Clozapine-Induced Agranulocytosis in Finland, 1982–2007: Long-Term Monitoring of Patients Is Still Warranted

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ABSTRACT

Objective: Recent studies suggest that restrictions on the use of clozapine should be reassessed considering the risk-benefit ratio. We analyzed all cases of clozapine-induced agranulocytosis reported to the Finnish National Agency for Medicines between 1982 and 2007.

Method: In this retrospective longitudinal study, we defined agranulocytosis as a neutrophil count below 0.5×10^9/L and, accordingly, identified a total of 163 patients with clozapine-induced agranulocytosis. We collected all available information on patient demography, as well as on daily clozapine doses, treatment duration, concomitant medication prior to the onset of agranulocytosis, and infections during the adverse event. The amount of clozapine used annually in Finland was estimated on the basis of the defined daily dose, and the frequency of agranulocytosis was calculated from the absolute number of cases in relation to the defined daily dose each year, as reported by the Finnish National Agency for Medicines.

Results: In 10.3% of cases, agranulocytosis occurred after the second treatment year, and, in some patients, agranulocytosis occurred even after 13, 14, and 22 years of clozapine treatment. Strikingly, a total of 40% of all patients and 80% of those with fatal agranulocytosis had received, concomitantly with clozapine, other medication associated with agranulocytosis.

Conclusions: Some restrictions and long-term blood monitoring during the use of clozapine are still needed. In addition, we raise the question of whether guidelines for concomitant use of drugs associated with agranulocytosis during clozapine therapy are warranted.

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Clozapine has proven to be the most effective antipsychotic in several areas of schizophrenia treatment.[1–5] However, its use is limited by a high incidence of a potentially lethal hematologic side effect. European monitoring routines therefore require that clozapine-treated patients undergo weekly white blood cell monitoring for the first 18 weeks of therapy and, thereafter, monthly monitoring for the remaining duration of clozapine therapy. The risk of agranulocytosis is highest during the first 6 months of clozapine treatment, and the incidence decreases dramatically after the first year.[6,7] On the basis of these facts, it has been suggested that blood monitoring after 6 months of treatment may not be necessary, as mortality at this point is the same as that expected with any other medication or in life in general.[7] Moreover, recent studies suggest that restrictions on the use of clozapine should be reassessed considering the risk-benefit ratio, and the need for large nationwide databases for the surveillance of drug safety is emphasized.[1,5] In the present retrospective longitudinal study, we evaluated all the reported cases of clozapine-induced agranulocytosis in Finland from 1982 to 2007.

METHOD

Data Source

The data consisted of all cases of clozapine-associated white blood cell adverse drug reactions reported by doctors to the Finnish National Agency for Medicines between December 17, 1982, and December 31, 2007. We defined agranulocytosis as a neutrophil count below 0.5×10^9/L and, accordingly, identified a total of 163 patients with clozapine-induced agranulocytosis. Our intention was to collect the following information for all reported cases of agranulocytosis: patient age and gender, daily dose of clozapine, duration of clozapine treatment before the onset of agranulocytosis, concomitant medication, and infections during agranulocytosis, as well as the outcome of the agranulocytosis. If this information was not in the original reports to the National Agency for Medicines, we tried to get the additional information from the patients' hospital and outpatient clinic records. Although we were able to obtain this information in the vast majority of cases, some information was still missing due to missing or incomplete hospital records and/or outpatient records. In 6 cases, only the year and month but not the exact date of starting clozapine treatment was known. In the analyses, we included cases in which the duration of clozapine treatment could be estimated with a maximal error of 25%, providing a total of 155 patients.

The amount of clozapine used annually in Finland was estimated on the basis of the defined daily dose each year, which was available from 1991 onward, when the marketing approval system in Finland was renewed. The defined daily dose is the assumed average maintenance dose per day. The frequency of agranulocytosis was calculated from the absolute number of cases in relation to the defined daily dose each year as obtained from the National Agency for Medicines. This figure was estimated on the basis of the absolute amounts of clozapine sold per year, considering 300 mg to be the average dose per patient.

The Finnish National Agency for Medicines and the Finnish Ministry of Social Affairs and Health approved the study design.

