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Differences between counties in the prescribing of clozapine

ORIGINALARTIKKEL

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BACKGROUND

Norwegian national guidelines recommend that clozapine be offered to patients with schizophrenia after two failed attempts with other antipsychotic drugs. One of the main objectives for the introduction of clinical pathways in mental health care is to provide an equal service to patients irrespective of where in the country they live. We wished to investigate the prescribing level of clozapine in various Norwegian counties.

MATERIAL AND METHOD

We retrieved aggregated data from the Norwegian Prescription Database, the Norwegian Patient Registry and Statistics Norway on prescribing of clozapine, number of patients in contact with the specialist health service with the diagnosis schizophrenia, and population figures for 2016.

RESULTS

Nationwide in 2016, there were 50 users of clozapine per 100 000 inhabitants (95 % confidence interval (CI) 48–52). The number of users was highest in Troms county (76 (95 % CI 63–89) per 100 000 inhabitants) and lowest in Akershus county (38 (95 % CI 33–43) per 100 000 inhabitants). We found no significant correlation between the prescribing rate for clozapine and the proportion of the population in the county who were undergoing treatment for schizophrenia in the specialist health service.

INTERPRETATION

Prescribing of clozapine varies among Norwegian counties and is not correlated with the proportion of the population who are undergoing treatment for schizophrenia in the specialist health service. Different levels of implementation of the national guidelines constitute a possible explanation for the geographic differences.

Clozapine is considered to be the most effective antipsychotic drug for treatment of schizophrenia (1). However, because of serious adverse effects, such as agranulocytosis, this is not a first-line drug. The Norwegian national guidelines for examination, treatment and follow-up of persons with psychotic disorders recommend that patients with treatment-resistant schizophrenia, defined as two failed treatment attempts with other antipsychotic drugs, be offered treatment with clozapine (2). This recommendation accords with international guidelines (3–5).

Despite these consistent international guidelines there is considerable variation in the use of clozapine between nations with comparable populations. For example, in 2014 this drug was prescribed to 50 per 100 000 inhabitants in Norway, compared to 58, 61, 100 and 189 per 100 000 inhabitants in Denmark, Sweden, Iceland and Finland respectively (6). The prevalence of schizophrenia may also vary (7, 8) and thus possibly represent a partial explanation for the variations in the use of clozapine between nations. On the other hand, studies show that clozapine is used more rarely (9–11) and later (12) than recommended, even when an indication is evident.

Patient pathways for examination and treatment in the mental health services for adults were implemented in Norway on 1 January 2019 (13). One of the five objectives of these patient pathways is to provide 'an equal service to patients […] irrespective of where in the country they live'. A study of geographical variation in the prescribing rate for clozapine may give an indication of the extent to which patients with treatment-resistant schizophrenia are provided with drug-based treatment of equal quality.

The main goal of this study was to investigate the extent to which the prescribing rate for clozapine varied between Norwegian counties in 2016. The first objective was to investigate whether this variation could be explained in terms of differences in the proportion of patients with schizophrenia who were followed up by the specialist health services in the different counties. The second objective was to describe the differences in prescribing rates between the country's four regional health authorities among men and women in different age groups. The third objective was to investigate whether the differences in prescribing practices for clozapine between the country's four regional health authorities could be explained by varying prescribing rates for antipsychotic drugs as a group.

Material and method

This ecological study investigated the prescribing of clozapine for Norwegian counties and regional health authorities. The data material was retrieved from the Norwegian Prescription Database (14), the Norwegian Patient Registry and Statistics Norway. Since the data stem from the time when Norway had 19 counties, the old county names are used.

THE NORWEGIAN PRESCRIPTION DATABASE

The Norwegian Prescription Database contains aggregated data for all prescriptions dispensed by Norwegian pharmacies (reseptregisteret.no). Prescribing in hospitals and nursing homes is not included. We retrieved data for prescriptions of clozapine (ATC code N05AH02) for the year 2016 nationwide, distributed by counties and regional health authorities, sex and the age groups 20–29, 30–39, 40–49, 50–59 and 60–69 years. We used regional health authorities as the basis for examining the prescribing of clozapine to different sexes and age groups, because the figures for some counties were too small to retrieve aggregated data.

