset of agranulocytosis was four weeks. The agranulocytosis was reversible in all but two cases (Atkin *et al*, 1996), giving a mortality rate of 0.016% (2/12760).

**Incidence of neutropenia**

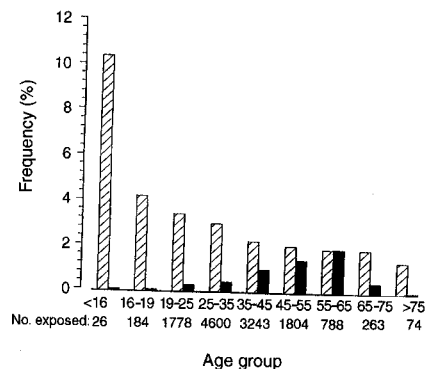
A total of 344 subjects discontinued because of neutropenia, mostly in the early phase of treatment, with 49% stopping within the first 18 weeks and 76% in the first year. The cumulative incidence of neutropenia in clozapine-treated patients was

2.7%. Peak risk occurred at 6–18 weeks with an incidence of 1.27%.

**Predisposing factors for agranulocytosis**

**Age**

For each ten-year increase in age on starting clozapine, the hazard of developing agranulocytosis increased by 53% ( $P=0.0001$ ; hazard ratio 1.528, 95% CI 1.315–1.777) (Fig. 3).



**Fig. 3** Bar graph showing frequency (%) of clozapine recipients discontinuing owing to agranulocytosis (■) and neutropenia (▨) by age.

### Ethnic origin

Compared with Caucasians, Asian subjects had 2.4 times the risk of developing agranulocytosis ( $P=0.03$ ; hazard ratio 2.388, 95% CI 1.098–5.194) (Fig. 4). The risk in Oriental/mixed-race and African–Caribbean subjects was unremarkable ( $P=0.84$  and  $P=0.61$ , respectively).

### Dose

For each 100 mg increase in the maximum dose of clozapine the risk of agranulocytosis decreased by 21% ( $P=0.0001$ ; hazard ratio 0.787, 95% CI 0.702–0.882).

### Predisposing factors for neutropenia

#### Age

By contrast with agranulocytosis, for each ten-year increase in age on starting clozapine the hazard of developing neutropenia decreased by 17% ( $P=0.0003$ ; hazard ratio 0.834, 95% CI 0.756–0.919) (Fig. 3).

#### Ethnic origin

The hazard ratio for African–Caribbean subjects was 1.77 (95% CI 1.208–2.583;  $P=0.0033$ ). The risk of neutropenia was 77% higher in African–Caribbean subjects than in Caucasians, but was not significantly different in Oriental/mixed-race or Asian subjects ( $P=0.25$  and  $P=0.497$ , respectively).

#### Dose

The maximum clozapine dose was inversely related to the hazard of developing neutropenia ( $P=0.0001$ ; hazard ratio 0.688, 95%

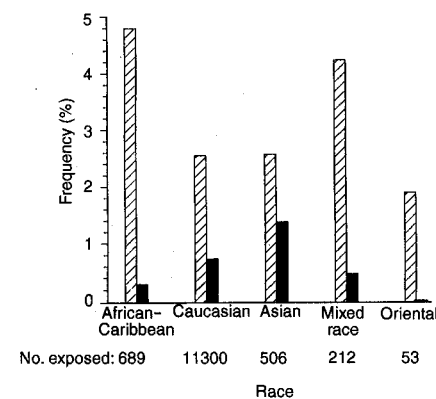


Fig. 4 Bar graph showing frequency (%) of clozapine recipients discontinuing owing to agranulocytosis (■) and neutropenia (▨) by racial subgroup.

Table 1 Baseline haematology: differences in those who later develop neutropenia between Caucasian and African–Caribbean clozapine recipients

	Caucasian subjects		African–Caribbean subjects	
	Currently on treatment	Withdrawn owing to neutropenia	Currently on treatment	Withdrawn owing to neutropenia
<i>n</i>	6198	283	294	33
<b>Neutrophils</b>				
Mean	5.16**	3.83	4.17*	3.00
95% CI	5.11–5.21	3.64–4.01	3.99–4.35	2.56–3.44
<b>Monocytes</b>				
Mean	0.53**	0.42	0.48*	0.35
95% CI	0.53–0.54	0.41–0.44	0.46–0.50	0.30–0.41
<b>White cells</b>				
Mean	7.84**	6.09	7.03*	5.11
95% CI	7.78–7.90	5.86–6.32	6.79–7.26	4.60–5.61

Wilcoxon two-sample tests: \* $P < 0.0001$  v. withdrawn owing to neutropenia, within racial group; \*\* $P < 0.0001$  v. African–Caribbean subjects, currently on treatment.

CI 0.647–0.731). Each 100 mg increase in maximum dose decreased the risk of neutropenia by 31%.

#### Baseline white blood count

The influence of baseline WBC on the hazard of developing neutropenia was highly significant ( $P=0.0001$ ; hazard ratio 0.687, 95% CI 0.583–0.809). For each  $1.0 \times 10^9/l$  decrease in initial WBC, the hazard of developing neutropenia increased by 31%. Caucasians and African–Caribbeans who developed neutropenia had lower baseline mean neutrophil, monocyte and WBC counts than those who did not develop neutropenia (Table 1).

#### Baseline haemoglobin

The hazard of developing neutropenia decreased by 14% for each 1.0 g/l increase in baseline haemoglobin ( $P=0.0004$ ; hazard ratio 0.86, 95% CI 0.79–0.94).

