Adverse drug reactions of antipsychotic drug treatment

How to balance evidence and values in relation to the use of clozapine in treatment-resistant schizophrenia

Oddur Ingimarsson

Thesis for the degree of Philosophiae Doctor

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Aukaverkanir geðrofslyfja

Gögn og gildi til að varða bestu leiðir til notkunar clozapine í geðklofa sem svarar illa meðferð

Oddur Ingimarsson

Ritgerð til doktorsgráðu

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Ágrip

Bakgrunnur: Geðklofi er langvinnur alvarlegur geðsjúkdómur með algengi nálægt 0,7%. Fyrstu einkenni geðklofa koma oftast fram seint á unglingsárum eða á þrítugsaldri, en þeim mun fyrr sem sjúkdómurinn kemur fram eru horfurnar að jafnaði verri. Einkennaróf geðklofa er margþætt og birtingarform veikindanna getur því verið talsvert mismunandi milli einstaklinga. Tvær helstu víddir sjúkdómsins eru svokölluð jákvæð einkenni og neikvæð einkenni (brottfallseinkenni). Algengustu jákvæðu einkennin eru: ofskynjanir og þá einkum ofheyrnir, ranghugmyndir, truflun á hugsun og aðsóknarkennd. Algengustu neikvæðu einkennin eru: félagsleg einangrun, skert persónuhirða, minni áhugahvöt, innsæisleysi og skert tilfinningaleg viðbrögð. Nú eru þekktir yfir 100 breytileikar í erfðamenginu sem auka líkur á geðklofa og samband erfða og svipgerðar því afar flókið. Talið er að umhverfisþættir komi auk þess við sögu í tilurð geðklofa, ekki síst regluleg notkun unglinga á kannabisefnum. Samfélagslegur kostnaður vegna geðklofa er hár þar sem sjúkdómurinn veldur mjög oft örorku ungs fólks. Sjúklingar með geðklofa lifa að meðaltali 22,5-25 árum skemur en aðrir. Helstu ástæður þess eru óheilbrigður lífstíll (flestir reykja, lítil hreyfing, óheilbrigt mataræði og notkun vímugjafa), hjarta og æðasjúkdómar og loks sjálfsvíg. Um 20-30% sjúklinga svara ekki hefðbundinni meðferð með geðrofslyfjum og eru þeir sagðir vera með meðferðarþráan geðklofa. Eina meðferðin sem hefur sannað sig sem gagnreynd meðferð hjá þeim hópi er geðrofslyfið clozapín, en oft er það notað frekar seint í sjúkdómsferlinu vegna margvíslega aukaverkana, sem sumar hverjar geta verið lífshættulegar. Mun fleiri sjúklingar með meðferðarþráan geðklofa falla þó fyrir eigin hendi en látast vegna þessara sjaldgæfu aukaverkana, en clozapín er það lyf sem helst minnkar líkur á sjálfsvígum og dregur úr dánartíðni í þessum hópi. Þrátt fyrir það eru margir læknar ragir við að bjóða sjúklingum meðferðina og hlutfall sjúklinga sem fær að reyna clozapín meðferð vegna meðferðarþrás geðklofa er hvarvetna mun lægra en 20-30%. Clozapín er ekki til sem forðalyf í sprautuformi. Það takmarkar notagildi þess í tilfellum þar sem sjúklingar hafa mjög skert innsæi eða ráða illa við að taka töflur daglega.

Markmið: Að rannsaka notkun clozapíns hér á landi í meðferð geðklofa og alvarlegar aukaverkanir geðrofslyfja með áherslu á clozapín. Skoða kyrningafæð (neutropenia) og tengingu hennar við algjöra kyrningafæð (agranulocytosis) og bera saman tíðnina hjá sjúklingum á clozapín og þeim sem hafa aldrei farið á clozapín. Einnig á að kanna tíðni sykursýki og blóðfituröskunar og bera saman við almennt íslenskt þýði. Síðast en ekki síst að þróa frekar gagnreynda og gildismiðaða meðferð og sameiginlega ákvarðanatöku í langtíma meðferð meðferðarþrás geðklofa.

Aðferð: Þýðið í rannsókninni samanstóð af sjúklingum sem hafa tekið þátt í geðrofsrannsókn LSH og Íslenskrar erfðagreiningar. Sjúklingum var safnað í rannsóknina á árunum 1986-2014. Samtals voru upplýsingar um 611 sjúklinga notaðar í rannsókninni. Til að finna sjúklinga sem höfðu notað geðrofslyfið clozapín var leitað að rafrænum skjölum í sjúkraskrá Landspítala sem bentu til clozapín notkunar. Þau skjöl voru lesin til að meta hvort hægt væri að staðfesta clozapín notkun. Til að finna upplýsingar um aukaverkanir var framkvæmd rafræn leit í sjúkraskrám auk þess sem aðgangur fékkst að blóðprufugagnagrunni Landspítala. Tölfræðiúrvinnsla var gerð í STATA.

Niðurstöður: Í grein I er fjallað um notkun clozapíns á Íslandi. Tvöhundruð og einn sjúklingur hafði fengið meðferð með clozapíni. Meðalaldur við upphaf clozapíns notkunar reyndist 37,8 ár á tímabilinu. Um 71,2% sjúklinga sem hófu meðferð með clozapíni voru enn á clozapín meðferð 20 árum síðar. Við áætluðum að 11,4% sjúklinga með geðklofa á Íslandi væru að taka clozapín og 16% þeirra hefðu einhvern tíma reynt meðferð með lyfinu. Fjöllyfjanotkun geðrofslyfja var algeng samhliða clozapín meðferð þar sem tveir af hverjum þremur sjúklingum eða 65,6% notuðu önnur geðrofslyf samhliða meðferð með clozapíni. Grein II fjallar um kyrningafæð og algjöra kyrningafæð. Eftir fyrstu 18 vikurnar á clozapín meðferð þá var miðgildi milli mælinga á kyrningum 124 dagar. Kyrningafæð greindist hjá 34 sjúklingum af 188 á clozapín meðferð en oftast var um að ræða væga kyrningafæð (kyrningar milli 1500-1900/mm^3) eða hjá 24 sjúklingum. Einu ári eftir kyrningarfæð voru 28 af 34 sjúklingum ennþá á clozapíni. Enginn munur kom fram á tíðni alvarlegrar kyrningafæðar (kyrningar á bilinu 0-1400/mm^3) hjá sjúklingum á clozapíni og sjúklingum með geðklofa

sem höfðu aldrei farið á clozapín meðferð. Í grein III kemur fram að konur sem hafa tekið clozapín voru 4,4 sinnum líklegri en konur í almennu þýði til að hafa greinst með sykursýki týpu 2. Karlar á clozapín meðferð voru 2,3 sinnum líklegri til að hafa greinst með sykursýki týpu 2 en karlar í almennu þýði. Þríglýseríð voru einnig hærri bæði hjá þeim sem höfðu tekið clozapín og hjá sjúklingum með geðklofa sem höfðu aldrei tekið clozapín samanborið við almennt þýði. Eitt tilfelli af ketónblóðsýringu greindist hjá sjúklingi með sykursýki af týpu 1.

Ályktanir: Hærra hlutfall sjúklinga með meðferðarþráan geðklofa á Íslandi og í öðrum löndum ætti að eiga þess kost að reyna meðferð með clozapíni. Stór hluti af kyrningafæð sem kemur fram hjá sjúklingum á clozapín meðferð stafar líklega ekki af lyfinu. Því þarf að ígrunda vel ákvarðanir um að hætta clozapín meðferð einstaklinga með meðferðarþráan geðklofa á grundvelli miðlungs alvarlegrar kyrningafæðar hafi meðferð skilað góðum árangri og þar sem þá er almennt ekki önnur meðferð með sambærilega virkni í boði. Læknar þurfa að vera vel vakandi fyrir efnaskiptavillu af völdum clozapíns og þá sérstaklega sykursýki týpu 2 hjá konum.

Lykilorð: Geðklofi, clozapín, sykursýki, kyrningafæð, blóðfituröskun, gildismiðuð meðferð.

Abstract

Background: Schizophrenia is a chronic serious mental disorder with prevalence close to 0.7%. Early symptoms of schizophrenia generally appear in late adolescence or the early twenties. The prognosis is usually worse in cases of early onset. The symptomatology of schizophrenia is complex and can vary a lot between individuals. The two main symptom dimensions are referred to as positive symptoms and negative symptoms. The most common positive symptoms are: hallucinations, particularly auditory hallucinations, delusions, disturbances of thought and persecutory ideation. The most common negative symptoms are: lack of social interest, loss of personal hygiene, reduced motivation, loss of insight and blunting of affect. Over 100 variants are now known in the genome that increase the risk of schizophrenia and the genetic pathogenesis is therefore very complex. Environmental risk factors are believed to play a role in the pathogenesis of schizophrenia, especially cannabis use in adolescence. The socioeconomic cost of schizophrenia is very high because the disease often causes disability among young sufferers. Patients with schizophrenia have a reduced life expectancy of 22.5-25 years. The main reasons are unhealthy lifestyle (most patients smoke, take little exercise, use alcohol or illicit substances and are on a poor diet), cardiovascular disease and suicide. About 20-30% of patients do not respond to conventional antipsychotic treatment and are said to have treatment-resistant schizophrenia (TRS). The only approved treatment that has proven to be efficacious in TRS and been shown to improve overall mortality as well as reduce suicide attempts and probably the odds of suicide is the antipsychotic clozapine. Despite this clozapine is often used rather late in the disease course, most probably due to many side effects and some rare adverse drug reactions (ADR) which can be life-threatening for a very small proportion of TRS patients. A much greater number of patients with TRS lose years of life because they commit suicide or die prematurely due to an unhealthy lifestyle than those who pass away as a result of these rare ADRs. Despite this the proportion of TRS patients with

schizophrenia that have ever had clozapine prescribed is much less than the expected 20-30% in most countries. Fewer still remain on the treatment long term for various reasons. Clozapine is not available in a depot injectable preparation and that limits its effectiveness in the treatment of patients with lack of insight or who have difficulty in taking tablets daily.

Objective: To study the use of clozapine in the treatment of schizophrenia in Iceland and to assess serious side effects of antipsychotics, focusing on clozapine. Assess neutropenia and the progression to agranulocytosis and compare the prevalence for patients on clozapine versus those that have never been on clozapine. Examine the proportion of patients who had developed diabetes or dyslipidemia and compare it to a standard Icelandic population. Finally, to contribute to Evidence-Based as well as Value-Based Practice and shared decision-making in the often challenging treatment and long term care of patients with TRS.