In the Norwegian Prescription Database, the clozapine dose is stated in terms of defined daily doses (DDD). This is an expression of the assumed average daily dose for adults, used for the main indication of the drug (300 mg for clozapine) (15). We investigated 1) the prescribing rate for clozapine (the number of persons with at least one prescription for clozapine during the year in question per 100 000 inhabitants), 2) the average prescribed clozapine dose per user (calculated as the number of DDDs per year divided by 365 and the number of users, reported in mg) and 3) the proportion of prescriptions for antipsychotic drugs (ATC N05A, excluding lithium (N05AN01)) that were accounted for by clozapine.

THE NORWEGIAN PATIENT REGISTRY

Data for the number of patients diagnosed with schizophrenia (ICD-10 F20.0-F20.9) were retrieved from the Norwegian Patient Registry, which records diagnoses for all patient contacts in the specialist health services. We were provided with data on the number of patients over the age of 18 who were recorded with schizophrenia as their primary or secondary diagnosis following contact with the specialist health services (mental health care, interdisciplinary specialised addiction therapy or contract specialists in psychiatry) in 2016, by county.

STATISTICS NORWAY

Population figures (> 18 years) by county were retrieved from Statistics Norway for the same period. The proportion of the population that was followed up by the specialist health services because of a schizophrenia diagnosis was calculated by dividing the number of patients with this diagnosis with the number of inhabitants for each county. This should not be regarded as an estimate of prevalence, but as the proportion of the population that has contact with the specialist health services due to a diagnosis of schizophrenia.

STATISTICAL METHODS

The estimation of a 95 % confidence interval (CI) for the prescribing rates for counties, regional health authorities, sexes and age groups was made according to the formula $p \pm 1{,}96 * \sqrt{p(1-p)/n}$, where *p* is the proportion prescribed with clozapine and *n* is the number of individuals in the whole population (16). A confidence interval for the average clozapine dose prescribed cannot be estimated on the basis of aggregated data without a measure of dispersion. In light of the literature (appendix), we assumed a standard deviation (SD) of 190 mg clozapine in the estimation of a 95 % confidence interval.

The CI was subsequently estimated according to the formula for mean $\pm 1{,}96 * sd/\sqrt{n}$, where n is the number of individuals who use clozapine (16). Spearman's correlation coefficient was used to investigate possible correlations between the number of patients

with a diagnosis of schizophrenia and the prescribing rate. The statistical significance level was set at 0.05. SPSS version 24 was used to perform the statistical analyses.

ETHICS

The study used aggregated data that are openly available online from the Norwegian Prescription Database and Statistics Norway. The data from the Norwegian Patient Registry were also aggregated information which is supplied for specific purposes without an application to the Regional Committee for Medical and Health Research Ethics.

Results

PRESCRIBING IN NORWEGIAN COUNTIES

In Norway, 50 (95 % CI 48–52) per 100 000 inhabitants were dispensed a prescription for clozapine in 2016. The prescribing rate varied between counties from 38 (95 % CI 33–43) to 76 (95 % CI 63–89) per 100 000 inhabitants (Figure 1 and Table 1). Nordland, Sør-Trøndelag and Troms counties stood out in having the highest prescribing rate (> 70 per 100 000 inhabitants), while Oslo and Akershus counties had the lowest prescribing rates (< 40 per 100 000 inhabitants).