### Comparison of haematological safety in two-weekly and four-weekly regimes

Of 5199 subjects (41%) who were monitored four-weekly, two thirds (68%) had a treatment duration of at least two years, and half (48%) had a treatment duration of greater than three years. Table 2 compares the two monitoring regimes according to agranulocytosis and neutropenia

Table 2 Comparison of safety in clozapine recipients between subjects monitored at two-weekly intervals and those monitored at four-weekly intervals after at least one year of treatment

	Monitoring interval	
	Four-weekly	Two-weekly <sup>1</sup>
Number of subjects treated	5199	1510
Number of haematological fatalities	0	0
Number (%) of neutropenia cases	13 (0.25%)*	71 (4.7%)
Number (%) of agranulocytosis cases	2 (0.04%)**	4 (0.26%)
95% CI	0.005–0.14	0.07–0.68
Lowest neutrophil count ( $\times 10^9/l$ )	0.19–0.39	0.19–0.45

\* $P < 0.0001$ , \*\* $P=0.0259$  (Fisher's exact test), v. two-weekly.

1. Haematologically unstable subjects may have undergone more frequent monitoring.

frequency in subjects treated for at least one year.

### Suicides

A total of 144 subjects died, as a result of many causes. Thirteen deaths were confirmed suicides. Literature on suicide and schizophrenia was reviewed. Studies presenting the expected number of suicides in the national population were available and are compared with suicides in the UK cohort in Table 3. These studies consistently revealed a suicide rate among subjects with schizophrenia about 20 times greater than that of the national population (median SMR=2034). Our cohort experienced a suicide risk five times greater than that expected for the UK population (SMR=498, 95% CI 257-876).

## DISCUSSION

### The value of drug-based case registration

The CPMS has reduced predicted agranulocytosis mortality (Atkin *et al*, 1996; Honigfeld, 1996) and prevented the accidental re-treatment of subjects. The case register allows absolute risk to be calculated. Analysis of risk factors necessitates having data from a large cohort with known denominator. Owing to the blood monitoring, subjects treated with clozapine are closely observed and reporting of adverse drug reactions increases, so it is unlikely that serious reactions remain unrecognised.

**Table 3** Standardised mortality rates (SMRs) for suicide in the CPMS sample compared with rates in other cohorts of people with schizophrenia

Study	Population	Country	Observed suicides	Expected suicides	SMR (95% CI)
Anderson <i>et al</i> (1991)	532	England	7	0.42	1666 (668-3432)
Newman & Bland (1991)	3623	Canada	97	4.95	1960 (1955-2002)
Helgason (1990)	107	Iceland	10	0.5 <sup>1</sup>	2000 <sup>2</sup> (960-3680)
Mortensen & Juel (1993)	9156	Denmark	508	24.58	2067 (2063-2093)
Black & Fisher (1992)	356	USA	16	0.69	2319 (1299-3824)
Tsoi & Wong (1991)	330	Singapore	34	0.57 <sup>1</sup>	6000 <sup>2</sup> (3882-8856)
CPMS (1990-98)	12 188 <sup>3</sup>	UK	13 <sup>3</sup>	2.61	498 <sup>4</sup> (257-876)

CPMS, Clozaril Patient Monitoring Service.

1. Calculated from the approximate SMR.

2. Approximate SMR as specified in the reference.

3. UK subjects only (excluding 572 Irish subjects).

4. Age-gender standardised mortality ratio.

### CLINICAL IMPLICATIONS

- The demonstrated ethnicity effect on risk of agranulocytosis necessitates research into genetic mechanisms.
- Adolescents have the lowest risk of agranulocytosis and the greatest likelihood of remaining on clozapine.
- The lower than expected rate of suicide underlines the need for further investigation of the anti-suicidal effect of clozapine.

### LIMITATIONS

- This is a survey of the naturalistic use of clozapine and does not fulfil the criteria of a formal clinical trial.
- The information on the drug registry is limited, owing to the remit of the registry. More complete information on blood levels of clozapine and concomitant medication would have been interesting.
- Clozapine registry data are not routinely subjected to source data verification.

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### Risk factors for agranulocytosis and neutropenia

#### Race

Asian race was a risk factor for agranulocytosis (hazard ratio 2.388,  $P=0.03$ ); this has not previously been reported and may

suggest mechanisms for agranulocytosis. Racial metabolic enzyme differences may alter the toxicity of drug metabolites. Genetic stratification may reflect an association between racial characteristics and immunological genes.

#### Age

This study confirms previous reports of increasing agranulocytosis risk with age on starting clozapine (Alvir *et al*, 1993; Atkin *et al*, 1996). The bone marrow of younger subjects may be more resistant to clozapine-induced agranulocytosis. In elderly subjects, clozapine metabolism may occur through different pathways that may cause increased haemopoetic toxicity.

#### Dose

Higher clozapine doses did not increase neutropenia or agranulocytosis risk. Toxicity may result from a particular ratio of metabolites rather than from dose.

### Clozapine in adolescence

The likelihood of remaining on treatment for more than one year was greatest for subjects aged under 19 years in this study. The previously reported increased incidence of agranulocytosis under 21 years of age was not confirmed (Alvir *et al*, 1993).

### Suicide

Suicide risk in schizophrenia is estimated as 20–50 times that of the general population (Meltzer & Okayli, 1995). Harris & Barraclough (1998) have shown that these figures may be overestimates. Table 3, which compares the SMR in subjects with schizophrenia with that of the general population (drawing data from similar studies), reveals a median SMR of around 2000, compared with 498 in our cohort. The growing evidence for an anti-suicidal effect of clozapine has prompted a prospective multi-national trial of novel anti-psychotics in suicide.

### Compliance

Subjects completing a full year of treatment have a high rate of continuation to two or

more years of treatment. Compliance is impressive in these subjects, who are renowned for poor treatment adherence.

### ACKNOWLEDGEMENTS

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