

Neutropenia and Agranulocytosis in England and Wales: Incidence and Risk Factors

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The objectives of this study were to estimate the incidence of idiosyncratic neutropenia and agranulocytosis in England and Wales and to evaluate their risk factors and outcomes. The study was conducted using data from the General Practice Research Database. All cases of idiosyncratic neutropenia or agranulocytosis were identified and the incidence was estimated. This was followed by a nested case-control study, estimating odds ratios with drug exposure from conditional logistic regression. From 1987 to 1999, 3,224 patients with idiosyncratic neutropenia (50 with agranulocytosis) were identified. The incidences of neutropenia and agranulocytosis were estimated to be 120 and 7 cases per million people per year, respectively. The adjusted odds ratios for neutropenia were 34.7 (95% confidence interval 12.0–99.7) for current users of thyroid inhibitors, 9.5 (4.4–20.8) for users of disease-modifying antirheumatic drugs, and 7.6 (4.9–11.9) for users of aminosaliclates. Other drugs with statistically significantly increased risks of neutropenia included antibacterial drugs, non-opioid analgesics, NSAIDs, antidepressants, ulcer-healing drugs, and anti-epileptics. The increase in risk of neutropenia predominantly occurred during the first months of treatment. For most drugs investigated in this study, there was no relationship to daily dose. The excess 1-year mortality was low among neutropenia and agranulocytosis cases and mostly explained by the underlying disease state. In conclusion, the highest risks of neutropenia were generally found in patients starting treatment. The excess 1-year mortality was low among neutropenia and agranulocytosis cases and can be mostly explained by the underlying disease state. *Am. J. Hematol.* 72:248–254, 2003. © 2003 Wiley-Liss, Inc.

Key words: neutropenia; agranulocytosis; incidence; risk factor; epidemiology

INTRODUCTION

Agranulocytosis is a syndrome characterised by severe neutropenia and manifested by sudden onset of signs and symptoms of bacterial infection, such as fever, malaise, and oropharyngeal or anorectal lesions. Although numerous drugs have been associated with an increased risk of agranulocytosis based on observations of individual patients, only a few epidemiological studies have evaluated its incidence [1–7]. Large inter-country variations in the incidence and excess risk due to drug treatment have been reported in these studies [3]. No study has yet been conducted in the United Kingdom. Furthermore, agranulocytosis was, reportedly, a condition with high mortality before the availability of granulocyte-stimulating factor

[8]. The outcome following the introduction of granulocyte-stimulating factor for the treatment of agranulocytosis has not yet been systematically assessed. The main

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objectives of our study were to estimate the incidence of idiosyncratic neutropenia and agranulocytosis in England and Wales and evaluate their risk factors and outcomes.

METHODS

Data

In the U.K., general practitioners (GPs) are responsible for primary health care and specialist referrals and remain central to the national health care delivery program. The information for our study was obtained from the General Practice Research Database (GPRD), which contains the computerized medical records of general practices in the U.K. [9], representing approximately 6% of the total registered population of England and Wales. The age and sex distribution of the patients enrolled is representative of the population in England and Wales. The GPRD data comprises demographic information about the patient (including sex and year of birth), prescription details, clinical events, preventive care provided, referrals to specialist care, hospital admissions, and their major outcomes. Several independent validation studies have shown that the GPRD database has a high level of completeness and validity [10,11]. The GPRD is owned by the Department of Health and managed by the Medicines Control Agency in the U.K.