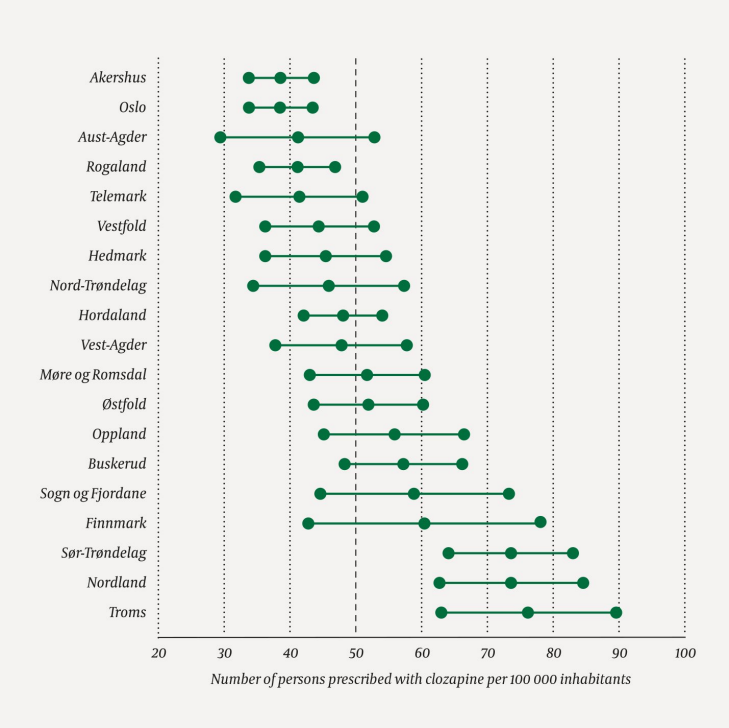

Figure 1 *Number of persons who were prescribed clozapine per 100 000 inhabitants in Norwegian counties in 2016. The vertical broken line (prescribing rate 50 per 100 000 inhabitants) shows the national average, while the mid-point and horizontal line show the prescribing rate and the 95 % confidence interval respectively.*

Table 1

Proportion of the population prescribed with clozapine in Norwegian counties in 2016.

County	Number prescribed with clozapine	Total population	Proportion of the population that uses clozapine (%)
Akershus	232	599 428	0.039
Aust-Agder	48	116 220	0.041
Buskerud	160	278 686	0.057

County	Number prescribed with clozapine	Total population	Proportion of the population that uses clozapine (%)
Finnmark	46	75 946	0.061
Hedmark	89	195 766	0.045
Hordaland	250	518 245	0.048
Møre og Romsdal	138	265 774	0.052
Nordland	179	242 408	0.074
Nord-Trøndelag	63	136 806	0.046
Oppland	106	189 214	0.056
Oslo	258	662 511	0.039
Rogaland	195	471 062	0.041
Sogn og Fjordane	65	109 904	0.059
Sør-Trøndelag	232	315 336	0.074
Telemark	72	172 908	0.042
Troms	126	164 974	0.076
Vest-Agder	88	183 409	0.048
Vestfold	110	246 698	0.045
Østfold	152	291 330	0.052
Total	2 609	5 236 625	0.050

PROPORTION OF PATIENTS AND PRESCRIBING RATE

The proportion of patients followed up by the specialist health services for the diagnosis of schizophrenia varied between the counties (0.13 %–0.27 %). There was no significant correlation between the proportion of patients followed up by the specialist health services for the diagnosis of schizophrenia on the one hand, and the prescribing rate for clozapine on the other (Spearman's correlation coefficient 0.17, p = 0.50). The county of Oslo stood out in having a low prescribing rate for clozapine in relation to the proportion of patients with schizophrenia. Nor was there any significant correlation when Oslo was excluded from the analyses (Spearman's correlation coefficient 0.36, p = 0.15).

PRESCRIBING RATES IN REGIONAL HEALTH AUTHORITIES

Figures 2a and 2b show the prescribing rates for clozapine in 2016 in the regional health authorities by sex and age group. Clozapine was prescribed 1.6 times more frequently in the region with the highest prescribing rate (Northern Norway Regional Health Authority, 73 (95 % CI 65–80) per 100 000 inhabitants) when compared to the region with the lowest prescribing rate (South-Eastern Norway Regional Health Authority, 45 (95 % CI 42–47) per 100 000 inhabitants).

