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RESEARCH ARTICLE

Clozapine treatment and discontinuation in Iceland: A national longitudinal study using electronic patient records

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ABSTRACT

Background: Clozapine is the only drug approved for treatment-resistant schizophrenia. There is evidence that clozapine is underutilized. **Aims**: To evaluate the initiation and discontinuation of clozapine at Landspitali University Hospital in Iceland and the prevalence of antipsychotic polypharmacy in clozapine-treated patients. **Methods**: The study is a part of an ongoing longitudinal study of schizophrenia in Iceland. We identified 201 patients on clozapine or who have been on clozapine by using a keyword search in the electronic health records and by reviewing their medical records. **Results**: Mean age at first treatment with clozapine was 37.8 years. Mean follow-up period on clozapine was 11 years. After 20 years of treatment 71.2% of patients were still on clozapine. After one year of treatment 84.4% of patients were still receiving clozapine treatment. We estimate that 11.4% of patients with schizophrenia in Iceland are taking clozapine and that 16% have been treated with clozapine at some point. Polypharmacy is common, since nearly 2/3, 65.6%, of patients taking clozapine use at least one other antipsychotic and 16.9% are also receiving depot injections. **Conclusions**: We need to increase the awareness of psychiatrists in Iceland with regard to treatment with clozapine, since only about half of the estimated population of patients with treatment-resistant schizophrenia in Iceland have ever been treated with clozapine. Nearly two thirds of patients who are prescribed clozapine in Iceland remain on it long-term.

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Around 20–30% of patients with schizophrenia prove to be treatment-resistant, and clozapine has been demonstrated to be the drug of choice to offer those patients (1). Treatment resistance has been defined as failure to respond to two or more antipsychotics (one of which should be an atypical) when given at an adequate dose for at least 6–8 weeks (2,3). Clozapine has also been found to be superior to other antipsychotic medications for non-treatment-resistant schizophrenia in a meta-analysis (4). In addition to having an indication for treatment-resistant schizophrenia, clozapine also has FDA approval for the prevention of recurrent suicidal behaviour, its effectiveness in this indication having been demonstrated in the international suicide prevention trial (InterSePT) (5).

There is evidence that clozapine remains underutilized despite being the only drug approved for treatment-resistant schizophrenia (6,7). Clozapine use in schizophrenia varies widely between countries: from being as high as 26.9% (8) in Taiwan, 26.7% in China (8), 15.2% in Australia (9), 10.1% in Denmark (10), to as low as 4.4% in the USA (11). It is not well understood why clozapine appears underutilized in some countries despite the strong evidence for its efficacy in treatment-resistant schizophrenia. Possible explanations include the strict haematological monitoring requirements and the potential for rare but potentially serious side effects such as agranulocytosis, myocarditis and seizures, and more common ones such as weight gain and type 2 diabetes mellitus.

Clozapine has been established as a cost effective treatment for treatment-resistant schizophrenia. Patients on clozapine have reduced frequency of hospital admissions (12). Schizophrenia is a disorder known in all settings and cultures. The prevalence of schizophrenia is more geographically varied than previously assumed, but it is estimated that 7 individuals per 1000 will be affected, but gender, urbanity, latitude and migration have been shown to influence incidence rates (13,14).

Aims of the study

The aim of the study is to describe clozapine treatment of patients with schizophrenia in Iceland; specifically to describe the proportion of patients taking clozapine, the pattern of discontinuation over time and the frequency of antipsychotic polypharmacy in patients treated with clozapine.

Materials and methods

Landspitali University Hospital (LUH) started to use electronic health records (EHR) in 1998, but older records are available

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on paper. Subsequently the proportion of medical, psychology and nursing data in EHR has been steadily growing and currently includes almost all patient data in the hospital.

This study constitutes a part of an ongoing longitudinal study in the LUH department of psychiatry focusing on patients with schizophrenia and bipolar disorder. Patients have been recruited to the study in several waves from 1986–2014. The majority of inpatients and outpatients at LUH with schizophrenia or bipolar disorder have been approached to take part in the study. Most of the patients were recruited between the years 2000 and 2004. In this study we looked at patients from the LUH study who were alive on 1 January 2003 and had a confirmed diagnosis of schizophrenia according to the Schedule for Affective Disorder and Schizophrenia – Lifetime version (SADS-L) (15). In total 611 patients met the inclusion criteria.

LUH is the only tertiary hospital for mental health services in Iceland and it also provides secondary psychiatric services and inpatient beds in psychiatry for over 90% of the Icelandic population. Therefore the overwhelming majority of Icelandic patients with treatment-resistant schizophrenia who have ever been on clozapine have been in regular or temporary contact with the mental health services or other services of LUH.