Study Design

Cases were defined as permanently registered patients (i.e., with residence in the practice neighbourhood) aged 3 years or older who had a diagnostic code for neutropenia (ICD-9 288.0) recorded in their medical records during the period of time from the enrolment date of their practice in GPRD up to the end of data collection (December 1999). The diagnostic codes also included agranulocytosis. Data collection for the GPRD began in 1987. Cases with a record of aplastic anaemia, myelodysplastic syndrome, or blood dyscrasia prior to the index date, or with a record of neutropenia or agranulocytosis prior to the enrolment date were excluded in order to restrict the analysis to incident cases of neutropenia. Given the interest in idiosyncratic disease, alternative causes of neutropenia were ruled out by further exclusions of cases and controls who received treatment involving chemotherapy (British National Formulary 8.1), immunosuppressive drugs (8.2), or hormone antagonists (8.3.4) prior to the index date and a medical history of malignancy (International Classification of Diseases 9th Revision 140–208), systemic lupus erythematosus (710.0), HIV or AIDS (42), sideroblastic anaemia (285.0), or splenomegaly (789.2). In patients without any of these diseases and use of these drugs, neutropenia was defined in this study as a record of neutropenia or agranulocytosis; agranulocytosis as a record of agranulocytosis or a record of neutropenia with a written diagnostic re-

port (as provided by the GP in the validation study), indicating a granulocyte count below $0.5 \times 10^9/L$.

To validate the outcome events, GPs were requested to confirm the diagnosis for a sample of cases, answer a brief questionnaire concerning the neutrophil count, clinical symptoms, and likely cause and to send anonymous copies of pertinent hospital letters or diagnostic reports. Patients who died or left the practice (as recorded in the computerised medical records) were excluded from the validation, as medical notes were no longer present at the practice. The validation was also restricted to the practices that were still registered with GPRD at the time of the validation; at the other practices the GPRD patient identifiers can no longer be linked to the patients at the practice, because of change of medical record software. Information was requested for three groups of neutropenia cases: the first group comprised 24 patients with a record of agranulocytosis; the second group consisted of 125 patients with neutropenia who either had been hospitalised at the date of neutropenia had a record of laboratory test results within 4 weeks of the index date that suggested a granulocyte count below $0.5 \times 10^9/L$ or cases with symptoms in the 4 weeks prior to the index date of fever, rigor/chills, sore throat, oropharyngeal lesions, septicemia, or pneumonia. The third group comprised a random sample of 95 remaining cases. Cases not confirmed in the validation were subsequently excluded from the analysis.

Point Incidence

An estimate for the point incidence of neutropenia/agranulocytosis was determined by dividing the total number of cases (during 1988–1999) by the total observation time of GPRD. The total observation time was the sum of patients registered in the database at July 1st of each calendar year (1988–1999). This information was available for 5-year age groups. The GPRD observation time at each age- and sex-band was reduced by the proportion of control patients with one of the disease or drug use exclusions. Associated 95% confidence intervals (CIs) around the incidence rates were calculated on the basis of the Poisson distribution. For agranulocytosis, we also estimated the overall incidence rate corrected for the proportion of cases to be found misclassified in validation study. This correction was done by first reducing the number of agranulocytosis cases by the proportion of cases not confirmed in the validation. Then, the number of cases was increased by the proportion of neutropenia cases classified as agranulocytosis in the validation study.

Case-Control Analysis

In the case-control study, each case was matched to three control patients by age, sex, and medical practice. Control patients were defined as patients without a his-

TABLE I. Number of Cases and Estimated Annual Incidence of Neutropenia per Million People per Year Among Those Aged 5 Years or Older and Registered in GPRD, 1988–1999

Age (years)	Women		Men		Total	
	No. of cases	Incidence rate (95% CI)	No. of cases	Incidence rate (95% CI)	No. of cases	Incidence rate (95% CI)
5–19	230	88 (77–100)	189	69 (59–79)	419	78 (71–86)
20–44	824	153 (143–164)	339	62 (55–69)	1,163	107 (101–113)
45–64	721	227 (210–243)	291	90 (80–101)	1,012	158 (148–168)
65–74	257	202 (177–226)	124	120 (99–141)	381	165 (148–181)
≥75	166	131 (111–151)	69	109 (83–134)	235	124 (108–139)
Total	2,198	160 (154–167)	1,012	77 (72–82)	3,210	120 (116–124)

of diseases of white blood cells (ICD-9 288), aplastic anaemia (284), myelodysplastic syndrome (238.7), or blood dyscrasia (289.9). If a control patient could not be matched to within 1 year of age, the age criterion was expanded consecutively at 1-year intervals to a maximum of 5 years. If no eligible control patient was identified within 5 years of age, then a control patient was selected from another practice. The index date of each control patient was that of the matched case patient (i.e., date of first neutropenia after enrolment in GPRD). The same exclusion criteria were used for controls as cases.