Method: The study population consisted of patients who had participated in an ongoing joint research project of Landspitali University Hospital and deCODE genetics on psychotic disorders. Patients were recruited to the study between 1986-2014. A total of 611 patients with schizophrenia took part in the study. Patients' health records were searched electronically to identify patients who had used clozapine. The health records were then reviewed to confirm use of clozapine. Patients´ health records were searched electronically to seek information on side effects and ADRs as well as the blood test database at Landspitali. Statistical analyses were performed using STATA.

Results: The use of clozapine in Iceland is described in paper I. Two hundred and one patients took clozapine at some point during the study. The mean age at the start of clozapine use was 37.8 years. Some 71.2% of patients who began treatment with clozapine remained on clozapine treatment 20 years later. It was estimated that 11.4% of patients with schizophrenia in Iceland were using clozapine and that 16% had ever tried clozapine treatment. Antipsychotic polypharmacy was common since two out of every three patients, 65.6%, also used other antipsychotics alongside treatment with clozapine. Paper II focuses on neutropenia and agranulocytosis in the course of treatment of TRS with

clozapine versus other antipsychotics. After the first 18 weeks of clozapine treatment the median number of days between neutrophil measurements was 124 days. Neutropenia was observed in 34 patients out of 188 on clozapine and of those 24 developed mild neutropenia (granulocytes between 1500-1900/mm^3). One year after the neutropenia 28 patients out of 34 were still on clozapine. No difference was observed in the proportion of patients who developed moderate to severe neutropenia (granulocytes in the range 0-1400/mm^3) between patients on clozapine versus TRS patients who had never been on clozapine. In paper III it was presented that women on clozapine were 4.4 times more likely to have been diagnosed with type 2 diabetes (T2D) than women in the general population. Males on clozapine were 2.3 times more likely to have been diagnosed with T2D than males in the general population. Triglycerides were higher both among those with schizophrenia who had been on clozapine as well as among patients with schizophrenia who had never received clozapine compared to the general population. One case of ketoacidosis was identified in a patient with type 1 diabetes.

Conclusions: More patients with TRS in Iceland and other countries should get the opportunity to be offered treatment with clozapine. A large proportion of neutropenia developing during clozapine treatment is probably not caused by clozapine. If clozapine treatment proves to be effective a decision to stop clozapine should only be taken following careful consideration of all possible options in cases of moderate neutropenia, because there are usually no other alternative treatment options available that offer comparable effectiveness available. Doctors must be well aware of the risk of metabolic syndrome during clozapine treatment, especially the high risk of T2D developing in women.

Keywords: Schizophrenia, clozapine, diabetes, neutropenia, dyslipidemia, value-based practice.

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Many people have contributed to this thesis and I would like to thank them all. Some people deserve special thanks for their help in making this thesis possible and for them I express my greatest appreciation and gratitude. Most of all I want to thank my supervisor and instructor, Professor Engilbert Sigurðsson for introducing me to research and for guiding me back to medicine and psychiatry after I had side-stepped into both banking and software development for several years. Without him this thesis would not have been possible.

I'm also very grateful to my co-authors and co-supervisors James H. MacCabe, Magnús Haraldsson and Halldóra Jónsdóttir for their guidance and help with the manuscripts. I'm very grateful for the help from my co-supervisor Hreinn Stefánsson even though our work on the polygenetic risk factors did not find its way into the thesis due to small sample sizes but hopefully we can complete and publish that work in the near future.

I would like to thank my family for their patience and especially my wife, Soffía Sigríður Valgarðsdóttir, and my parents, Ingimar Jóhannsson and Lillý Valgerður Oddsdóttir, for their support over the years.

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I am grateful to my employer, Landspitali, The National University Hospital, for providing me with facilities to conduct the study and also for supporting me with a grant from the Landspitali Research Fund to complete the last steps of this long but stimulating journey. Finally, I would also like to thank María Einisdóttir, executive director of mental health services of Landspitali, The National University Hospital, for her ongoing support during this work.

Contents

List of abbreviations

ADR	Adverse drug reaction
ATP-III	Adult Treatment Panel III
BEN	Benign Ethnic Neutropenia
CI	Confidence Interval
DDD	World Health Organizations Defined Daily Dose
EBP	Evidence-Based Practice
EHR	Electronic Health Records
FDA	US Food and Drug Administration
FGA	First Generation Antipsychotics
HbA1c	Hemoglobin A1c
HDL	High Density Lipoprotein
ICD	International Classification of diseases
LDL	Low Density Lipoprotein
LUH	Landspitali University Hospital
SD	Standard Deviation
SE	Standard Error
SGA	Second Generation Antipsychotics
T1D	Type 1 Diabetes
T2D	Type 2 Diabetes
TRS	Treatment-Resistant Schizophrenia
US/USA	United States of America
VBP	Value-Based Practice
WHO	World Health Organization

List of figures

List of tables

List of original papers

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals (I-III).

I. Oddur Ingimarsson, James H. MacCabe, Magnús Haraldsson, Halldóra Jónsdóttir & Engilbert Sigurdsson (2016). Clozapine treatment and discontinuation in Iceland: A national longitudinal study using electronic patient records. Nordic Journal of Psychiatry, 70:6,450-455, DOI: 10.3109/08039488.2016.1155234

II. Oddur Ingimarsson, James H. MacCabe, Magnús Haraldsson, Halldóra Jónsdóttir & Engilbert Sigurdsson (2016). Neutropenia and agranulocytosis during treatment of schizophrenia with clozapine versus other antipsychotics: an observational study in Iceland. BMC Psychiatry, DOI: 10.1186/s12888-016-1167-0

III. Oddur Ingimarsson, James H. MacCabe, Magnús Haraldsson, Halldóra Jónsdóttir & Engilbert Sigurdsson (2017). Risk of diabetes and dyslipidemia during clozapine and other antipsychotic drug treatment of schizophrenia in Iceland. Nordic Journal of Psychiatry, 71:7,492-502, DOI: 10.1080/08039488.2017.1334821

In addition, some unpublished data may be presented.

Declaration of contribution

I started working on the CRESTAR project in January 2012. This thesis is based on the research work that followed alongside my specialist training and clinical work in psychiatry over the ensuing 6 years.

The studies and protocols were designed and written for the studies by me and Engilbert Sigurðsson.

Those involved in the data collection for all the studies were I, Engilbert Sigurðsson, Halldóra Jónsdóttir and Magnús Haraldsson. I collected most of the data, parts of it with the aid of others, and set up the database used in all three studies. I performed the statistical analyses following discussions with Engilbert Sigurdsson, James MacCabe and Ubaldo Benitez Hernandez. I collected the results from the studies and developed the conclusions with support from the members of the doctoral committee but mostly following discussions with my supervisor, Engilbert Sigurðsson.

I wrote the first draft of all manuscripts and the thesis and amended these drafts following revision by members of the doctoral committee. I, James H. MacCabe and Engilbert Sigurðsson managed the literature searches and analyses.

Hreinn Stefánsson and colleagues at deCODE genetics undertook the polygenetic risk score analyses with data collected by me, but the samples proved to be too small for a meaningful interpretation. However, we plan to continue working on the genetic data and hopefully it will lead to a publication in the near future.

All authors of the three papers approved the final version of the manuscripts before publication. All members of the doctoral committee reviewed and approved the final draft of the doctoral thesis but I take full responsibility for the final conclusions and any errors which may remain therein

1 Introduction

Schizophrenia is most commonly a chronic and disabling mental disorder that usually has a major impact on patient's quality of life, their vocational prospects, social function and life expectancy. Most patients develop symptoms that modulate their interpretation of reality and adversely affect their interactions with others, often resulting in social isolation. In 1896 Emil Kraepelin described the disorder and called it dementia praecox. The term schizophrenia was first used in 1908 by Eugen Bleuler (Fusar-Poli & Politi, 2008).

1.1 Symptoms and diagnosis

The cardinal symptoms of schizophrenia are usually divided into positive symptoms and negative symptoms. Positive symptoms are new or added features that the patient did not experience before developing the illness, while negative symptoms are behaviors or abilities that the patient has lost or that have deteriorated in the wake of the disorder developing. The symptom dimensions vary between individuals and often fluctuate over time. The most common positive symptoms are: auditory hallucinations, most often hearing voices (74%), ideas of reference (70%), delusions of reference (67%), suspiciousness (66%), flatness of affect (66%), delusional mood (64%), delusions of persecution (64%), thought alienation (52%) and thoughts spoken aloud (50%) (WHO, 1973). Lack of insight is almost always present to some degree (97%), a feature which is associated with suboptimal adherence to treatment (WHO, 1973). The negative symptoms, which often precede the positive symptoms, include: social withdrawal, self-neglect, loss of motivation and initiative, emotional blunting and paucity of speech (WHO, 1973).

In Europe and most other countries worldwide schizophrenia is diagnosed using the International Classification of Diseases (ICD) classification system developed by World Health Organization (WHO). The 10th version of the ICD has been in use since 1994. Schizophrenia is often not diagnosed at the time

when typical full blown symptoms emerge for the first time. In the UK, for example, the mean time-lag of untreated psychoses (the time between full symptoms emergence and starting antipsychotic treatment) has been reported to be around one to two years (Boydell et al., 2004). This can adversely affect prognosis since it has been shown that the length of time of untreated psychosis is associated with worse outcome (Boonstra et al., 2012). In low income countries the time-lag and treatment gap is much larger since it has been estimated that treatment is not available for up to 89% of patients in some developing countries (Lora et al., 2012).

1.2 The incidence and prevalence of schizophrenia

Schizophrenia is observed in all countries and cultures. The reported incidence of the disorder varies between studies but is usually reported in the range of 7.7-43 per 100.000 persons per year (McGrath et al., 2008). The prevalence estimates of schizophrenia also show a great deal of variance with the median being 7.2 per 1000 persons (Saha et al., 2005). The relatively high prevalence compared to the low incidence reflects the fact that schizophrenia usually starts in adolescence or early adult life and most often becomes chronic (Saha et al., 2005). Study designs of prevalence vary with regards to age. While some studies estimate the prevalence among subjects older than 15 years others estimate the prevalence in the whole population (Messias et al., 2007). Men are affected more often than women but the male-female incidence risk ratios to develop schizophrenia has been estimated to be 1.42 in a large meta-analysis (Aleman et al., 2003). Men also have an earlier onset of symptoms, on average 1.49 years earlier than women (Eranti et al., 2013).