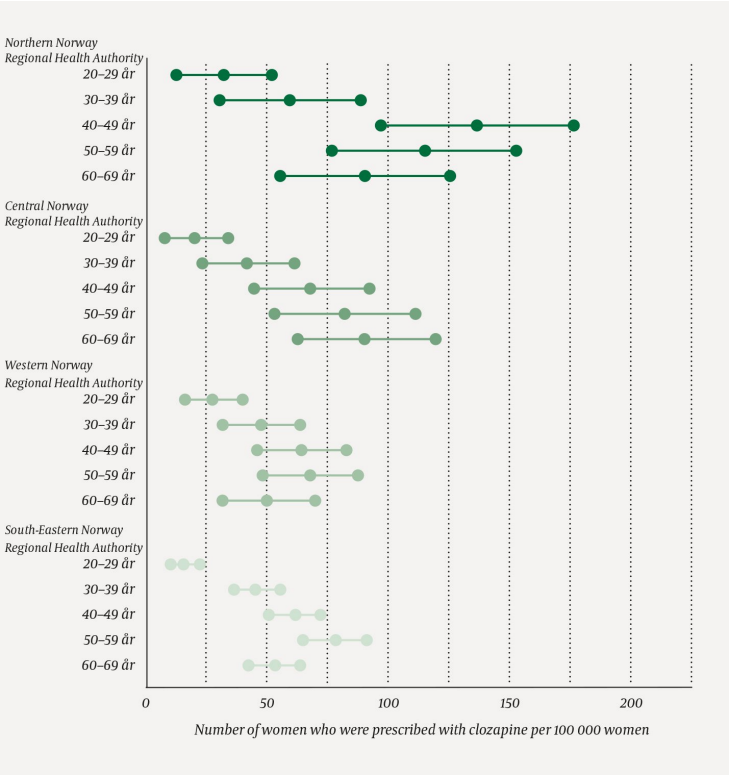

Figure 2a *Number of women who were prescribed with clozapine per 100 000 women in different age groups and regional health authorities. The mid-point and horizontal line show the prescribing rate and the 95 % confidence interval respectively.*

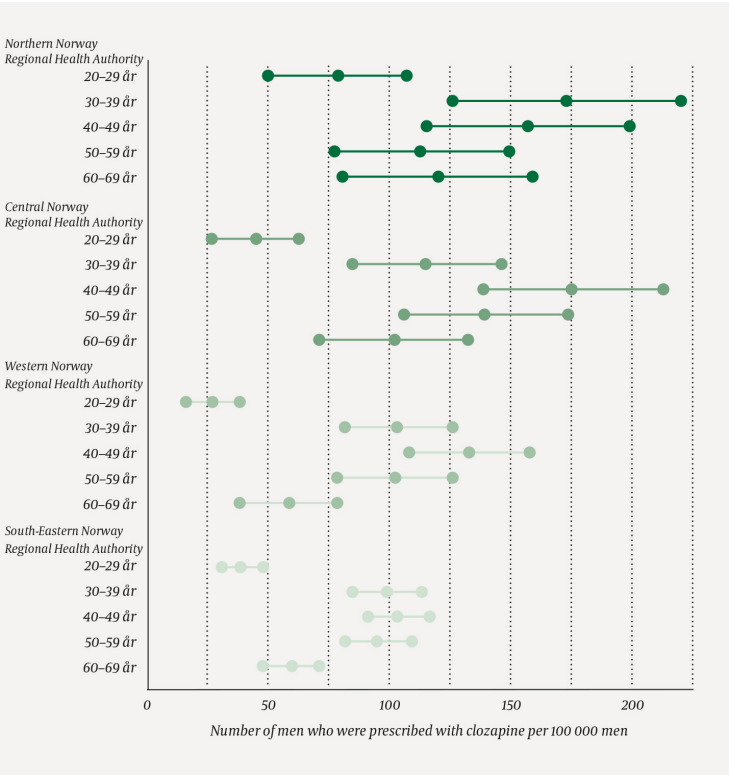

Figure 2b *Number of men who were prescribed with clozapine per 100 000 men in different age groups and regional health authorities. The mid-point and horizontal line show the prescribing rate and the 95 % confidence interval respectively.*

The greatest difference in the prescribing rate was observed among men in the age group 20–29 years, where clozapine was prescribed 2.9 times more frequently in the region with the highest prescribing rate when compared to the region with the lowest prescribing rate. In Northern Norway Regional Health Authority, the highest prescribing rate was among women in the age group 40–49 years, whereas in the other regional health enterprises the

peak in the prescribing rate came later (50–59 years and 60–69 years). Among men, the prescribing rate peaked ten years earlier in Northern Norway Regional Health Authority (30–39 years) than in the other health authorities (40–49 years).