Statistical Analysis

All demographic results were summarized as means or percentages. The differences in means were analyzed using the Kruskal-Wallis 1-way analysis of variance test for sex differences in clozapine doses and the treatment duration. Significance was set at $P < .05$. Statistical analyses were performed using SYSTAT software package, Version 13 (Aspire Software International, Ashburn, Virginia).

- This study shows that 40% of all the patients with agranulocytosis, and 80% of those with fatal agranulocytosis, had received, concomitantly with clozapine, other medication associated with agranulocytosis.
- Concomitant treatment with other potentially agranulocytosis-inducing drugs may be a risk factor during clozapine therapy. New treatment guidelines may be warranted to enhance patient safety.

Clinical Points

RESULTS

Altogether, 163 reports of clozapine-induced agranulocytosis were made to Finland's National Agency for Medicines between 1982 and 2007. All information was available for a total of 138 patients. The number of patients studied in each category varied slightly, as the information was incomplete for some patients.

Demographics and Treatment Characteristics

Table 1 shows demographics and treatment characteristics at the onset of agranulocytosis: 47.9% (n = 78) of the patients were women and 52.1% (n = 85) were men. The mean age of the affected patients receiving clozapine was 44.6 years; the women were significantly older than the men ($P < .0001$). The mean clozapine dosage was moderate (393 mg/day), with no significant gender differences. The treatment duration of 95.1% (155 of 163) of the patients before the onset of the adverse event was known: duration ranged from 2 days to 22 years. The mean duration of clozapine treatment was 332 days (median = 59 days). Women developed agranulocytosis a mean of 143 days earlier than men, and the difference between women and men was statistically significant ($P = .018$). In 6 of 155 patients, the duration of clozapine treatment could be estimated only with a maximal margin of error of 21.7% because the exact date of starting treatment was not known (only the year and month were known). These 6 patients had a very long treatment period, averaging 1,819.2 days. The exact dates of drug initiation and discontinuation could be retrieved for the remaining 149 patients.

The presence or absence of infection was recorded for 145 patients (see Table 1). An infection during agranulocytosis was present in 78.6% of cases. Patients with an agranulocytosis-associated infection developed agranulocytosis in 272 days, compared to 302.7 days in the group with no infection, but the difference was not significant.

Concomitant medication was described in the medical records of 151 patients (see Table 1). Sixty patients (39.7%) had received concomitant medication reported to be associated with agranulocytosis[8] during the week prior to the onset of agranulocytosis. The administered medications included chlorpromazine, thioridazine, doxepin, carbamazepine, lamotrigine, fluoxetine, olanzapine, ibuprofen, cefuroxime, trimethoprim, and omeprazole. Data on the patients receiving comedication potentially inducing agranulocytosis are shown in Table 2. The age and daily clozapine dose of these patients did not differ significantly from those of the patients with no other agranulocytosis-inducing medication. These patients had already developed agranulocytosis after a mean of 183 days, in contrast to the group of all patients (mean = 333 days). The difference between the 2 groups was even more pronounced in women (mean = 258 days vs 80.6 days). These differences were nevertheless statistically nonsignificant.

Time to Onset of Agranulocytosis

A total of 79.4% of all agranulocytosis cases (123 of 155) occurred within 5 months of starting clozapine treatment, whereas 83.9% of all agranulocytosis cases (130) occurred within 12 months (Figure 1).

Figure 2 shows the yearly incidence of agranulocytosis related to the defined daily dose each year. This figure also shows that the use of clozapine increased between 1991 and 2007.

Agranulocytosis Within 18 Weeks

During the first 18 weeks (126 days) of clozapine therapy, European monitoring routines require that patients undergo weekly white blood cell monitoring. Altogether, 76.8% of patients with known duration of clozapine treatment (119 of 155) developed agranulocytosis within 126 days (see Table 2).

There were more women in this group, compared to all patients with agranulocytosis, ie, 53.8% (64 of 119) compared to 47.7% (74 of 155), and the patients developed agranulocytosis in a mean of 56 days. Information on the presence or absence of an infection was available for 111 patients, and 80.2% had a concomitant infection during agranulocytosis.

In a total of 96.7% of cases (115 of 119), information on concomitant medication was found in the patient records. Of these patients, 41.7% had received concomitant medication that has been shown to be associated with agranulocytosis.[8] Two patients receiving comedication developed agranulocytosis very quickly. A 36-year-old male patient receiving carbamazepine as comedication developed agranulocytosis in 2 days, and a 16-year-old girl on chlorpromazine comedication developed the condition in 3 days after clozapine initiation.