As with many disorders the incidence of schizophrenia is affected both by environmental and genetic factors. Schizophrenia does, however, not have a Mendelian inheritance pattern. Currently it is apparent that both multiple common genetic variants where each has a small effect as well as more rare variants, each of large effect, contribute to this risk (Owen et al., 2010). A large collaborative international study published in Nature in 2014, reported that 108 independent loci were associated with schizophrenia. Environmental factors

that have been associated with schizophrenia include substance abuse, especially regular cannabis use among adolescents and young adults (Andréasson et al., 1987; Manrique-Garcia et al., 2012). Cannabis use has also been linked to earlier onset of psychosis (Large et al., 2011). Daily tobacco use has also more recently been associated with an increased risk of psychosis and an earlier age at onset of psychotic illness in a South-London population (Gurillo et al., 2015). Other risk factors include being born in the winter or in the spring (Davies et al., 2003; Torrey et al., 1997), high paternal age (Malaspina et al., 2001; Wohl & Gorwood, 2007), obstetric complications (Cannon et al., 2002) and urban birth and living (Krabbendam & van Os, 2005).

1.3 Social cost

The social burden of schizophrenia is very high. In England the cost was estimated to be 11.8 billion pounds annually in 2011. That equates to an average annual cost per person with schizophrenia of 60,000 pounds per year which equals approximately 8 million Icelandic krona (Andrew et al., 2012). The early onset of schizophrenia is a major reason for the high social cost of the disease but the main factors influencing such estimates are loss of productivity, health care costs, institutional costs and unpaid care (Andrew et al., 2012). Schizophrenia accounts for 1.1% of the total disability adjusted life years worldwide and 2.8% of the years lived with disability worldwide (Jablensky, 2000). A Danish study reported that 65% of patients with schizophrenia received disability pension (Nielsen et al., 2011).

1.4 Life expectancy

Life expectancy has been reported to be 22.5-25 years lower in patients with schizophrenia than in the general population due to relatively poor physical health and a high suicide rate (Tiihonen et al., 2009). For patients with schizophrenia antipsychotic medication use is associated with higher life expectancy even though most antipsychotics have well established side effects, including metabolic side effects that can increase the risk of cardiovascular disease (Tiihonen et al., 2009). Clozapine has been reported to have more metabolic side effects than other antipsychotics (Newcomer, 2005).

Interestingly, there is evidence that clozapine reduces the risk of repeated self-harm and suicide as well as overall mortality compared to other antipsychotics (Hennen & Baldessarini, 2005; Tiihonen et al., 2009; Wimberley et al., 2017).

1.5 Pharmacological treatment

Pharmacological treatment of schizophrenia consists of antipsychotic medications that are traditionally divided into first and second generation antipsychotics (SGAs), the latter are also referred to as atypical antipsychotics. The SGAs are atypical in the sense that they are less likely than FGA to give rise to extrapyramidal side effects. The SGAs on the other hand are more prone to cause metabolic side effects (Citrome & Volavka, 2005). The first antipsychotic medication for schizophrenia was chlorpromazine, discovered in 1952, and clozapine was the first SGA, discovered in 1958 (Crilly, 2007). Leucht et al. (2013) compared the efficacy and tolerability of 15 antipsychotic medications and showed that clozapine had the highest effect size of 0.88. Amisulpride, olanzapine and risperidone also stood out as relatively efficacious antipsychotics in this comparison.

1.6 The background of clozapine

Clozapine was first discovered in 1958 by Wander AG, a Swiss pharmaceutical company (Crilly, 2007). Clozapine differed from other antipsychotics at the time by its low risk of extrapyramidal side effects. Its road to the market was long and winded as many believed that extrapyramidal side effects were an indicator of antipsychotic efficacy. Clozapine was marketed in Europe, Austria and Switzerland in 1972 under the brand name “Leponex” and a few years later in most other European countries, including Iceland. Studies in the US were underway when in 1975 it was reported that 8 patients treated with Leponex in Finland had died because of agranulocytosis (Idänpään-Heikkilä et al., 1975). After that influential report, clozapine was withdrawn from the Finnish market and from several other European markets. It was never withdrawn in Iceland but used very cautiously in the wake of the Finnish report. Most studies of clozapine were halted in due course by the manufacturer, Sandoz. In countries where the use of clozapine continued it became apparent over the ensuing

years, that its effect in the treatment of schizophrenia was considerable and that it was effective also for the most resistant, most difficult to treat patients who had not responded to conventional antipsychotics. In 1982 Sandoz decided to reassess the withdrawal of the medication. It was introduced to the US market in 1990 following the publication of a pivotal study by Kane et al. (1988) using the brand name “Clozaril”. It has been available since then in the US and most European countries, but under very strict demands for blood-monitoring (Nielsen et al., 2016).

1.7 Clozapine and treatment resistant schizophrenia (TRS)

Around 20-30% of patients with schizophrenia do not respond to antipsychotic treatment where two or more such trials fail to lead to an adequate response. These patients are referred to as having TRS (Meltzer, 1997; Picchioni & Murray, 2007). One of the antipsychotics tried should have been an atypical and the medication should have been taken in an adequate dose for at least six to eight weeks (Lehman et al., 2004; Suzuki et al., 2012). In the seminal study of Kane et al. (1988) the 268 participants had not responded to at least three previous first generation antipsychotics (FGA) which included haloperidol for 6 weeks. In the study clozapine was compared with chlorpromazine and around 30% of those receiving clozapine responded as opposed to 4% of those on chlorpromazine. A recent meta-analysis reported that around 40% of patients with TRS respond to clozapine and its advantage over other antipsychotics is rather associated with reduction of positive symptoms than negative symptoms (Siskind et al., 2017). Patients with TRS treated with clozapine are observed to have decreased hospitalization, lower direct and indirect costs, fewer suicide attempts and increased life expectancy (Land et al., 2017; Wimberley et al., 2017). Males are less likely than females to respond to treatment (Robinson et al., 1999). Early onset of schizophrenia has been associated with TRS and poor outcomes (Meltzer et al., 1997). Clozapine has been found to be the medication of choice for patients with TRS and is the only licensed treatment for these patients (Kane et al., 1988; Picchioni & Murray, 2007). Studies have also shown that clozapine is a cost-effective treatment for TRS and that it reduces the frequency and length of hospital admissions (Hayhurst et al., 2002; Land et al., 2017).

Despite clozapine being the recommended treatment after two failed attempts of antipsychotic treatment, it is seldom the third medication of choice in real world practice. A study by Young et al. (2003) reported that patients treated with clozapine had used on average 5.5 different antipsychotics before commencing clozapine treatment. So even though clozapine is the only medication approved in the treatment of TRS there is evidence that it remains underutilized globally (Himanshu & David, 2011; Manuel et al., 2012). There are major geographical differences in clozapine use in the treatment of schizophrenia with high usage in Taiwan, where it has been reported to be used for 26.9% of patients and for 26.7% in China (Xiang et al., 2011). The use in Australia has been reported to be 15.2%, in Denmark 10.1% and in the USA only 4.4% (Conley et al., 2005; Meltzer, 2012; Nielsen et al., 2012). A large international study on clozapine use in 17 countries in 2017 gives similar results when clozapine use is estimated in TRS assuming a prevalence of schizophrenia of 0.7% and that all clozapine is used in the treatment of schizophrenia (Bachmann et al., 2017). Using those assumptions clozapine use in schizophrenia ranged from 0.13% in Japan, 11.2% in Iceland and highest 24.7%, in Finland with the unweighted overall average being 9.2% in these 17 countries.

Clozapine has other indications than TRS and it has been approved by the Food and Drug Administration (FDA) for prevention of recurrent suicidal behavior but its effectiveness for this indication was demonstrated in the international suicide prevention trial (InterSePT) (Meltzer et al., 2003). Clozapine still remains only available as oral medication in most countries but in the Netherlands it is available as an intramuscular injection (Nielsen et al., 2016). One of the reasons for it not being available as a depot medication is the fact that clozapine can cause agranulocytosis. If agranulocytosis develops and is diagnosed in a blood sample treatment must be stopped without delay.

1.8 Clozapine side effects

Clozapine has many known side effects (Nair & MacCabe, 2014). Almost every patient feels sedated when clozapine therapy is initiated. The sedation usually

improves somewhat with time and can be minimized by slowly increasing the dose. Clozapine lowers the threshold for seizures but the risk is dependent on plasma concentration and it is recommended to use an anticonvulsant when the blood level exceeds 0.5 mg/l or at a dose greater than 600 mg/day (Nair & MacCabe, 2014). Myoclonus, a brief involuntary twitching of muscles, can also occur (Nair & MacCabe, 2014). The gastrointestinal side effects include hypersalivation that is usually most prominent at night, nausea, especially for the first 6 weeks, and constipation, a frequently overlooked side effect which is approximately three times more common on clozapine than on other antipsychotics (Shirazi et al., 2016). Cardiovascular side effects include hypotension and hypertension, especially when clozapine treatment is being initiated. Tachycardia is common and usually benign but can be a harbinger of more serious side effects such as myocarditis and cardiomyopathy (Nair & MacCabe, 2014). Metabolic side effects, neutropenia and agranulocytosis are covered in a separate section. Other side effects include fever, nocturnal enuresis, worsening OCD symptoms and blurring of vision (Nair & MacCabe, 2014).

1.8.1 Neutropenia and agranulocytosis

Doctors, including some experienced psychiatrists, are often reluctant to prescribe clozapine, despite patients having met criteria for TRS (Tungaraza & Farooq, 2015). One reason might be the high burden of side effects that can be troublesome but others may be reluctant to prescribe it due to rare but potentially life-threatening adverse reactions developing like agranulocytosis. The risk of patients with TRS dying due to a low neutrophil count is though probably much lower than initially feared in the 1970s following the influential report from Finland (Idänpään-Heikkilä et al., 1975). The report described the deaths of the 8 Finnish patients that had been treated with clozapine, who developed agranulocytosis and died as a result. This report and drug monitoring that followed in due course is the root cause to the current stringent licensing system in the US and the UK where patients need to have blood taken and have their neutrophils measured very regularly in order to get clozapine dispensed in these two countries. Patients who do not adhere to the strict

neutrophil monitoring requirements in the UK, i.e. weekly for the first 18 weeks, fortnightly for the next 34 weeks, and monthly in due course, cannot get clozapine dispensed even though it is deemed to be essential for their successful treatment (Dixon & Dada, 2014). In Iceland the recommended blood monitoring is once weekly for the first 18 weeks and then once a month (Lyfjastofnun, 2014).