The average prescribed dose of clozapine for women and men in different age groups in 2016 is shown in Figures 3a and 3b. The age group 20–24 years is not included because of missing data from the Norwegian Prescription Database. Clozapine was prescribed in doses that were 1.4 times higher in the region with the highest average dose (Central Norway Regional Health Authority, 331 mg (95 % CI 313–349)) when compared to the region with the lowest prescribed average dose (Northern Norway Regional Health Authority, 235 mg (95 % CI 215–255)). Northern Norway Regional Health Authority had the lowest prescribed average dose in all age categories for both women and men, with the exception of the age group 60–69 years.

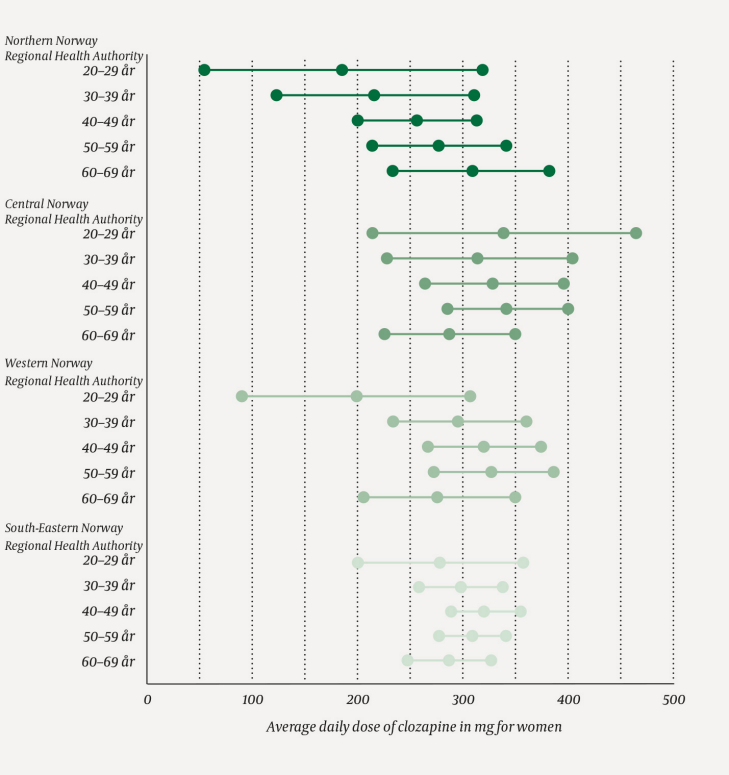

Figure 3a *Average daily dose of clozapine for women in different age groups in regional health authorities. The mid-point and horizontal line show the prescribing rate and the 95 % confidence interval respectively. The age group 20–24 years is not included because of missing data from the Norwegian Prescription Database.*