Exposure to drugs was determined by reviewing all prescription information prior to the index date. Current drug users were patients who had received their last prescription within 3 months of the index date. The daily dose of drug exposure was obtained from the written dosage instructions for the last prescription prior to the index date and the strength of the application. The drugs included in the analyses were drugs that have previously been associated with neutropenia and agranulocytosis [3,4,7,12] and for which the U.K. Committee on Safety of Medicines (CSM)/Medicines Control Agency had received more than 10 suspected adverse drug reaction reports as of 5 February 2001 [CSM, personal communication].

Statistical Methods

Crude odds ratios (ORs) for current, recent, and past drug exposure were estimated using matched conditional logistic regression. Adjusted ORs were estimated using models that also included an indicator of current use of any of the other drug classes investigated in this study. Given the small number of cases, exact methods for conditional logistic regression were performed for the agranulocytosis analysis. All analyses were performed using SAS version 8.1 (SAS Institute, Cary, NC).

Survival rates in the first year following neutropenia were calculated using Kaplan–Meier life-table methodology. Cases and controls were followed from the index date to death, date of censoring, or 1 year (whichever date came first). The relative rate (RR) of mortality was estimated using Cox proportional hazards models. The cause of death was determined by reviewing the medical records at the date of death.

RESULTS

There were 4,373 patients aged 3 years or older with a record of neutropenia in the GPRD (including about 5 million people aged 5 years or older). Of these patients, 1,149 were excluded from the analysis for the following reasons: patients with a history of white-cell disorders ($N = 156$); patients with one of the disease or drug use exclusions ($N = 967$); and patients whose neutropenia was not confirmed in the validation or for whom no control was available due to disease or drug use exclusions ($N = 26$).

The questionnaires were returned for 211 of the 244 neutropenia cases included in the validation study. No information was available for 13 patients who had either left the practice or died. Of the 22 agranulocytosis cases with returned questionnaires, 18 patients (81.8%) had neutropenia. Of these patients, 10 patients' cases could be classified as incident agranulocytosis, 1 agranulocytosis case had a history of neutropenia and 7 patients had moderate neutropenia. Of the neutropenia patients who were hospitalized or had symptoms or low granulocyte counts, the diagnosis was confirmed in 99 of the 102 cases (97.1%). The reported neutrophil count was as follows: $0.5 \times 10^9/L$ for 14 cases; 0.5–1.0 for 15 cases; 1.0–2.5 for 56 cases (no data for 14 cases). Of the 14 cases with severe neutropenia, 13 could be classified as incident agranulocytosis and 1 patient had a history of neutropenia. For the random sample of other neutropenia cases, the diagnosis of neutropenia was confirmed in 70 of the 74 cases (94.6%). The reported neutrophil count was as follows: $0.5 \times 10^9/L$ for 5 cases; 0.5–1.0 for 12 cases; 1.0–2.5 for 50 cases (no data for 3 cases). Of the 5 cases with severe neutropenia, 3 cases would be classified as agranulocytosis, 1 case had congenital neutropenia, and 1 case had Felty's syndrome. Most of the patients with unconfirmed neutropenia had other white blood cell disorders.