Most guidelines state that clozapine treatment should be stopped when neutrophils drop below 1500/mm^3 (Nielsen et al., 2016). This criterion for stopping clozapine treatment does not apply to people of certain ethnic groups. Yemenite Jews and 25-50% of black Africans commonly have an intrinsic low neutrophil count, counts in the range of 1000/mm^3 to 1500/mm^3, without any observed adverse clinical effects such as more frequent bacterial infections. These individuals are said to have benign ethnic neutropenia (BEN) (Rajagopal, 2005). It can be difficult to follow this recommendation for patients where clozapine is the only medication they have responded to and which has made a major impact on their quality of life. This reality was acknowledged in October 2015 when the FDA adjusted the requirement to stop clozapine treatment when neutrophils drop below 1500/mm^3 (FDA, 2015). Prescribers in USA can accordingly now continue to use clozapine in the general population until neutrophils fall below 1000/mm^3 and even until the number of 500/mm^3 is observed for patients with BEN (FDA, 2015). Prescribers can also continue to prescribe clozapine when neutrophils drop below 1000/mm^3 if in their judgement they believe that the benefits of continuing clozapine treatment outweigh the risk of severe neutropenia (FDA, 2015).

The risk of agranulocytosis during clozapine treatment has been estimated to be close to 0.7% but the risk is greatest during the first year when about 90% of cases are diagnosed (Munro et al., 1999; P. Schulte, 2006). Agranulocytosis is a life-threatening condition where the mortality is close to 3% (Alvir et al., 1993; Lahdelma & Appelberg, 2012). That translates into an absolute mortality of agranulocytosis during clozapine treatment as close to 0.02% or 2 patients dying from this adverse drug reaction (ADR) out of every 10.000 patients receiving the treatment (Alvir et al., 1993; Lahdelma & Appelberg, 2012). There

are other medications that are associated with an increased risk of agranulocytosis where such a strict WBC monitoring system has though not been made mandatory. Among these are dapsone with an observed agranulocytosis risk of 0.24-0.42% (Hörnsten et al., 1990), the widely used antipsychotic chlorpromazine with a risk of 0.13% (Flanagan & Dunk, 2008) and sulfasalazine with a risk of at least 0.06% (Keisu & Ekman, 1992). Ticlopidine is an antiplatelet medication in the thienopyridine family (FDA, 2001). Today its use has largely been taken over by clopidogrel which is associated with a lower hematologic risk. The risk of agranulocytosis for ticlopidine is rather similar to clozapine or 0.8%, most of it occurring in the first 2-3 months of treatment (FDA, 2001). The FDA recommends that patients on ticlopidine should have neutrophil measurements done every two weeks during the first three months of treatment. Neutrophil monitoring after the first three months is only indicated in patients with clinical symptoms or laboratory signs of hematological adverse reactions (FDA, 2001). Several mood stabilizers are also known to increase the risk for leucopenia (Flanagan & Dunk, 2008) while lithium increases the measured number of neutrophils in circulation (Focosi et al., 2009). It is not at all apparent why the FDA-recommended monitoring for clozapine is so much stricter than e.g. for ticlodipine, and in particular why the FDA has recommended that the time frame of monitoring the neutrophil count long-term is so widely divergent for ticlodipine and clozapine, 3 months versus lifelong monitoring, respectively. It has been estimated that 80% of cases of agranulocytosis occur in the first 5 months of treatment. Therefore, the risk of dying from agranulocytosis drops to 0.004% (0.7% x 3% x 20%) after the first 5 months of treatment (Alvir et al., 1993; Lahdelma & Appelberg, 2012; Schulte, 2006).

It is conceivable that the low mortality from agranulocytosis may in some way stem from the intensive blood monitoring, but enforcing strictly demands such as the “no blood, no drug” policy of the FDA places limitations on clozapine use in many ways (FDA, 2015; Honigfeld et al., 1998). Firstly, patients living in areas where a functioning clozapine monitoring system is not in place may be excluded from receiving the best treatment available for TRS,

in fact the only treatment for that indication. Secondly, it can make some doctors reluctant to prescribe clozapine. Thirdly the monitoring can be time consuming and even relatively costly for the patients most of whom are poor, either on disability benefits or modest incomes. Last, but not least, it can lead to unnecessary discontinuation of clozapine treatment if neutrophil counts fall below 1500/mm^3. These hurdles reduce the chance of most TRS patients being treated with clozapine for patients in most countries, although such treatment happens to be the only evidence-based treatment that exists for patients in great need.

It would be most useful if a simple pharmacogenetic test was available with adequate predictive validity to predict which patients are likely to develop agranulocytosis on clozapine treatment but such a test does not exist and would moreover present ethical challenges (Spencer et al., 2013; Verbelen & Lewis, 2015). Therefore, the small but well established risk of agranulocytosis is still managed in most countries with mandatory blood monitoring during treatment (Nielsen et al., 2016).

1.8.2 Metabolic side effects

It has been widely reported that the SGAs can increase the risk of metabolic syndrome, a syndrome that includes obesity, type 2 diabetes (T2D) and dyslipidemia (Newcomer, 2005). In a study by Mitchell et al. (2013) the proportion of schizophrenia patients taking clozapine who had developed metabolic syndrome was 51.9% but 32.5% for patients taking other antipsychotics. An Icelandic study showed that the prevalence of metabolic syndrome was 14% in the general Icelandic population compared to 57% among patients with schizophrenia (Sveinsson et al., 2012). In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study it was reported that 54.2% of females with schizophrenia, who had an average age of 43.7 years, had developed metabolic syndrome while it was less common in males, 36.6% (McEvoy et al., 2005). The male patients were younger, their average age being 39.2 years.

Most antipsychotics can cause weight gain but the risk varies from one medication to another, olanzapine and clozapine having the highest associated risk for weight gain (Newcomer, 2005). Risperidone and quetiapine are associated with an intermediate risk and ziprasidone, aripiprazole and amisulpride with the lowest reported risk for weight gain (Newcomer, 2005). Obesity is a well-known risk factor for T2D and it is the main modifiable risk factor since 80% of patients are overweight at the diagnosis of T2D (Haslam & James, 2005). Females may be at a higher risk for antipsychotic induced weight gain (Seeman, 2009). Genetic variants of the neuropeptide Y (NPY) receptor, the melanocortin 4 receptor (MC4R), the cannabinoid receptor 1 (CNR1) and the serotonin 2C receptor (HTR2C) have all been reported to be associated with weight gain in patients on antipsychotics (Shams & Müller, 2014). There are also reports that switching from an antipsychotic that has high risk for weight gain to an antipsychotic with lower risk can help patients lose weight in due course (Newcomer et al., 2008).

The SGAs have been shown to be associated with greater risk of T2D developing than FGAs (Smith et al., 2008). Patients with schizophrenia have a high risk of T2D, a study by Henderson et al. (2007) reported that during a 7 year period 18,4% of patients with schizophrenia were diagnosed with diabetes compared with 6,6% in the general hospital population. The risk of T2D varies between SGAs. Ziprasidone and aripiprazole are associated with a lower risk and in some studies the risk of T2D is not increased on such treatment (ADA et al., 2004). For some antipsychotics the risk of T2D has been reported to be dose dependent, this applies to quetiapine, olanzapine and risperidone (Ulcickas Yood et al., 2011).

The risk of ketoacidosis has been estimated to be increased by a factor of 10 for patients with schizophrenia treated with antipsychotics compared to the normal population (Polcwiartek et al., 2016) and case reports of ketoacidosis during clozapine treatment have been published (Nihalani et al., 2007).

Dyslipidemia is characterized by high cholesterol, low levels of high density lipoproteins (HDL), high levels of low density lipoproteins (LDL) and elevated triglycerides (Stone et al., 2014). Clozapine and olanzapine have been

associated with an increase in triglyceride levels and in total cholesterol in patients with schizophrenia (Henderson et al., 2005; Rettenbacher et al., 2006; Wirshing et al., 2002; Wu et al., 2006). They have also been associated with a decrease in HDL-cholesterol (Wirshing et al., 2002). The risk of dyslipidemia is not the same for all antipsychotics but ziprasidone and amisulpride have been reported to have a more benign effect on blood lipid profiles and may therefore be more suitable for patients who have developed the metabolic syndrome or are at risk of developing metabolic syndrome (Rettenbacher et al., 2006).

1.9 Balancing evidence-based practice (EBP) and value-based practice (VBP) in clozapine treatment of TRS

Over the past three decades EBP has become part of routine clinical work in many hospitals and primary health care centers (Sackett et al., 1996). EBP in routine care may at times appear to focus solely on research evidence while it should aim to integrate best research evidence, clinical experience and patients´ values. The National Institute of Clinical Excellence (NICE) guidelines for the UK National Health Service (NHS) indeed state: "...*When exercising their judgement professionals are expected to take this guideline fully into account, alongside the individual needs preferences and values of their patients and service users…"* (NICE, 2014). While there can be disagreements about what constitutes good evidence such issues can often be resolved with meta-analyses and other systematic reviews or debates at meetings and conferences. However, values differ very much from one individual to another, including patients and family members. Doctors and other health professional cannot take for granted that their patients share their values, views and assessment of risk (Fulford, 2011). Values vary so much among subjects because they are based on needs, wishes, concerns, preferences and personality to name a few relevant factors (Fulford, 2011). VBP is guided by law, ethics, decision analysis and health economics as well as research evidence (Fulford, 2011).

It is not well understood why clozapine is not used more widely despite the strong available evidence for its effectiveness in TRS and explanations may

differ between countries, hospitals, departments and doctors. There are many possible and not mutually exclusive explanations including the rare but potentially serious side effects such as agranulocytosis, seizures at high doses, myocarditis, the strict mandatory hematological monitoring requirements in some countries, the high risk of weight gain, metabolic syndrome and T2D as well as the impact of opinion leaders in some countries and hospitals. Other factors include availability of psychiatrists with adequate experience of using clozapine in the treatment of TRS, neutrophil monitoring and inadequate appreciation of clozapine's unique nature by policy makers and payers (Kelly et al.,2017).

As recently as 2015 FDA in the USA enforced new guidelines for treatment with clozapine and subsequently patients who receive the drug must be registered into a specific database, the Clozaril REMS program (FDA, 2015). It remains to be seen how these guidelines will affect the real-life availability, prescribing and use of clozapine for TRS in a country where its usage has for many years been much lower than the estimated prevalence of TRS and lower than in most western European countries (Meltzer, 2012; Sultan et al., 2017).

The issue of clozapine treatment becomes even more complex when we apply Codex Ethicus to our decision-making: "First do no harm". One is then faced with a dilemma, namely, whether we place more value or relevance to a miniscule risk of lethal harm from prescribing a drug than the quantifiably much greater harm of not offering this medication, the one and only evidence-based treatment for TRS to our patients or by stopping it immediately and not offering it again if severe, moderate or even mild neutropenia develops? These complex issues will be discussed and reviewed further in the discussion part of the thesis.