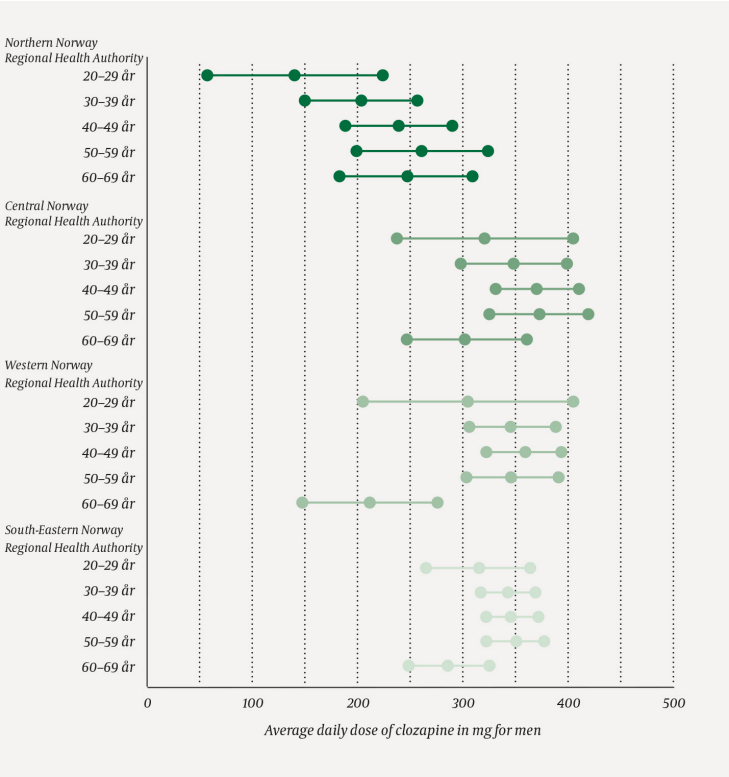

Figure 3b *Average daily dose of clozapine for men in different age groups in regional health authorities. The mid-point and horizontal line show the prescribing rate and the 95 % confidence interval respectively. The age group 20–24 years is not included because of missing data from the Norwegian Prescription Database.*

The prescribing rates per 100 000 inhabitants for antipsychotic drugs as a group were for Northern Norway Regional Health Authority 1 746 (95 % CI 1 709–1 783), Central Norway Regional Health Authority 1 814 (95 % CI 1 783–1 845), Western Norway Regional Health Authority 1 959 (95 % CI 1 933–1 985) and South-Eastern Norway Regional Health Authority 2 319 (95 % CI 2 302–2 336). Clozapine accounted for a small proportion of the prescribing of antipsychotic drugs as a group: 4.2 % in Northern Norway Regional Health Authority; 3.3 % in Central Norway Regional Health Authority; 2.4 % in Western Norway Regional Health Authority: and 1.9 % in South-Eastern Norway Regional Health Authority.

Discussion

This study describes geographical variations in prescribing practices for clozapine in Norway in terms of the prescribing rate, average doses and the sexes and age groups for which this drug is most frequently used.

DIFFERENCES BETWEEN NORWEGIAN COUNTIES

In 2016, clozapine was prescribed nearly twice as frequently in Nordland, Sør-Trøndelag and Troms counties as in Oslo and Akershus county. A possible explanation for these differences could be variations in prevalence of the diagnosis of schizophrenia. Having reviewed data from the Norwegian Patient Registry, however, we cannot find any significant correlation between the prescribing rates for clozapine and the proportion of the population followed up by the specialist health services for the diagnosis of schizophrenia. A number of previous studies have shown an elevated risk of schizophrenia among people resident in urban areas, when compared to rural areas (7, 17). We nevertheless find that the Oslo county stands out in having a low prescribing rate for clozapine. Possible explanations could be that the average patient with schizophrenia in Oslo has a better treatment response to other antipsychotic drugs or has less severe symptoms, and thus is not prescribed with clozapine.

The topic of geographical variations in treatment response has been little explored. In a Danish registry study, the authors found that the prevalence of treatment resistance was

lower in urban areas (18), but it is unclear whether this is a matter of genuine differences in illness, or whether other factors, such as treatment practices, play a role. Whether patients with schizophrenia in Oslo have a higher prevalence of co-morbid addiction disorders when compared to other Norwegian regions is also a matter for speculation. An unstable lifestyle with little opportunity for follow-up with regular blood sampling might be a reason to preclude the choice of this drug. Finally, relative underuse, in the sense that the drug is used more rarely in Oslo than in other counties even though all patient-related characteristics are identical, may explain our findings.

DIFFERENCES BETWEEN REGIONAL HEALTH AUTHORITIES

Northern Norway Regional Health Authority differed from the other regional health authorities in several respects. They had by far the highest prescribing rate for clozapine, and prescribed it more frequently to younger patients and in smaller average doses when compared to the other regional health authorities. These figures are in apparent contradiction to the observation that Northern Norway Regional Health Authority has the lowest prescribing rate for antipsychotic drugs as a group.