The study population consisted of 3,224 patients with neutropenia, of whom 50 patients had agranulocytosis. Table I shows the age- and sex-specific incidence of idiosyncratic neutropenia in the GPRD population. Although women were more likely to get neutropenia compared to men, incidence increased with age among both

TABLE II. Characteristics of Neutropenia Cases and Controls at Index Date

		Cases (N = 3,224)	Controls (N = 9,321)
Age (years)	3–19	433 (13.4%)	1,296 (13.9%)
	20–44	1,163 (36.1%)	3,442 (36.9%)
	45–64	1,012 (31.4%)	2,918 (31.3%)
	65–74	381 (11.8%)	1,046 (11.2%)
	≥75	235 (7.3%)	619 (6.6%)
Sex	Female	2,204 (68.4%)	6,350 (68.1%)
	Male	1,020 (31.6%)	2,971 (31.9%)
Years of GPRD registration prior to the index date	0–1	631 (19.6%)	1,685 (18.1%)
	1–3	957 (29.7%)	2,906 (31.2%)
	3–5	763 (23.7%)	2,238 (24.0%)
	≥5	873 (27.1%)	2,492 (26.7%)
		750 (23.3%)	4,589 (49.2%)
No. of prescriptions in the preceding 3 months	1–2	1,029 (31.9%)	2,299 (24.7%)
	3–5	717 (22.2%)	1,223 (13.1%)
	≥6	728 (22.6%)	1,210 (13.0%)

men and women. The incidence of agranulocytosis, corrected for the proportion of cases recorded as neutropenia, was 7 cases per million patients per year (95% CI 6–8).

The cases were matched to 9,321 controls (more than 99% of the cases and controls were matched by year of birth, sex, GP practice, and calendar time). Almost 70% of the study patients were women and the average age was 44 years (Table II). Table III shows the OR of agranulocytosis and neutropenia for current use of various groups of drugs. Aminosaliclates and thyroid inhibitors were associated with large increases in risk. For thyroid inhibitors: the adjusted OR for agranulocytosis was 20.9 (95% CI 3.3–∞) and 34.7 (95% CI 12.0–99.7) for neutropenia. Users of aminosaliclates had an OR of 9.2 (95% CI 1.3–400.8) for agranulocytosis and 7.6 (95% CI 4.9–11.9) for neutropenia. Statistically significant increases in the risk of neutropenia were also observed in users of antibacterial drugs, non-opioid analgesics, NSAIDs, antidepressants, ulcer-healing drugs, anti-epileptics, and disease-modifying antirheumatic drugs. We found no major differences between different types of antibacterial drugs and NSAIDs in the risk of neutropenia (data not shown). In contrast, users of sulfasalazine had a considerably higher risk of neutropenia (OR 11.6; 95% CI 7.0–19.0) compared to users of mesalazine (OR 2.2; 95% CI 1.0–4.8).

Table IV shows the relationship between number of previous prescriptions and the OR of neutropenia. Generally, the highest risks of neutropenia were found in patients starting treatment. Patients starting aminosaliclate treatment had an OR of 28.1 (95% CI 3.6–219.2) for neutropenia, compared to an OR of 4.9 (95% CI 3.0–8.2) in users who had previously received four or more prescriptions. Further analysis was also conducted

for the effects of daily dose on the risk of neutropenia (Table V). The risk of neutropenia was substantially higher in patients using higher daily doses of sulfasalazine and carbimazole compared to patients using lower daily doses. No effects of daily dose were seen in patients using amoxicillin, ibuprofen, or carbamazepine.

We found that 2.4% of the neutropenia cases died within 1 year compared to 0.8% of the control patients (adjusted RR 1.9; 95% CI 1.4–2.8). The main causes of death among the 71 cases and 69 controls who died within 1 year after the index date were cancer and circulatory diseases. Five of the neutropenia cases died due to an infectious disease compared to 1 control patient, although this difference was not statistically significant. An analysis was conducted restricting the analysis to patients without a record ever of one of the exclusion diseases or drugs (in the main analysis only patients with a history prior to the index date were excluded). A total of 271 (8.4%) neutropenia patients and 294 (3.2%) control patients were excluded. It was found that 1.3% of the neutropenia cases and 0.6% of the controls died within 1 year after the index date. The RR of mortality was statistically comparable between neutropenia cases and controls (adjusted RR 1.4; 95% CI 0.9–2.3). These findings suggest that the difference in mortality between the total group of neutropenia cases and controls can be explained by the differences in the underlying disease state. The mortality was substantially higher in the excluded patients: 13.2% among the excluded cases and 5.9% among the controls. None of the agranulocytosis cases died within 1 year of the index date.