2 Aims

Clozapine is the only drug indicated for treatment resistant schizophrenia and it is underutilized in all European and indeed almost all countries worldwide. Therefore, it is very important to study how commonly clozapine is used in Iceland, its pattern of use and the adverse drug reactions or side effects of clozapine which appear to be the major barriers to treatment. A better understanding can lead to improved treatment of treatment resistant schizophrenia in Iceland and elsewhere.

The main aims of the three papers described in this thesis were:

I. To assess how commonly clozapine is used and its pattern of use in Iceland. Specifically to describe at what age patients start clozapine treatment, what doses are used, what proportion of patients remain on clozapine in the short- and long-term, the proportion of patients with schizophrenia that are being treated and have ever been treated with clozapine and how commonly other antipsychotics are prescribed with clozapine.

II. To describe the prevalence of neutropenia and how often it is observed to progress to agranulocytosis in patients with schizophrenia treated with clozapine. To compare the prevalence of neutropenia in patients with schizophrenia treated with clozapine versus patients never treated with clozapine. Also to describe how frequently neutrophils have been monitored in the course of treatment.

III. To assess the prevalence of diabetes and dyslipidemia in patients with schizophrenia in Iceland. Specifically to examine the risk of type 2 diabetes and dyslipidemia in patients with schizophrenia on clozapine treatment, patients with schizophrenia that have never been on clozapine treatment and compare their risk to age-matched controls from the general Icelandic population.

Last, but not least, the overall aim of the thesis is to use the findings from papers I-III to inform discussions on evidence-based practice and patients´ values with regard to shared decision-making before and during clozapine treatment in treatment-resistant schizophrenia.

3 Materials and methods

Landspitali University Hospital (LUH) started to implement electronic health records (EHR) in 1998. Older medical records are available on paper only. Subsequently the proportion of medical, psychological and nursing data in EHR has been growing steadily and currently includes almost all patient data in the hospital. The thesis is a part of an ongoing longitudinal study in the LUH Department of Psychiatry focusing on patients with schizophrenia and bipolar disorder. The study was approved by the Icelandic National Bioethics Committee (FS-02-041(03-030)) and the Data Protection Authority (2009090737ÞS). STATA, version 13, was used for statistical analyses.

3.1 Study population

The majority of inpatients and outpatients at LUH with schizophrenia were approached and invited to take part in the study. Patients have been recruited into the study in several waves from 1986-2014 but most of the patients were recruited between the years 2000 and 2004. In this thesis the focus is on patients from the LUH study that were alive on 1.1.2003 and had a confirmed diagnosis of schizophrenia according to the "Schedules for Affective Disorder and Schizophrenia-Lifetime version" (SADS-L) (Endicott & Spitzer, 1978). There were 611 patients who met the inclusion criteria.

LUH is the only tertiary hospital for mental health services in Iceland. LUH in fact provides psychiatric services and inpatient beds in psychiatry for over 90% of the Icelandic population. Therefore, the overwhelming majority of patients with TRS in Iceland, who have ever been on clozapine, have been in regular or temporary contact with mental health services or other services of LUH. Figure 1 describes the study cohort in papers I-III whose data were used in the various statistical analyses done in papers I-III.

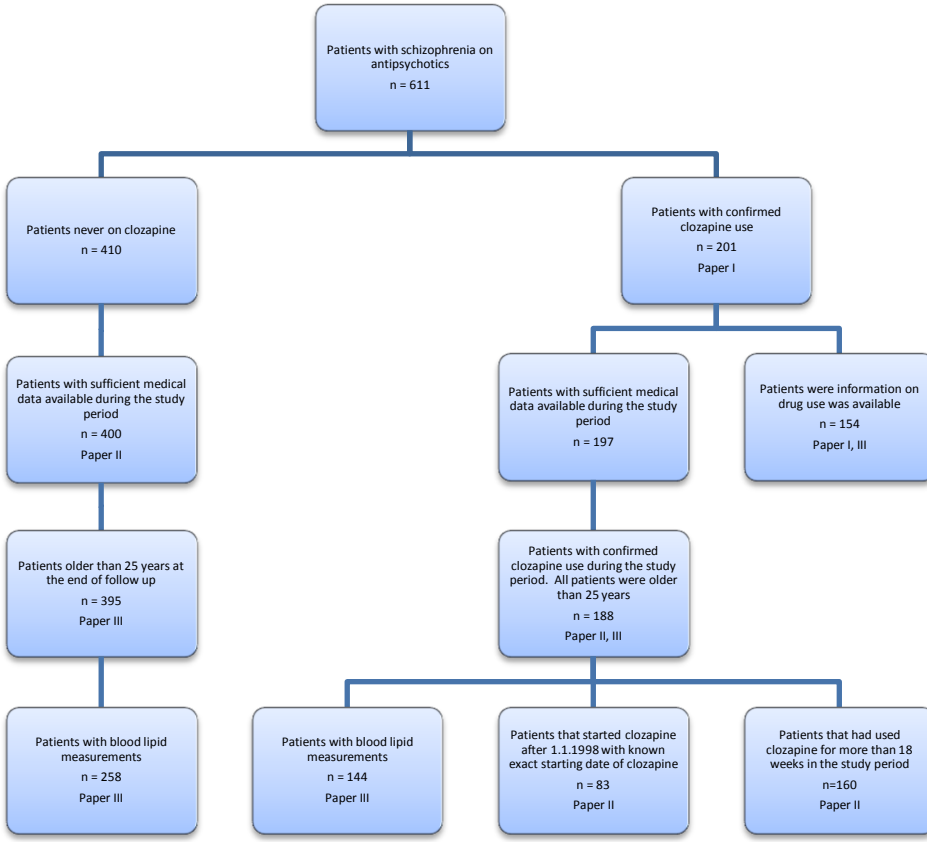

Figure 1 Description of the study cohort.

3.2 Case identification

To identify patients who had used clozapine, a keyword search in the EHR for the text strings “clozapin”, “closapin” and “Leponex” was performed. Leponex was the only brand name of clozapine in Iceland until the generic “Clozapine Actavis” was introduced to the market in May 2014. All patients’ medical notes where the clozapine keywords were identified were reviewed to confirm that clozapine had been used. The medical records on paper were reviewed for clozapine use of patients who had insufficient documentation of prior psychiatric illness and medication use in the EHR. Two hundred and one patients out of

611 patients were identified to have used clozapine with a confirmed diagnosis of schizophrenia. The remaining 410 patients with schizophrenia who had never used clozapine but had been treated with other antipsychotics comprised the comparison group in papers II and III. In paper III the general Icelandic population served as controls for both patient groups.

3.3 Paper I

3.3.1 Clozapine discontinuation

Information on the onset of clozapine treatment was available for 195 patients out of 201 and of these, the exact start date of clozapine treatment was found for 167 patients. It was not possible to set an exact date for the initiation of clozapine treatment for 28 patients but from medical records it was possible to narrow the first day of treatment down to a couple of weeks to a couple of months. Of those 28 patients, 24 initiated clozapine treatment before 1998 which is when LUH started using EHR.

A Kaplan-Meyer survival analysis was used to assess the proportion of patients continuing on clozapine. The onset of clozapine treatment was defined from the last start of clozapine treatment if a patient had tried clozapine, then stopped clozapine and then restarted again. Patients who were still taking clozapine at the end of follow up or died during follow up were censored from time of death or end of follow up. Patients who were still taking clozapine at the end of follow-up or died during follow-up were censored from time of death or end of follow-up. A Kaplan-Meyer estimate was also used to estimate the percentage of patients ever discontinuing clozapine treatment during the first year and first two years of treatment. Patients who died during the first two years of clozapine use and patients who did not have a full two years follow-up of clozapine use were censored from those two time points.

3.3.2 Clozapine use and polypharmacy

Data used to assess all antipsychotic medication use in Iceland in 2013 was collected from the Icelandic Medicines Agency. To estimate how many patients with schizophrenia had used clozapine in 2013, the mean clozapine dose

prescribed in the study cohort and the total clozapine sales in Iceland in 2013 were used assuming that the use of clozapine for other disorders than schizophrenia and bipolar disorder had negligible effect on this mean dose estimate. When analyzing use of other antipsychotics while patients were taking clozapine the last known medication use described in the medical notes before the end of follow-up or the date that the patient discontinued clozapine, was looked up. It may take up to 6 months of clozapine treatment to have full effect in improving positive symptoms (Meltzer, 2012). Dosing adjustment of clozapine therefore can take even longer so patients had to have been on clozapine for at least one year to be included in the polypharmacy analysis. There was no minimum dose of clozapine set for these analyses. Therefore, patients using low doses of clozapine were also included. Detailed medication information was available for 154 patients with schizophrenia and of these 145 were prescribed 100 mg or more of clozapine daily.

3.4 Paper II

3.4.1 Frequency of neutrophil blood monitoring

The frequency of blood measurements for patients treated with clozapine from 1.1.1998 until 21.11.2014 was analyzed. The frequency of blood measurements was calculated by dividing the total time on clozapine treatment by the number of neutrophil measurements. The frequency of blood measurements during the first 18 weeks was analyzed separately from the subsequent time period. Patients restarting clozapine treatment were excluded in the frequency analysis for neutrophil measurements, thus only patients who were using clozapine for the first time were included. Eighteen patients for whom the exact clozapine start date was not known and four patients who did not live in the Reykjavik metropolitan area, where LUH is situated, were excluded from the neutrophil blood monitoring analyzes for the first 18 weeks.

3.4.2 Identification of neutropenia and agranulocytosis

An electronic search was done for all available neutrophil counts at LUH. The LUH database is linked to regional laboratory databases in Iceland using the Icelandic social security number, “kennitala”, which is a unique personal

identifier for each Icelander. One of the databases that is linked to LUH is the database in the regional hospital in Akureyri in northern Iceland, where Iceland's only other department of psychiatry is located in the country´s second largest hospital. That department provides mental health services for the remaining 10% of Iceland's population. A keyword search was done in the EHR with the following keywords to find medical notes where the terms neutropenia or agranulocytosis were used; "Neutropaenia", "neutropenia", "leucopaenia", "leucopenia", "kyrningafæð", "hvítkornafæð". The complete medical notes, electronic as well as on paper, were reviewed in order to confirm the diagnosis of neutropenia and agranulocytosis.