To identify patients that have used clozapine we used a keyword search in the EHR for the text "clozapin", "closapin" and "Leponex". The "e" at the end of clozapin was omitted because of possible spelling errors in the EHR, but a keyword search of "clozapin" will find "clozapin" and "clozapine". "closapin" with an "s" was also used in the keyword search. Leponex was the only brand name of clozapine in Iceland until May 2014 when the generic "Clozapine Actavis" was introduced to the market. All medical notes with the clozapine keywords were reviewed to assess whether clozapine had been used. For patients who had insufficient documentation of prior psychiatric illness and medical use in the EHR the paper medical records were reviewed for clozapine use. The time period of clozapine use was documented. We identified 201 patients with schizophrenia and 23 patients with bipolar disorder who had used clozapine.

Information on the first period of clozapine treatment for patients with schizophrenia was available for 195 patients out of 201. We had the exact date of clozapine initiation for 167 patients. For 28 patients it was not possible to set an exact date for the initiation of clozapine treatment but from medical records it was possible estimate the time from a couple of weeks to a couple of months. Of those 28 patients, 24 patients started clozapine before 1998 which is when LUH started using EHR.

When assessing the proportion of patients continuing on clozapine we used a Kaplan–Meyer survival analysis. If a patient had tried clozapine, then stopped clozapine and then restarted then the start of clozapine treatment was defined from the last start of clozapine treatment. Patients who died during follow-up or were still taking clozapine at the end of follow-up were censored from time of death or end of follow-up.

In the "ever discontinued clozapine" analyses we examined the time from the first treatment with clozapine until the patient discontinued clozapine treatment regardless of whether they later restarted clozapine treatment.

When analysing concomitant medication use while patients were taking clozapine we considered the last known medication regime stated in the medical notes before the end of follow-up or the date that the patient discontinued. It may take up to 6 months of clozapine treatment to observe full improvement in positive symptoms (11). Dosing adjustment of clozapine therefore can take even longer so patients had to have been on clozapine for at least 1 year to be included. There was no minimum dose of clozapine so patients using low doses of clozapine were also included. In total we had detailed medication information for 154 patients with schizophrenia and 145 out of them used 100 mg of clozapine or more.

We used the mean clozapine dose prescribed in the cohort and the total clozapine sales in 2013 to estimate how many patients with schizophrenia in Iceland had used clozapine that year, assuming that the use of clozapine for disorders other than schizophrenia and bipolar disorder was negligible.

Data used to assess antipsychotic drug use in Iceland in 2013 was collected from the Icelandic Medicines Agency.

The study was reviewed and approved by the Icelandic National Bioethics Committee (FS-02-041(03–030)) and the Data Protection Authority (2009090737þS).

Results

Age at first treatment with clozapine

The mean age at first treatment with clozapine was 37.8 years (SD 12.2), 36.5 years (SD 12.5) for men and 41.0 years (SD 11) for women. On average men started clozapine treatment 4.5 years earlier than women ($p = 0.008$).

Figure 1 describes the age of patients when clozapine treatment was first started. The mean was 37.8 (SD 12.2) with a range of 16.4–69.6 years.

The mean follow-up time on clozapine was 11.1 (SD 9) years for men and 10.9 (SD 8.5) years for women.

Discontinuation of clozapine

Figure 2 is a Kaplan–Meier survival graph that displays the proportion of patients that were on clozapine for the first 20 years of treatment. After 1 year of treatment 84.4% of patients were still on clozapine and after 2 years 81.8% of patients were still on clozapine. After a 20-year follow-up 71.2% of patients were still on clozapine, 71.5% of the men and 70.1% of the women.

We also estimated with a Kaplan–Meier survival estimate the proportion of patients who had ever discontinued clozapine treatment after the first start of clozapine treatment with a Kaplan – Meier survival estimate. One year after the first start of clozapine treatment 17.6% of patients had discontinued clozapine treatment, and 2 years after the start of clozapine treatment 22.7% of patients had discontinued clozapine treatment. Eighteen patients restarted clozapine treatment after having discontinued clozapine use and 14 of them were still on clozapine at the end of follow-up or when they died.