Table 1. Characteristics of Patients at the Onset of Clozapine-Induced Agranulocytosis

Characteristic	N	Women/Men Ratio, n/n	Women (n = 78) Mean (SD)	Women (n = 78) Median (Range)	Men (n = 85) Mean (SD)	Men (n = 85) Median (Range)	Total (N = 163) Mean (SD)	Total (N = 163) Median (Range)
Age, y	160	78/82	48.4 (11.9)	49 (16–81)	41.1 (11.8)	42 (17–77)	44.6 (12.4)	45 (16–81)[a]
Daily dose of clozapine, mg	151	71/80	369.5 (136.0)	400 (50–800)	414.1 (152.9)	400 (100–850)	393.1 (146.4)	400 (50–850)
Treatment duration, d	155	74/81	257.6 (994.3)	54.5 (3–8,030)	400.6 (863.2)	79 (2–4,966)	332.4 (927.8)	59 (2–8,030)[a]
			% (N)		% (N)		% (N)	
Infection during agranulocytosis	145	69/76	78.3 (54)		78.9 (60)		78.6 (114)	
No infection during agranulocytosis	145	69/76	23.2 (16)		19.7 (15)		21.3 (31)	
Concomitant medication related to agranulocytosis	151	71/80	46.5 (33)		33.8 (27)		39.7 (60)	

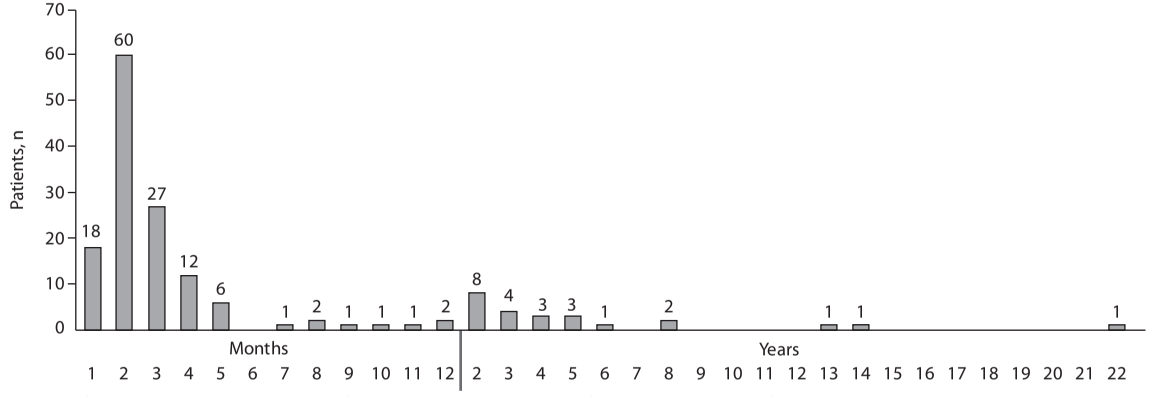
[a]The difference between women and men is statistically significant ($P < .0001$).

Table 2. Characteristics (age, clozapine dose, treatment duration before onset of agranulocytosis, presence of infection, and comedication) of Patients With Comedication Potentially Inducing Agranulocytosis, With Onset of Agranulocytosis Within 126 Days After Treatment Initiation, and With Onset of Agranulocytosis > 365 Days After Treatment Initiation

	Age				Clozapine Dose				Treatment Duration Before Onset				Presence of Infection			Comedication		
Variable	N	Women/Men Ratio, n/n	Mean (SD), y	Median (Range), y	N	Women/Men Ratio, n/n	Mean (SD), mg	Median (Range), mg	N	Women/Men Ratio, n/n	Mean (SD), d	Median (Range), d	N	Women/Men Ratio, n/n	n (%)	N	Women/Men Ratio, n/n	n (%)
Comedication	60	33/27	43.8 (11.7)	45.5 (16–68)	59	32/27	400.8 (155.8)	400 (150–800)	59	33/26	182.7 (367.7)	57 (2–1,869)	…[a]	…[a]	…[a]	…[a]	…[a]	…[a]
Onset ≤ 126 days after treatment initiation	118	64/54	45.8 (12.0)	46.5 (16–77)	114	61/53	366.3 (135.3)	350 (50–850)	119	64/55	56.1 (25.5)	51 (2–125)	111	60/51	89 (80.2)	115	62/53	48 (41.7)
Onset > 365 days after treatment initiation	23	7/16	42.4 (10.6)	42 (24–65)	23	7/16	473.9 (168.5)	400 (200–800)	24	7/17	1,751.9 (1,804.1)	1,191 (403–8,030)	19	6/13	13 (68.4)	22	6/16	6 (27.3)

[a]Not applicable.