Neutropenia was defined as mild when neutrophil counts were in the range of 1500/mm^3-1900/mm^3. Moderate neutropenia was defined when neutrophil counts were in the range of 1000/mm^3-1400/mm^3 and severe neutropenia was defined when neutrophils were in the range of 500/mm^3-900/mm^3 (TEVA, 2014). Agranulocytosis was defined when neutrophil count fell below 500/mm^3 which literally means the absence of circulating granulocytes (TEVA, 2014). Neutrophil counts in Iceland are rounded to the nearest 100/mm^3.

A Cox proportional hazard model was used to assess which factors were associated with neutropenia. One patient was excluded from the Cox proportional hazards model because he used clozapine only for one day.

3.5 Paper III

3.5.1 Diagnosis of T2D, ketoacidosis and blood lipid disorders

T2D was diagnosed if a patient was confirmed to have any of the following: a) a formal diagnosis of T2D, b) two measurements of fasting plasma glucose over 12.6 mg/l (7.0 mmol/l) or c) hemoglobin A1c (HbA1c) >=6.5% on two separate occasions. The patient's primary physician was contacted if additional blood samples were needed to confirm whether the patient met criteria for T2D or not. Patients were labeled with "high risk of T2D" if the last measurement of HbA1c was in the range 6.0% to 6.4%. Ketoacidosis was diagnosed if a clinical diagnosis of ketoacidosis was confirmed. In accordance with the ATP-III guidelines LDL in the range 160-189mg/dl (4.13-4.89 mmol/l) was defined as

high levels and LDL over 190mg/dl (4.90 mmol/l) as very high levels (Stone et al., 2014). Total cholesterol levels over 200mm/dl (5.17 mmol/l) were defined as high levels. Triglyceride levels between 200-499mg/dl (2.56-5.63 mmol/l) were defined as high levels and triglycerides over 500mg/dl (5.65 mmol/l) as very high levels.

A keyword search in the EHR was performed to identify medical notes where metabolic disorders were mentioned. To find a diagnosis of diabetes an electronic search was done for the key words "diabetes", "*sykursýki*", "metformin", "glucophage" and "T2D". For ketoacidosis the words "ketoacidos" and "ketona" were searched. For dyslipidemia, the blood lipid measurements in the blood measurement database were analyzed. All blood measurements of: Glucose, HbA1c, total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides were collected electronically via the EHR. The latest measurements of blood lipids were used when assessing dyslipidemia. For patients on clozapine the latest blood measurements while the patient was still taking clozapine were used. When analyzing statin medication use while patients were taking clozapine, the last known medication information stated in the medical notes before the end of follow-up or clozapine discontinuation was used.

3.5.2 Statistical analysis

A Cox proportional hazard model was used to assess the association of blood sugar values over 13 mm/l with the following factors: "average time at risk", "clozapine ever used" and "T2D at the end of follow-up". The start of "time at risk" for patients on clozapine was defined as the start of clozapine treatment or the start of the study period if the patients had commenced clozapine treatment before the onset of the study period. The end of "time at risk" was defined as one of the following end points: a) a measurement of blood sugar value over 13 mm/l, b) end of the study period, c) patient died or d) when the patient discontinued clozapine treatment. Time at risk for patients never on clozapine was defined as the start of the study period, until one of the following end points was reached: a) a measurement of blood sugar value over 13 mm/l, b) end of the study period or c) when the patient died. The proportional hazards

assumption in STATA was tested using the estat phtest function.

The prevalence of T2D and blood lipid levels were compared to a control population of Icelanders using data from two separated datasets from the Icelandic National Heart Association; the AGES (Olafsdottir et al., 2009) and the Risk Evaluation For INfarct Estimates (REFINE) datasets. The prevalence of T2D and blood lipid levels were compared for men and women by age ranges of five years from 25 to 90. The prevalence of T2D and blood lipid levels in different age ranges of the Icelandic population group was used to calculate the expected prevalence of T2D and blood lipid levels in patients with schizophrenia both on clozapine and never on clozapine. The Chi-squared test was used to test the significance of the difference between the observed prevalence of T2D and blood lipids in the study cohorts to the expected prevalence from the control population.

4 Results

This chapter summarizes the main results from the three papers.

4.1 Clozapine treatment and discontinuation in Iceland (Paper I)

4.1.1 Clozapine use and discontinuation

In the study cohort clozapine use in Iceland was first documented in 1974. The mean duration of clozapine treatment at the end of follow up was 11.1 years (SD = 9.0) for males and 10.9 years (SD = 8.5) for females. The mean age at the end of follow up was 50.0 years (SD = 11.9) for males and 54.0 years (11.5) for females. The mean age at the start of clozapine treatment was significantly lower (p = 0.008) for males, 36.5 years (SD = 12.5) versus 41 years (SD = 11) for females. Figure 2 displays the starting age of clozapine treatment for males and females in the cohort.

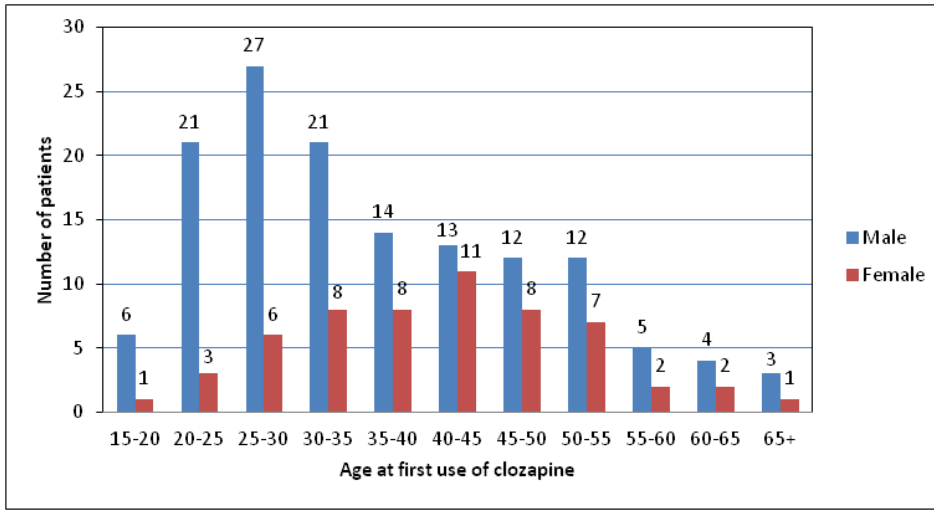

Figure 2 Age range at first use of clozapine.

Figure 3 shows the percentage of patients still taking clozapine at the end of follow-up with a Kaplan-Meier estimate. After the first year 84.4% of patients

were still on clozapine, 81.8% were still on clozapine after the first two years and after 20 years 71.2% of patients were still taking clozapine with no significant gender difference observed (71.5% of males and 70.1% of females).

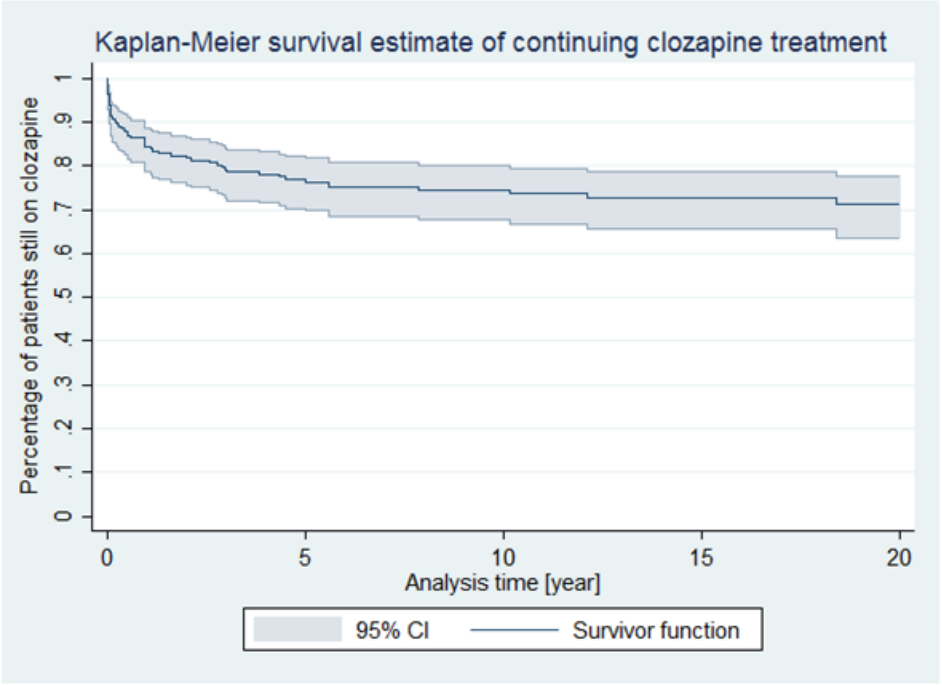

Figure 3 The proportion of patients who stayed on clozapine after their latest start of clozapine treatment (n = 201).

Eighteen patients discontinued clozapine and later restarted clozapine treatment. The percentage of patients who at some point discontinued clozapine treatment during the first two years of treatment was also estimated with a Kaplan-Meier estimate. During the first year 17.6% of patients discontinued clozapine and the proportion rose to 22.7% during the first two years.

4.1.2 Clozapine dose and polypharmacy

The mean dose of clozapine in the cohort was 304.6 mg (SD = 172 mg). There was some variance in clozapine doses as shown in figure 4.3 with a dose range of 25-800 mg. No gender difference was observed in the dose of clozapine, the mean dose being 307.4 mg for females and 303.5 mg for males.

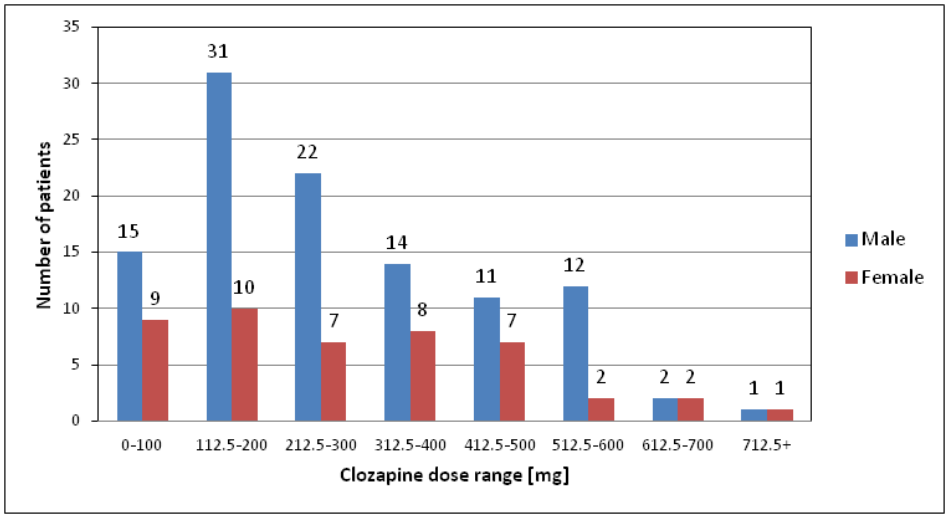

Figure 4 Clozapine dose range.