One possible interpretation of these figures is that Northern Norway Regional Health Authority more frequently initiates the recommended drug-based therapy for treatment-resistant schizophrenia (clozapine) at an earlier stage and thus needs smaller doses, and secondary to this has a lower total use of antipsychotic drugs. It is important to emphasise, however, that no conclusions regarding treatment quality can be drawn on the basis of observational registry studies such as this one. Other possible explanations for the low average doses in Northern Norway Regional Health Authority could be that combination therapies involving multiple antipsychotic drugs are used more frequently, or that clozapine is used for other indications (for example Parkinson's disease, for which considerably smaller doses are recommended (19)). The low total prescribing rate of antipsychotic drugs as a group and the relatively low prescribing rate and large average dose of clozapine to the oldest patient groups in Northern Norway Regional Health Authority run counter to these explanations.

Figures from the regional health authorities show that the prescribing of clozapine reaches its peak later for women than for men. This could possibly be explained by the later debut of schizophrenia among women compared to men (20). Furthermore, the figures show that women are prescribed with clozapine more rarely than men. One explanation for this could be that schizophrenia in general (8), and possibly also treatment resistance (20), occur more rarely in women than in men. Determining whether these sex differences reflect a practice of prescribing clozapine more rarely to women, even when an indication of treatment-resistant schizophrenia has been established, will be an important topic for further research.

Geographical differences in the prescribing of clozapine have also been described in other countries (9, 21). The authors of these articles point to local variations in treatment practices as a key cause. Variations in psychiatrists' attitude to and knowledge about clozapine are likely to be an important element of this explanation (22). In light of the fact that clozapine is prescribed more rarely (9, 10, 21) and later (12) in the course of illness than what is recommended, one interpretation of the geographical differences shown in this study is that a proportion of the patients with treatment-resistant schizophrenia are not provided with optimal drug-based therapy.

Future research should seek to clarify the extent to which clinicians possess sufficient knowledge about clozapine to make this drug a real alternative for patients with treatment-resistant schizophrenia. A more consistent practice can be achieved by increasing the focus on identification of and interventions against treatment-resistant schizophrenia in the training of mental healthcare personnel.

STRENGTHS AND WEAKNESSES

The strength of this study is that the analyses have been undertaken on complete national data on clozapine dispensed from pharmacies. This comprehensive material has enabled comparisons not only between regions, but also between sexes and age groups. It is a weakness that prescribing in hospitals, where treatment with clozapine tends to be initiated (21), is not included in the data. We cannot exclude the possibility that clozapine is more often tried out in outpatient settings in counties where patients need to travel long distances. If so, the data from the Norwegian Prescription Database will overestimate the relative prescribing in counties where the hospitals are far apart. Moreover, our data reveal no information regarding the indications for prescribing clozapine, combination therapy with other antipsychotic drugs or whether the drug has been used as prescribed. Another key point is that clozapine is also used for other chronic psychoses such as delusional disorder (F22.0) and schizoaffective disorder (F25.0), as well as psychosis associated with Parkinson's disease. We chose to retrieve data for the proportion of patients with the diagnosis of schizophrenia in different regions and did not include the other diagnostic groups.

Conclusion

The Norwegian national guidelines recommend clozapine to patients with schizophrenia after two failed treatment attempts with other antipsychotic drugs. In this study we found differences by county in the prescribing of clozapine that cannot be explained by variations in the proportion of the population that receives treatment for the diagnosis of schizophrenia. Patients with treatment-resistant schizophrenia tend to have serious illness trajectories, and local guidelines need to ensure that the patients are offered the recommended drug-based treatment.

MAIN FINDINGS

Prescribing practices for clozapine vary considerably between different counties

Oslo, Akershus and Rogaland counties have a lower prescribing rate than the national average

Nordland, Troms and Sør-Trøndelag counties stand out in having a higher prescribing rate

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