Figure 1. Number of Patients With Agranulocytosis (N = 155)[a]



[a]Frequency (no. of patients per month or year) of agranulocytosis during the first 12 months and after 1 year up to 22 years between 1982 and 2007.

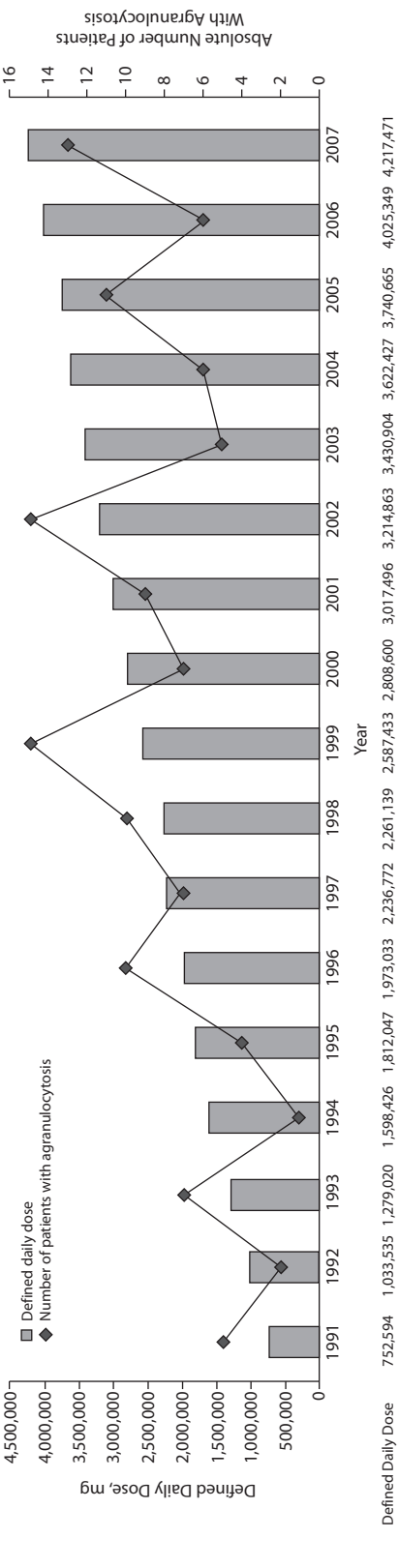


Figure 2. Absolute Number of Patients With Clozapine-Induced Agranulocytosis Per Year Related to Yearly Increase in Defined Daily Dose of Clozapine From 1991 to 2007 (N = 133)

Late Agranulocytosis

Altogether, 15.5% of patients with known treatment duration (24 of 155) developed agranulocytosis more than 1 year after starting clozapine therapy (see Table 2). The majority in this group, 70.8% (17 of 24), were men. Again, women were older, a mean of nearly 9 years older than the men (data not shown). The women in the group with delayed onset developed agranulocytosis a mean of 2,145 days after clozapine initiation, and the men, a mean of 1,590 days; the difference is not statistically significant. The presence or absence of an infection was reported in 79.2% (n = 19), and an infection was reported in 68.4% of these. A total of 27.3% of the patients (6 of 22) had received concomitant medication associated with agranulocytosis. The latest onset of agranulocytosis occurred 8,030 days (22 years) after the start of clozapine therapy.

Fatalities

Five patients (of 163) died of complications due to agranulocytosis, giving a case-fatality rate of 3.1%. Their characteristics are shown in Table 3.

These patients were a mean of 13 years older than the patients who survived agranulocytosis (57.4 vs 44.6 years). Three of the patients were women and 2 were men. The mean drug dose was within the recommended range, and the dose was lower than in the total group of patients with agranulocytosis.