Polypharmacy was common in the cohort as is shown in table 1. Only one third of patients received clozapine monotherapy. The WHO defined daily dose (DDD) figures for antipsychotics were used to calculate the daily dose of antipsychotic medication (WHO, 2003). The mean DDD was 1.67 and it increased with number of antipsychotics and was highest in patients using clozapine and three additional antipsychotics where it was 3.01. Patients on clozapine monotherapy had the lowest DDD usage, 1.01.

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

Table 2 describes which antipsychotic medications were used orally in addition to clozapine treatment in the cohort. Sixteen different antipsychotics were used with clozapine. Chlorpromazine was the most frequent add on treatment with 10 patients being on chlorpromazine and clozapine. The mean

daily dose of chlorpromazine was 110 mg for these patients, corresponding to 0.37 DDD.

Table 2 Oral antipsychotics used for patients on clozapine (n = 154).

	n	%	Mean dose [mg]	DDD used	DDD [mg]
Chlorpromazine	16	10%	110.0	0.37	300
Amisulpride	14	9%	421.4	1.05	400
Quetiapine	13	8%	282.7	0.71	400
Olanzapine	11	7%	13.0	1.30	10
Aripiprazole	9	6%	13.3	0.89	15
Levomepromazine	8	5%	73.0	0.24	300
Perphenazine	9	6%	21.3	0.71	30
Chlorprothixene	6	4%	67.8	0.23	300
Risperidone	8	5%	2.5	0.50	5
Zuclopenthixol	6	4%	43.3	1.44	30
Flupentixol	5	3%	1.7	0.28	6
Sertindole	2	1%	14.0	0.88	16
Clopenthixol	1	1%	25.0	0.83	30
Haloperidol	1	1%	1.0	0.13	8
Pimozide	1	1%	2.0	0.50	4
Prochlorperazine	1	1%	10.0	0.10	100

Table 3 shows that 26 patients out of 154 (16.9%) were receiving a depot injection along with clozapine treatment. The most commonly used depot injection was perphenazine, 6.5% of the cohort used this medication, an antipsychotic which has remained a popular treatment choice for psychosis in the Nordic countries for decades.

Table 3 Depot injections used for patients on clozapine (n = 154).

	n	%	Mean 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
*One patient was on two depots	*26	16.9%		

4.1.3 Sales of clozapine and other antipsychotics in Iceland and the proportion of patients with schizophrenia on clozapine

Table 4 shows that clozapine was the 5th most sold antipsychotic in Iceland in 2013 with a 6.2% market share of total sold DDD. In our cohort there were 201 patients with schizophrenia that had used clozapine at some point, with a mean clozapine dose of 304.6 mg and 23 patients with bipolar disorder where the mean dose was 215.8 mg.

The estimated clozapine use in schizophrenia was 92.7% ((23/224) x (215.8 mg/304.6 mg) of all clozapine sales. Total sales of clozapine were 24,524,967 mg in 2013 with 92.7% of that being 22,734,664 mg. Using the amount of clozapine sold it was estimated that 204 (22,734,644 mg/(304.6 mg x 365) schizophrenia patients in Iceland were using clozapine daily at the end of 2013. The total population of Iceland was 325,671 and 255,391 were 15 years or older at the end of 2013 (Hagstofan, 2015). The estimated prevalence of schizophrenia is 0.7% (McGrath et al., 2008; Saha et al., 2005). That gives an estimation of 1,788 schizophrenia patients 15 years or older in Iceland in 2013. The percentage of patients with schizophrenia in Iceland using clozapine that year was therefore estimated to be 11.4% (204/1,788). The proportion of patients remaining on clozapine long term was 71.2% in the cohort. It was estimated that 287 (204/71.8%) patients in the cohort had received clozapine treatment and the proportion of schizophrenia patients who had ever used clozapine was 16% (11.4%/71.2%).

Table 4 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%

4.2 Neutropenia and agranulocytosis (Paper II)

4.2.1 Neutrophil blood monitoring

Table 5 shows the frequency of neutrophil monitoring following the initiation of clozapine treatment. During the first 18 weeks of treatment the mean time between neutrophil measurements was 25 days (SD = 28) and the median time was 18 days. After excluding 7 patients for whom no neutrophil measurements where found the calculated mean time between measurements after the first 18 weeks of treatment was 229 days (SD = 329). The median time between measurements was 124 days.

Table 5 Neutrophil monitoring during clozapine treatment.

First 18 weeks (n = 83)	n	%
Weekly	12	14.5
Every 1-2 weeks	22	26.5
Every 2-3 weeks	15	18.1
Every 3-4 weeks	6	7.2
Every 4-5 weeks	6	7.2
Less than every 5 week	22	26.5
After 18 weeks (n = 160)	n	%
Monthly	6	3.8
Every 1-2 months	33	20.6
Every 2-3 months	25	15.0
Every 3-6 months	31	19.4
Every 6-12months	37	21.3
Less than every year	31	20.0

4.2.2 Comparisons of neutropenia in patients ever on clozapine and never on clozapine

Table 6 shows that the combined number of cases of moderate neutropenia, severe neutropenia and agranulocytosis was 10 cases out of 188 (5.3%) patients in the clozapine group and 27 cases of 400 (6.8%) patients in the never-on-clozapine group. All cases of moderate neutropenia in both groups were either 800/mm^3 or 900/mm^3 and there were no cases of neutropenia in the 500-700/mm^3 range. All patients who developed agranulocytosis had medical

co-morbidities that might have contributed to the agranulocytosis. In the clozapine group the only patient with agranulocytosis was 56 years old and developed lymphoma a few years later. In the never-on-clozapine group two patients were on cytotoxic treatment, one patient was receiving interferon treatment because of hepatitis C and a fourth patient suffered from malnutrition, hepatitis C and alcohol abuse.

Table 6 Lowest neutrophil count in the clozapine group and never-on-clozapine group.

	Clozapine		Never-on-clozapine		
Mean age at follow up [Years]	51.2		58.1		
Mean number of neutrophil measurements per patient	32.4		15.8		
Mean time of follow up [Years]	9.2		13.8		
	n	%	n	%	P-value
No neutrophil measurements performed in study period	6	3.2%	8	2.0%	
Never neutropenia, neutrophils 2000/mm^3 or higher	148	78.7%	335	83.8%	0.23
Mild neutropenia, neutrophils 1500-1900/mm^3	24	12.8%	30	7.5%	0.04
Moderate neutropenia, neutrophils 1000-1400/mm^3	8	4.3%	20	5.0%	0.69
Severe neutropenia, neutrophils 500-900/mm^3	1	0.5%	3	0.8%	0.76
Agranulocytosis, neutrophils 0-400/mm^3	1	0.5%	4	1.0%	0.56

Table 7 shows which factors were associated with different severity levels of neutropenia. Clozapine use was at the significance level for mild neutropenia ($p = 0.05$) but otherwise it was not significantly associated with neutropenia in any other severity level that was analyzed. The number of neutrophil measurements was consistently associated with the diagnosis of neutropenia. Lower age and being female were also associated with neutropenia in 3 out of 4 severity levels of neutropenia.

Table 7 Cox proportional hazards model with possible factors associated with detecting moderate to severe neutropenia and agranulocytosis.

	Hazard ratio	SE	Z-score	95% CI	P-value
A. Neutrophils 0-1900/mm^3					
Patient on clozapine	1.33	0.33	1.14	0.81-2.18	0.25
Sex (female)	1.82	0.40	2.76	1.19-2.80	0.01
Mean age at risk	0.97	0.01	-3.75	0.96-0.99	0.001 >
Measurements per year	1.14	0.02	6.32	1.09-1.18	0.001 >
B. Neutrophils 0-1400/mm^3 (equivalent to red result)					
Patient on clozapine	0.74	0.33	-0.68	0.31-1.76	0.50
Sex (female)	2.00	0.67	2.08	1.04-3.88	0.04
Mean age at risk	0.98	0.01	-1.47	0.96-1.00	0.14
Measurements per year	1.17	0.04	4.66	1.10-1.26	0.001 >
C. Neutrophils 1000-1900/mm^3					
Patient on clozapine	1.44	0.37	1.39	0.86-2.40	0.18
Sex (female)	1.76	0.41	2.46	1.12-2.77	0.03
Mean age at risk	0.97	0.01	-3.85	0.95-0.98	0.001 >
Measurements per year	1.13	0.02	5.98	1.09-1.18	0.001 >
D. Neutrophils 1500-1900/mm^3 (equivalent to amber result)					
Patient on clozapine	1.86	0.58	1.99	1.00-3.43	0.05
Sex (female)	1.70	0.49	1.85	0.97-3.00	0.09
Mean age at risk	0.96	0.01	-3.70	0.94-0.98	0.001 >
Measurements per year	1.12	0.03	4.62	1.06-1.17	0.001 >

A) n = 587, 89 cases. B) n = 587, 37 cases. C) n = 587, 80 cases. D) n = 587, 52 cases

4.2.3 Neutropenia progressing to agranulocytosis and its effect on clozapine discontinuation

As shown in table 8 there were 34 cases of neutropenia in the clozapine group. For mild to moderate neutropenia no progression was observed directly to agranulocytosis and 28 of the 32 patients continued using clozapine for at least a year after the neutropenia had developed. There were two patients identified who developed severe neutropenia on clozapine and one of them developed agranulocytosis. Neutropenia did not have much effect on clozapine discontinuation since 87.5% of patients with mild neutropenia were still on clozapine at the end of follow-up as well as 75% of patients with moderate neutropenia. The two patients who developed severe neutropenia and agranulocytosis discontinued clozapine.

Table 8 Progression of lowest neutrophil count to agranulocytosis.