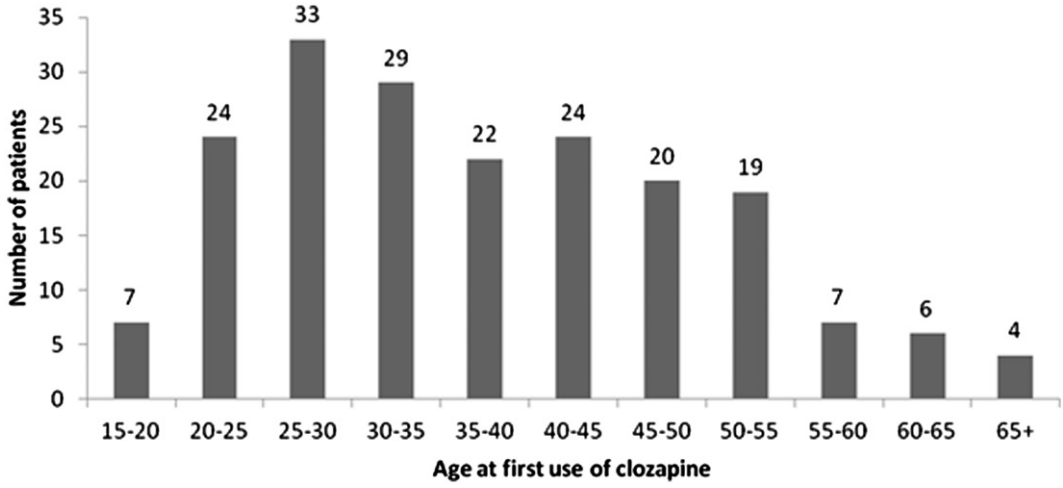

Figure 1. Age of patients when clozapine treatment was first used (n = 195).

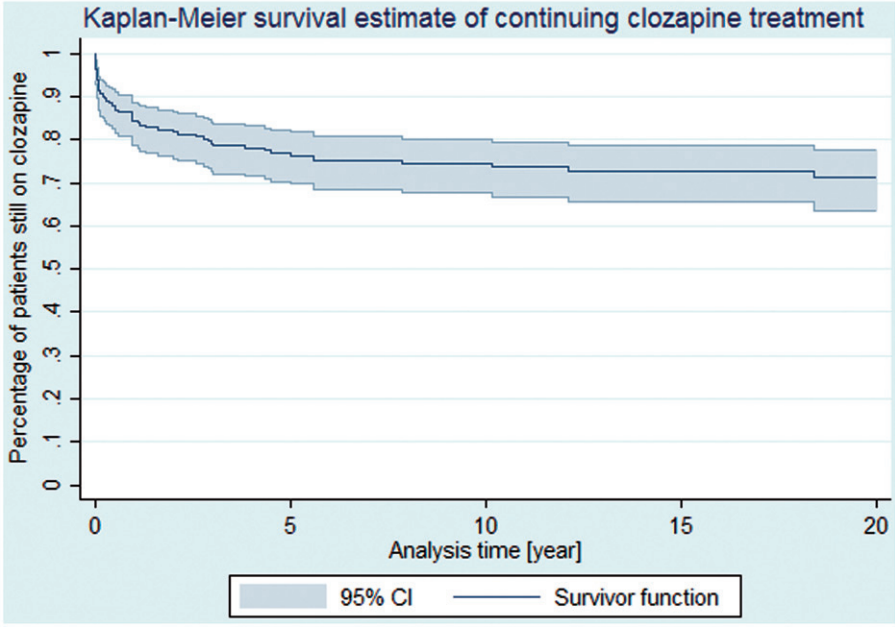

Figure 2. Proportion of patients who stay on clozapine after the latest start of clozapine treatment (n = 201).

Most patients who come off clozapine do so early on. In the first 6 months 33 patients out of those 68 who ever discontinued it (48.5%) came off clozapine, three had died and one was censored because of a follow-up time of less than 1 year. Two years after the first start of clozapine treatment 49 patients had stopped clozapine treatment (72% of total discontinuation), four had died and two were censored. Clozapine discontinuation did continue to occur at a slower rate though during subsequent years of treatment.

Clozapine dosing and concomitant treatments

The mean dose of clozapine was 304.6 mg (SD 172 mg) and the median dose was 262.5 mg, range 25–800 mg.

Table 1 describes polypharmacy in the cohort. About a third of the patients received clozapine as their only antipsychotic. About two thirds of patients (65.5%) were prescribed more than one antipsychotic. The average World Health Organization defined daily dose (DDD) of antipsychotics was 1.67 in the cohort (16). As the number of regular antipsychotic drugs increased, the DDD also increased. The average DDD: antipsychotic usage for patients whose sole antipsychotic was clozapine was 1.01. For patients on four or more antipsychotics the average DDD: antipsychotic usage was 3.01.