A female patient developed fatal agranulocytosis nearly a year after clozapine initiation. Compared to all cases of agranulocytosis (N = 155), the fatal cases developed quickly (mean = 115.6 days and median = 57 days for the fatal cases, versus mean = 332.4 and median = 59 for the nonfatal cases), but the difference was not statistically significant. An infection was reported in all of the fatal cases. Concomitant medication associated with agranulocytosis,[8] ie, chlorpromazine, doxepin, propranolol, or olanzapine, was administered to 4 of the 5 patients (80%) who developed fatal agranulocytosis.

DISCUSSION

Clozapine was taken into clinical use in several European counties in 1972. In Finland, it was withdrawn from the market in 1975, only 6 months after its introduction, after an alarming report by Idänpään-Heikkilä et al[9] in which clozapine use was connected with 17 cases of agranulocytosis, 8 of which were fatal. The estimated incidence rate was at least 0.5% for agranulocytosis and 0.6% for neutropenia.[10] The Finnish market withdrawal of clozapine was soon followed by withdrawal in other countries.

Initially, clozapine-induced agranulocytosis was considered as an "epidemic" confined to Finland, but, later on, it became evident that the Finnish population was not particularly susceptible to clozapine-induced agranulocytosis.[11–13] Subsequent studies in different populations have estimated the incidence to be about 0.8%.[14–20]

We analyzed the data on all reported cases of clozapine-induced agranulocytosis in Finland between 1982 and 2007 and were able to identify 163 patients. Among the cases we found, women and men were affected equally. However, women who developed agranulocytosis were significantly older than the men, by 7 years on average. This may reflect the earlier onset of schizophrenia in men but is also in line with some earlier findings indicating that an increased risk of agranulocytosis is linked with older age and female sex.[6,16] A novel

Table 3. Characteristics of Patients With Fatal Agranulocytosis (n = 5)

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Totals	Mean (SD)	Median (Range)
Gender	Female	Male	Female	Female	Male	…[a]	…[a]	…[a]
Age, y	53	58	58	62	56	…[a]	57.4 (3.3)	58 (53–62)
Daily dose of clozapine, mg	200	300	500	300	200	…[a]	300.0 (122.5)	300 (200–500)
Treatment duration, d	29	99	344	49	57	…[a]	115.6 (130.2)	57 (29–344)
Infection during agranulocytosis	Yes	Yes	Yes	Yes	Yes	5	…[a]	…[a]
Comedication associated with agranulocytosis	Yes	No	Yes	Yes	Yes	4	…[a]	…[a]

[a]Not applicable.

finding in our study was that women developed agranulocytosis earlier (on average, 143 days earlier) after initiation of clozapine treatment than did men. The explanation for this is unclear, as are the mechanisms underlying clozapine-induced agranulocytosis. It is possible that the older age of the women may contribute to the earlier onset.

We found that concomitant medication associated with agranulocytosis was common, despite recommendations to restrain from such medication. Forty percent of all patients had, during the week prior to the onset of the adverse event, received other compounds linked with agranulocytosis. This is a high number. It would be very important to know how many clozapine-treated patients comedicated with other potentially agranulocytosis-inducing drugs do not develop agranulocytosis. To our knowledge, no such data are presently available. We have to bear in mind that patients treated with clozapine are often very therapy-resistant. Although comedication with other potentially agranulocytosis-inducing agents displays an increased risk,[21] this risk may be clinically justified on occasion.

Strikingly, our study shows that 4 of 5 cases (80%) with a fatal outcome had concomitant medication associated with agranulocytosis. Also, in both of the cases with very rapid onset (after 2 and 3 days, respectively, of clozapine treatment), the use of concomitant medication associated with agranulocytosis was reported. This finding is in line with previous reports that link coadministration of other drugs with agranulocytosis.[10,20,22,23] Also, an earlier report from Finland found coadministration of a potentially agranulocytosis-inducing drug (chlorpromazine) in 6 of 8 fatal cases.[10] The observations possibly point to a synergistic mechanism behind this type of agranulocytosis.

As coadministration of clozapine with other potentially agranulocytosis-inducing agents seems to be common, we suggest that guidelines should be issued for treating these high-risk patients. We also believe that it would be very important to study this group more thoroughly in prospective studies.