DISCUSSION

This study examined the incidence and risk factors of idiosyncratic agranulocytosis and neutropenia, using data from GPRD, a large, primary care, record-linkage resource. The International Aplastic Anemia and Agranulocytosis Study (IAAAS) has previously provided estimated incidence of agranulocytosis of 3.4 cases per million persons per year. Large differences in incidence were reported between regions (with no British site included). The lowest incidence was found in Milan (1.5 cases per million person-years) and the highest in Budapest (5.5) [3]. Similar results were also found in a U.S.-based study; the overall incidence was 7.2 cases per million per year, ranging across states from 2.3 to 15.4 [5]. A recent Dutch study of hospitalised cases of agranulocytosis found an incidence of approximately 2 per million persons per year [7], while a Canadian study reported an incidence of 3.0 [4]. The rate of hospitalisations for patients with a neutrophil count of below 1,000 was 2.7 per million during 1972 to 1981 [2].

TABLE III. Risk of Agranulocytosis and Neutropenia According to Current Drug Use

Drug group	Agranulocytosis			Neutropenia		
	No. of cases (N = 50)	No. of controls (N = 144)	Adjusted OR (95% CI)	No. of cases (N = 3,224)	No. of controls (N = 9,321)	Adjusted OR (95% CI)
Antibacterial drugs	14	12	3.1 (1.4–7.9)	603	830	2.7 (2.3–3.1)
Non-opioid analgesics	13	17	1.9 (0.8–4.6)	475	700	1.7 (1.5–2.0)
NSAIDs	13	10	2.9 (1.3–7.3)	438	585	2.1 (1.8–2.4)
Antidepressants	4	10	0.6 (0.2–1.9)	208	325	1.6 (1.3–2.0)
Diuretics	4	18	0.4 (0.2–1.2)	205	577	0.9 (0.7–1.1)
Hypnotics/anxiolytics	8	10	2.2 (0.8–6.4)	180	331	1.1 (0.9–1.4)
Ulcer-healing drugs	4	10	0.9 (0.3–2.9)	171	290	1.4 (1.1–1.8)
β-Adrenoceptor blockers	8	6	3.0 (1.0–11.2)	153	411	1.0 (0.8–1.2)
Anti-epileptics	2	1	6.0 (0.7–276.0)	128	90	3.8 (2.8–5.0)
Antiplatelets/aspirin	3	5	2.3 (0.4–17.0)	108	251	1.1 (0.9–1.5)
Calcium blockers	2	6	0.8 (0.2–3.3)	107	278	1.1 (0.8–1.4)
Aminosalicylates	5	2	9.2 (1.3–400.8)	98	30	7.6 (4.9–11.9)
Renin-angiotensin system	2	3	1.7 (0.3–12.4)	72	208	0.9 (0.6–1.2)
Nitrates	2	5	0.8 (0.2–3.6)	67	183	0.8 (0.6–1.2)
Corticosteroids	4	4	2.1 (0.6–9.2)	65	111	0.9 (0.6–1.3)
Thyroid inhibitors	7	0	20.9 (3.3–∞)	44	4	34.7 (12.0–99.7)
Antipsychotics	1	3	0.5 (0.1–5.6)	41	79	0.9 (0.6–1.4)
Lipid-regulating drugs	0	3	0.4 (0–3.9)	39	88	1.2 (0.8–1.9)
Disease-modifying antirheumatic drugs ^a	2	0	5.8 (0.8–∞)	41	8	9.5 (4.4–20.8)
Anticoagulants	0	3	0.3 (0.2–2.4)	27	41	1.6 (0.9–2.7)
Anti-arrhythmic drugs	0	1	0.2 (0–6.9)	11	16	1.2 (0.5–2.9)

^aSodium aurothiomalate, auranofin, pencillamine, or hydroxychloroquine sulfate.