Table 1. Antipsychotic polypharmacy (N = 154).

Daily antipsychotic use	N	%	Mean DDD
Clozapine only	53	34.4	1.01
Clozapine plus one additional antipsychotic	70	45.5	1.79
Clozapine plus two additional antipsychotics	23	14.9	2.37
Clozapine plus three additional antipsychotics	8	5.2	3.01
			1.67

DDD, defined daily dose by the World Health Organization.

When analysing polypharmacy in the cohort we found 16 different antipsychotic drugs used with clozapine. Chlorpromazine was the most commonly used antipsychotic in oral preparations in addition to clozapine treatment, with 16 patients (10.4%) receiving chlorpromazine with clozapine.

Table 2. Depot injection used for patients on clozapine (N = 154).

	n	%	Mean daily dose* (mg)	DDD (mg)
Perphenazine	10	6.5	7.3	7
Risperidone	9	5.8	3.4	2.7
Zuclopenthixol	4	2.6	14.3	15
Flupentixol	3	1.9	1.9	4
Olanzapine	1	0.6	21.4	10
	26**	16.9		

*Mean daily dose is the depot injection dose divided by the number of days between injections. DDD, defined daily dose by the World Health Organization.

Table 2 describes the depot injections used with clozapine; 6.5% of all patients receiving clozapine also received perphenazine depot injections and 5.8% received risperidone depot injections. In total there were 26 patients out of 154 (16.9%) that received depot antipsychotics alongside their clozapine tablets. **One patient received two depot injections with clozapine.

Regular use of benzodiazepine drugs (anatomical therapeutic chemical codes NO3AE** and N05BA**) was common in the cohort but 69 patients out of 154 (44.8%) used them daily. The average age of patients on benzodiazepine drugs was 53.8 years and the average age for patients not using benzodiazepine drugs daily was 50.0 years. Clonazepam was the most commonly used benzodiazepine; 45 patients out of 154 (29.2%) used it daily. Antidepressants use was also common with 74 patients out of 154 (48.1%) using antidepressants daily, sertraline being the most common antidepressant (16.2%).

Antipsychotic sales in Iceland

Table 3 describes antipsychotic sales figures in Iceland in 2013. Clozapine was the fifth most common antipsychotic in Iceland with 224 DDD: sold per day and a market share of 6.2%.

The average clozapine dose in the group of patients with schizophrenia was 304.6 mg. There were 23 patients out of 224 (10.3%) with SADS-L confirmed bipolar disorder who had used clozapine. The average dose of clozapine for those with bipolar disorder was 215.8 mg (SD 150) and the median dose was 200 mg, range 50–500 mg.

We estimated that patients with schizophrenia used 92.7% of the clozapine prescribed, and patients with bipolar disorder used around 7.3% of total clozapine sold (23/224) × (215.8 mg/304.6 mg). The total population in Iceland at the end of 2013 was 325,671 and the population aged 15 years and older was 255,391 (17). We used the prevalence of schizophrenia as 0.7% (13,14) and extrapolated that for the population 15 years and older we could estimate that there were 1,788 (0.7% × 255.391) patients with schizophrenia in Iceland in 2013. Total mg of clozapine sold in 2013 in Iceland was 24,524,967 mg. We estimated that the total amount of clozapine sold for schizophrenia was 22,734,644 mg (92.7% × 24,524,967 mg). Dividing the total amount of clozapine sold with the mean dose used in schizophrenia in Iceland gave us an estimated number of total patients using clozapine in 2013 as 204 (22,734,644)/(304.6 × 365 days). We know that 71.2% of patients stay on clozapine so using that percentage we estimated the number of patients with schizophrenia that had ever used clozapine in 2013 to be 287 (204/71.2%). We therefore estimated the proportion of patients with schizophrenia in Iceland using clozapine in 2013 to be 11.4% (204/1.788) and the proportion of patients with schizophrenia that have ever used clozapine to be 16% (204)/(1.788 × 71.2%).

Table 3. Antipsychotics sold in Iceland in 2013.

Drug name	DDD (mg)	Total DDD in 2013	Total DDD/day	Proportion of total sales (%)
Quetiapine	400	339.981	931	26.0
Olanzapine	10	325.269	891	24.9
Risperidone	5	159.052	436	12.2
Aripiprazole	15	95.152	261	7.3
Clozapine	**300**	**81.750**	**224**	**6.2**
Perphenazine	30	72.593	199	5.5
Other antipsychotics	–	241.672	662	17.9
			3604	

DDD, defined daily dose by the World Health Organization.