Five fatal cases of agranulocytosis in our sample of 163 patients gives a mortality rate of 3.1%, which is in agreement with other studies estimating the mortality rate at 3%–4%.[7] The fatal cases developed agranulocytosis faster than did the patients who survived agranulocytosis; this finding is also in line with earlier reports.[6,17] Importantly, 1 patient developed fatal agranulocytosis nearly a year after clozapine initiation. Moreover, all 5 patients with irreversible agranulocytosis had an infection. This finding is consistent with earlier reports associating infections in clozapine-induced agranulocytosis with a higher mortality.[14]

A total of 74.8% of patients developed agranulocytosis within 18 weeks of initiation of treatment, 79.4% of cases occurred within the first 5 months of treatment, and 83.9% occurred within the first year of treatment. Other studies have reported that agranulocytosis developed within 18 weeks in 53.7%–89.6% of all cases[16,17,19] and that the risk was highest during the first 3 months.[6,19] Our study confirmed these findings. However, in 15.5% of our cases, agranulocytosis occurred after 1 year of treatment, and 10.3% of cases occurred after 2 years of treatment. Strikingly, in a few patients, agranulocytosis occurred even after 13, 14, and 22 years of clozapine treatment, which is much later than reported earlier.[19] Late-onset agranulocytosis may affect men more than women. Moreover, the mean duration before the onset of agranulocytosis in our study was 332 days (47 weeks). This finding reflects great variation in treatment duration before the onset of the adverse event. However, the median time before onset was 59 days—consistent with previous reports.[6,19]

Clozapine-induced agranulocytosis has not been related to dosage.[23] In our study, the last recorded mean doses of clozapine were moderate and within the recommended range of 150–450 mg/d in all groups except the group with delayed onset of agranulocytosis, because higher doses are usually required in long-term treatment.

The incidence of agranulocytosis was calculated on the basis of the defined daily dose each year, giving a yearly incidence rate of 0.02%–0.2%. This rate seems quite low compared to earlier reports.[14–20] One possible explanation could be that all cases of agranulocytosis were not reported to the authorities. Moreover, the frequent and consequent blood monitoring may prevent neutropenia from progressing into its most severe form if the drug is discontinued early.

This study is one of the largest nationwide studies analyzing detailed data on patients who develop clozapine-induced agranulocytosis. The study extended over several decades. It comprised all reported cases of clozapine-induced agranulocytosis in Finland; for 85% of the total sample, all needed information could be obtained either from original reports or from additional source data acquired from hospitals or outpatient clinics.

Our study had some limitations, however. We could not verify all the data reported at source (15% was unverified). In

addition, the exact numbers of patients using clozapine each year could not be obtained, and, thus, the estimated incidence of agranulocytosis was based on defined daily dose.

CONCLUSIONS

Even though clozapine-induced agranulocytosis developed mainly during the first year of drug treatment, over 10% of cases developed after the second year of treatment, and agranulocytosis was reported even after 22 years of treatment. Despite the superiority and unique benefits of clozapine, this study demonstrates that restrictions and long-term blood monitoring during use of clozapine are still needed. Furthermore, concomitant treatment with other potentially agranulocytosis-inducing medication was common and may be a risk factor, especially for rapidly developing and fatal agranulocytosis. The present study implicates the need for further research in this area and the necessity of formulating new treatment guidelines to enhance safety.

Drug names: carbamazepine (Carbatrol, Equetro, and others), cefuroxime (Ceftin, Zinacef, and others), clozapine (Clozaril, FazaClo, and others), doxepin (Zonalon, Silenor, and others), fluoxetine (Prozac and others), ibuprofen (Caldolor, Ibu-Tab, and others), lamotrigine (Lamictal and others), olanzapine (Zyprexa), omeprazole (Prilosec and others), propranolol (Inderal, InnoPran XL, and others), trimethoprim (Primsol and others).

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Author contributions: Both authors designed the study and constructed the database. Dr Lahdelma wrote the first draft, and Dr Appelberg performed the statistical analyses. Both authors took part in interpretation of the results and preparation of the final version.

Potential conflicts of interest: In the last 3 years, **Dr Lahdelma** has received lecture fees from Novartis and MSD and has participated in clinical drug trials by AstraZeneca and Lundbeck. **Dr Appelberg** has received lecture fees from AstraZeneca, GlaxoSmithKline, Orion, and Pfizer and has participated in clinical drug trials by Pfizer and AstraZeneca.

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