This study estimated an incidence of agranulocytosis of 7 cases per million per year. It was found in the validation study that cases of agranulocytosis were frequently reported by the hospital or laboratory as severe neutropenia and recorded as neutropenia into the GPRD. Our incidence estimate was corrected for this proportion of misclassified cases.

Similar to other epidemiological studies [3,4,7], we found substantially elevated risks of neutropenia for thyroid inhibitors and aminosalicylates. NSAIDs have been associated with significantly elevated risks of neutropenia in all epidemiological studies [3,6,7]. Both this study and the study by Strom et al. found that different classes of NSAIDs had comparable risks of neutropenia [6]. However, our results vary from other epidemiological studies with respect to oral corticosteroids, diuretics, and acetaminophen. The Dutch study reported a significantly increased risk of agranulocytosis following treatment with diuretics or acetaminophen [7], while this study and IAAAS found no elevated risks [3]. Oral corticosteroids were not associated with increased risks in this study in contrast to the IAAAS and the Dutch studies [3,7]. But the authors of the Dutch study did not consider this association to oral corticosteroids to be causal [7]. Clozapine, an atypical antipsychotic agent with a high incidence of agranulocytosis [13], was only used infrequently in the study population.

Two main types of idiosyncratic drug-induced neutro-

penia are recognised [12]. One type is a dose-related toxicity due to interference of the drug with protein synthesis or cell replication. Patients receiving high doses are more prone to develop these reactions. A second type of drug-induced neutropenia, of immunologic origin, may not be dose-related. It tends to occur relatively early in the course of treatment with drugs to which the patients has been previously exposed [12]. Although these data need to be confirmed, the results of this study suggest that immunologic aetiology may be more prevalent in idiosyncratic neutropenia.

Agranulocytosis has traditionally been regarded as a condition with a high mortality. Palva reported a fatality rate of 22% among 63 cases studied from 1950 through 1968, with the highest mortality among the cases that occurred in the early 1950s and a lower mortality at the end of the 1960s [8]. Other case series found fatality rates ranging from 2% to 40%, with the majority of case series reporting mortality rates of 10% or lower [1,14–22]. Reports of drug-associated agranulocytosis as received by regulatory authorities observed fatality rates of 11–32% [23,24]. Health professionals submit such reports voluntarily, and fatal cases may be more likely to be submitted. Similarly, reporting rates and characteristics may change over time. Taking into account these caveats, it is of interest that the fatality rate of the cases submitted more recently to the MCA in the U.K. was considerably lower than that of cases in the past (1964–1970, 44%; 1971–

TABLE IV. Risk of Neutropenia for Current Drug Users According to the Number of Prior Prescriptions

Drug group	No. of Rx	Neutropenia		Adjusted OR (95% CI)
		No. of cases	No. of controls	
Antibacterial drugs	1	138	174	3.1 (2.4–3.9)
	2, 3	183	270	2.4 (2.0–3.0)
	4+	282	386	2.7 (2.2–3.2)
Non-opioid analgesics	1	87	108	2.3 (1.7–3.1)
	2, 3	97	110	2.2 (1.6–2.9)
	4+	291	482	1.5 (1.2–1.8)
NSAIDs	1	85	112	2.7 (2.0–3.6)
	2, 3	90	115	2.4 (1.8–3.3)
	4+	263	358	1.8 (1.4–2.2)
Antidepressants	1	37	34	3.5 (2.2–5.8)
	2, 3	23	36	1.6 (0.9–2.8)
	4+	148	255	1.4 (1.1–1.8)
Ulcer-healing drugs	1	34	29	3.0 (1.8–5.2)
	2, 3	28	38	2.0 (1.2–3.4)
	4+	109	223	1.1 (0.8–1.4)
Anti-epileptics	1	6	4	3.0 (0.8–11.9)
	2, 3	14	9	4.5 (1.9–10.8)
	4+	108	77	3.7 (2.7–5.1)
Aminosalicylates	1	14	1	28.1 (3.6–219.2)
	2, 3	29	3	25.0 (7.2–87.5)
	4+	55	26	4.9 (3.0–8.2)
Thyroid inhibitors	1	6	1	14.0 (1.6–119.1)
	2, 3	16	1	57.8 (7.4–453.7)
	4+	22	2	34.4 (7.7–154.2)
Disease-modifying antirheumatic drugs	1	4	0	—
	2, 3	8	0	—
	4+	29	8	—