Discussion

The proportion of patients that remained on clozapine during 20 years of follow-up in the study proved to be very high, or 71.2%. In view of the multiple side effects of clozapine, this high proportion appears to indicate that clozapine is an effective drug for patients with treatment-resistant schizophrenia in our cohort. The high proportion may also reflect to a degree the fact that there are no other available drugs indicated for treatment-resistant schizophrenia. One year after starting clozapine treatment 84.4% of patients remained on clozapine, which is higher than in a study by Essock et al. where 74% of patients were still taking clozapine after 1 year of treatment (18). Two years after starting treatment the proportion still taking clozapine was 81.8% which is higher than in the study by Essock et al. where it was 66%. In a naturalistic Chinese study which compared the discontinuation rate of clozapine to other antipsychotics 1 year after starting treatment in early stage schizophrenia, 62.3% of patients remained on clozapine (19). We can only speculate why the proportion is even higher in Iceland. This may be the result of several factors: most patients start on clozapine as inpatients, the mean dose of clozapine is fairly low, it is often prescribed only in the evening to reduce daytime sedation, blood monitoring is less stringent than in some countries such as the UK and the USA, and finally, continuity of care is probably overall more common than in larger societies.

In the clozapine phase of the CATIE trial the time to discontinuation was significantly longer for clozapine than for other antipsychotics. Despite the treatment resistance requirement and the multiple side effects many patients experience on clozapine treatment, patients with schizophrenia tend to stay on it longer than on other antipsychotics (20).

The mean clozapine dose of 304 mg a day used in our sample is a similar to the average dose of 284 mg in Europe as reported by Fleischhacker and colleagues (21). The same study reported a higher mean clozapine dose in the USA of 444 mg daily. In a recent study by Nielsen and colleagues the mean clozapine dose in a Danish cohort was reported to be 382 mg (10). In a small Swedish cohort (n = 33) the clozapine

dose was recently reported to be somewhat higher at 460 mg, and closer to doses seen in the USA (22).

Polypharmacy was common in our cohort, with 65.6% of patients using clozapine and at least one another antipsychotic, which was about the same percentage as recently reported in the Danish cohort, 64.2% (10). There is, though, little evidence to support such widespread antipsychotic polypharmacy in schizophrenia treatment, as was observed in the cohort (23).

The proportion of patients defined as treatment-resistant has been estimated in the range of 20–30% (1). We estimate that 16% of all patients with schizophrenia in Iceland have at some point been treated with clozapine. This is somewhat lower than the estimated proportion of patients with treatment-resistant schizophrenia. This suggests that psychiatrists need to be more alert in considering clozapine as an option and address issues that might contribute to the low use of clozapine.

Clinicians might overestimate the risk benefit ratio of agranulocytosis and associated mortality versus the benefits of treatment. Even though clozapine can very rarely cause fatal agranulocytosis it has been shown that clozapine use reduces total mortality of patients with schizophrenia (24) and reduces the risk of suicide attempts (5). The risk of agranulocytosis is estimated to be around 0.68% (25). Mortality in agranulocytosis has been estimated to be about 2.7–3.1% and therefore the absolute mortality of patients on clozapine because of agranulocytosis is very low at around 0.02% (25,26). Life expectancy in schizophrenia is reported to be reduced by 22.5–25 years, which is about 40% of their total adult years, due to poor physical health and a high suicide rate (27). If we set the low risk of mortality due to agranulocytosis in the context of increased survival by those on clozapine and that living with schizophrenia reduces adult years by about 40%, then the absolute mortality rate of 0.02% or one in 5000 due to agranulocytosis seems clinically insignificant. We can also compare the mortality for agranulocytosis to dying in an automobile accident in Iceland. The average number of people dying annually in an automobile accident in Iceland in 1995–2014 was 16.3 (28). The mean population in Iceland in the years 1995–2014 was 296,004 (17). The risk of dying in an automobile accident over a 40-year period is estimated to be 0.22% ($1-[(1-16.3/296{,}004)^{40}]$). We therefore estimate that it is 10 times more likely that a patient with schizophrenia who is taking clozapine dies in an automobile accident in adulthood than from agranulocytosis. Neutrophil monitoring for patients on clozapine has not been shown to be cost effective, which reflects the very low mortality of agranulocytosis (29). In light of the above we recommend that the risk of agranulocytosis should not be the main or the only decisive factor when clinicians assess whether patients with treatment-resistant schizophrenia are offered commencement of clozapine treatment.

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