TABLE V. Risk of Neutropenia for Individual Drugs Stratified by Daily Dose

Drug	Daily dose	No. of cases	No. of controls	Adjusted OR (95% CI)
Amoxicillin	250–750 mg	156	221	2.1 (1.7–2.4)
	≥1,000 mg	38	66	1.6 (1.2–2.2)
Ibuprofen	400–900 mg	17	15	2.9 (1.5–5.3)
	1,200 mg	43	106	1.1 (0.8–1.4)
	≥1,600 mg	23	29	2.5 (1.6–3.9)
Dosulepin/dothiepin	25–75 mg	43	69	1.7 (1.3–2.3)
	≥100 mg	5	13	0.8 (0.4–1.8)
Ranitidine	150 mg	10	30	1.0 (0.6–1.6)
	≥300 mg	55	81	1.6 (1.2–2.1)
Carbamazepine	100–300 mg	16	12	3.3 (1.7–6.3)
	≥400 mg	21	15	3.5 (1.9–6.3)
Sulfasalazine	500–1,500 mg	20	9	5.1 (2.4–10.7)
	≥2,000 mg	54	8	18.3 (8.5–39.4)
Carbimazole	5–15 mg	15	2	17.3 (4.2–72.2)
	≥20 mg	24	2	32.9 (8.0–135.7)

1980, 34%; 1981–1990, 18%; 1991–2000, 4%) [MCA, personal communication]. However, this substantive decrease in mortality was not observed in the U.S. FDA database of spontaneous reports [FDA, personal communication]. A mortality rate of 26.1% was found in 2,606 reports submitted prior to November 1997 and 20.1% in the 1191 reports submitted between November 1997 and

December 2000. The more recent epidemiological studies found fatality rates of 0–10% [3,4,7] while post-marketing follow-up studies of drug users found rates below 5% [13,25–27]. A possible explanation for this improvement in the prognosis of agranulocytosis may be the increased use of antibiotics and, possibly, the availability of granulocyte stimulating factor [16].

Medical records of general practitioners were used in this study to identify the cases. Our validation study showed that the diagnosis of neutropenia had primarily been made on the basis of laboratory measurements, which are standardized across the U.K. It was found that agranulocytosis was frequently reported as severe neutropenia by the hospital and recorded as neutropenia by the general practitioners. The likely consequence of this was that we underestimated the incidence of agranulocytosis. The validation study was conducted only in practices that were still registered with GPRD at the time of the validation. Of the 598 practices included in the study, 297 practices were participating in validation. However, we did not find any differences in data quality between practices that left GPRD and those that are still registered (the number of prescriptions and the number of entries into the medical records were similar between these two groups of practices). The results for neutropenia did not change materially when restricting the analysis to validating practices. Furthermore, like any other retrospective study, there is also the potential of surveillance bias. Patients using medication known to cause neutropenia may have been monitored more closely than patients not using this medication. Similarly, drugs such as anti-infectives may have been prescribed to treat early symptoms of neutropenia or agranulocytosis. This bias could overestimate the extent that these drugs cause neutropenia.

In conclusion, thyroid inhibitors, aminosalicylates, antibacterial drugs, non-opioid analgesics, NSAIDs, antidepressants, ulcer-healing drugs, anti-epileptics, and disease-modifying antirheumatic drugs were associated with increased of neutropenia. The increases in risk of neutropenia predominantly occurred in the first 3 months of treatment. For most drugs investigated in this study, there was no relationship to daily dose. The excess 1-year mortality was low among patients with neutropenia and agranulocytosis and can be mostly explained by the underlying disease state.

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