Lowest neutrophil count (excluding counts taken during episode of agranulocytosis)	Amber: Mild neutropenia 1500-1900/mm^3	Red: Moderate neutropenia 1000-1400/mm^3	Severe neutropenia 500-900/mm^3
	n = 24	n = 8	n=2
One year after lowest level of neutrophils			
Still on clozapine	22	6	0
Clozapine discontinued	2	2	1
Developed agranulocytosis (and then discontinued)	0	0	1
Clozapine and agranulocytosis status unknown	0	0	0
Three years after lowest level of neutrophils			
Still on clozapine	18	4	0
Clozapine discontinued	3	2	1
Developed agranulocytosis (and then discontinued)	0	0	1
Clozapine and agranulocytosis status unknown	3	2	0

4.3 Risk of diabetes and dyslipidemia (Paper III)

4.3.1 Diabetes in patients with schizophrenia

Table 9 describes the prevalence of T2D in the study cohort. The observed prevalence of T2D in patients in the clozapine group was 14.3%. Of the 27 cases of T2D in the clozapine group 16 were diagnosed during clozapine treatment. In the never-on-clozapine group the observed prevalence of T2D was 13.7%. The mean age in the clozapine group at the end of follow up was 51.2 years and 58.6 years in the never-on-clozapine group. There were 10 patients in the clozapine group who used metformin without having a diagnosis of diabetes, of these 5 had a high risk of T2D. The time from the initiation of clozapine treatment to the diagnosis of T2D varied from 43 days to 25.3 years with a mean time lag of 7.7 years (SD = 6.7) and a median time lag of 7.3 years for patients diagnosed with T2D during clozapine treatment. Four patients were diagnosed with T2D after clozapine discontinuation, they were diagnosed with T2D 69 days, 3.2 years, 5.6 years, and 7.8 years, respectively, following clozapine discontinuation.

Table 9 Diabetes in patients with schizophrenia treated with clozapine and those never treated with clozapine.

	Clozapine		Never-on-clozapine	
	Male (n = 132)	Female (n = 56)	Male (n = 245)	Female (n = 150)
Patients with T2D	18	9	31	23
T2D diagnosed before clozapine treatment	4	3	-	-
T2D diagnosed during clozapine treatment	11	5	-	-
T2D diagnosed after discontinuation of clozapine treatment	3	1	-	-
Patients with type 1 diabetes (T1D)	1	0	2	0
Patients with T1D or T2D	19	9	33	23
Patients with a high risk of T2D (HbA1c in range of 6.0% - 6.4%)	13	9	15	8
Patients with T1D, T2D or a high risk of T2D	32	18	48	31
Prevalence of T2D	13.6%	16.1%	12.7%	15.3%
Prevalence of T1D, T2D or a high risk of T2D	23.5%	32.1%	18.8%	20.7%
Patients on metformin without a diabetes diagnosis	5	5	-	-
Mean age at end of follow up	50.0 (11.9)*	54.3 (11.4)*	56.7 (14.2)*	61.5 (16.1)*
Mean follow up period during clozapine treatment in years	9.3 (5.9)*	8.9 (5.6)*		
Mean follow up period in years			14.0 (3,9)*	13.5 (3.8)*

*Standard deviation

4.3.2 Prevalence of T2D in schizophrenia patients compared to Icelandic population controls

Table 10 shows that the standardized morbidity ratio for T2D was, as expected, higher in both schizophrenia groups compared to Icelandic population controls. The two highest standardized morbidity ratios were 4.4 for females in the clozapine group and 2.6 for females in the never-on-clozapine group.

Table 10 Type 2 diabetes in patients with schizophrenia ever on clozapine and never on clozapine compared to Icelandic population controls, age and sex adjusted.

	Clozapine	Never-on-clozapine
Male		
T2D	13.6%	12.7%
Expected T2D from Icelandic population	5.8%	8.5%
P-value	< 0.001	0.029
Standardized morbidity ratio	2.3	1.5
Confidence interval (95%)	1.42-3.54	1.02-2.04
Female		
T2D	16.0%	15.3%
Expected T2D from Icelandic population	3.6%	5.5%
P-value	0.001 >	0.001 >
Standardized morbidity ratio	4.4	2.6
Confidence interval (95%)	2.10-7.80	1.68-3.73

4.3.3 Ketoacidosis and high blood sugar

Table 11 shows that there was only one case of ketoacidosis in both study cohorts, 0.2% (1/583). That patient had never taken clozapine and had type one diabetes (T1D). The highest measurement of glucose in patients, without T1D or T2D, was 15.0 mmol/l.

Table 11 High blood sugar and ketoacidosis in patients with schizophrenia ever on clozapine and never on clozapine.

	Clozapine n = 188					Never-on-clozapine n = 395				
Highest glucose measurement (mmol/l)	13-19.9	20-29.9	30-39.9	40+	Ketoacidosis	13-19.9	20-29.9	30-39.9	40+	Ketoacidosis
Glucose status										
T2D (n = 81)	7	1	2	0	0	14	12	0	3	0
T1D (n = 3)	0	1	0	0	0	1	0	0	0	1
High risk of T2D (n = 45)	1	0	0	0	0	0	0	0	0	0
No glucose dysregulation (n = 454)	0	0	0	0	0	9	0	0	0	0

Table 12 shows that T2D was associated with blood sugar values over 13 mmol/l in both males and females. Clozapine use was not associated with blood sugar values over 13 mmol/l. Lower age was significantly associated with glucose values over 13 mm/l in males but not females. Clozapine was also tested with a Cox proportional hazard model to assess the association with glucose over 20 mmol/l and glucose over 30 mmol/l and was not associated with either of these response variables.

Table 12 Cox proportional hazards model with possible factors associated with glucose over 13 mmol/l.

	Hazard ratio	SE	Z-score	95% CI	P-value
A. Male with glucose > 13 mmol/l					
Age	0.97	0.01	-2.38	0.94-0.99	0.02
Clozapine	1.03	0.38	0.08	0.50-2.12	0.94
T2D	18.7	6.54	8.38	9.4-37.1	0.001 > p
B. Female with glucose > 13 mmol/l					
Age	1.01	0.02	0.47	0.97-1.05	0.64
Clozapine	0.62	0.47	-0.63	0.14-2.78	0.53
T2D	69.2	72.5	4.04	8.86-539	0.001 > p

A) n = 377, 39 cases. B) n = 206, 15 cases

4.3.4 Blood lipids

Blood lipid measurements were available for 144 patients on clozapine and 258 patients in the never-on-clozapine group as is shown in table 13. Very high levels of LDL (over 4.9 mmol/l) were identified in 9 patients (6%) in the clozapine group and in 13 patients (5%) in the never-on-clozapine group. High levels of total cholesterol (over 5.2 mmol/l) were identified among 89 patients (62%) in the clozapine group and 133 patients (52%) in the never-on-clozapine group. In the clozapine group 5 patients (3%) who had very high levels of triglycerides (over 5.65 mmol/l) were identified while no patients in the never-on-clozapine group had very high levels of triglycerides. Information on blood lipid lowering medications was available for 154 patients and 16 (10%) of them used statins and one used a fibrate medication used to lower triglyceride levels.

Table 13 Blood lipids in patients with schizophrenia on clozapine and never on clozapine versus expected values from Icelandic population controls.

	Clozapine	Expected from Icelandic population	P-value	Never-on-clozapine	Expected from Icelandic population	P-value
Male	n = 99			n = 175		
Mean age at last blood lipid test	47.7	-	-	54.4	-	-
Mean total cholesterol (mmol/l)	5.43	5.23	0.28	5.17	5.25	0.58
Mean LDL (mmol/l)	3.15	3.31	0.27	3.19	3.31	0.36
Mean total HDL (mmol/l)	1.21	1.31	0.04	1.26	1.33	0.10
Mean total triglycerides (mmol/l)	2.34	1.36	0.01 >	1.58	1.35	0.04
Female	n = 45			n = 83		
Mean age at last blood lipid test	51.9	-	-	58.0	-	-
Mean total cholesterol (mmol/l)	5.84	5.35	0.16	5.39	5.49	0.89
Mean LDL (mmol/l)	3.55	3.22	0.15	3.25	3.32	0.90
Mean total HDL (mmol/l)	1.40	1.65	0.01	1.40	1.66	0.34
Mean total triglycerides (mmol/l)	1.95	1.07	0.01 >	1.64	1.13	0.03

5 Discussion and conclusions

There is a major discrepancy between what should be offered to patients with the more treatment resistant forms of schizophrenia, TRS, and what happens in real life clinical practice as reviewed above. The size of the discrepancy varies enormously as described by Bachmann (2017) and the reasons for this variability may be several and remain not well documented or understood. On the one hand due to a low but well established risk for neutropenia and full-blown agranulocytosis, there are obstacles like demands for regular monitoring in most countries. On the other hand there is also a risk of other side effects developing gradually during treatment with clozapine over months and years, in particular weight gain and metabolic side effects such as dyslipidemia and T2D (Newcomer, 2005).

In Iceland, a country with only about 340 thousand inhabitants, most who live in and around the capital, Reykjavik, the LUH and primary care services have been developing EHR over the past two decades. This offers a unique setting to study the descriptive epidemiology of clozapine use in the short and long term and the frequency of side effects developing in the course of treatment of schizophrenia. Moreover, because the guidelines for taking blood to count neutrophils have not been enforced rigidly in Iceland, i.e. the drug can be dispensed although a blood sample has not arrived, this allowed us to put to the test one common assumption: namely, that a large part of the reason for how long patients remain on clozapine and for how well they do on it is simply the regular contact with doctors, nurses or technicians when mandatory blood samples are drawn weekly, fortnightly or monthly. The results discussed in this section describe how clozapine has been prescribed in Iceland focusing on variables such as age at onset of clozapine use, gender differences, doses prescribed, discontinuation and antipsychotic polypharmacy. The well-known and uncommon side effect of clozapine treatment neutropenia that can develop into full blown agranulocytosis will be compared to observations in patients with schizophrenia who have been followed up by the

same department of psychiatry but have never been on clozapine. The results will be discussed in light of current FDA as well as UK-guidelines on neutrophil monitoring during clozapine treatment. Side effects such as T2D and dyslipidemia in patients with schizophrenia ever or never treated with clozapine will be discussed and compared to the Icelandic population with emphasis on how complex it is to associate the risk of T2D with a particular type of medication. Moreover it will be addressed what do to when dyslipidemia is diagnosed in a patient with schizophrenia in Iceland.

5.1 Clozapine treatment and discontinuation in Iceland (Paper I)

In paper I the aim was to set the scene for the thesis by describing the pattern of clozapine use in Iceland in general and to compare the findings to clozapine use in other countries. The mean age at first treatment with clozapine was 37.8 years. After one year of clozapine treatment 84.4% of patients were still taking clozapine and after 20 years of treatment the vast majority, 71.2%, 7 out of every 10 patients, were still taking clozapine. Polypharmacy was common with two thirds of patients taking one or more antipsychotics in addition to clozapine, and 16.9% were on a depot injection along with the clozapine treatment. The mean DDD was 1.67, increasing as a rule as more antipsychotic medications were being used alongside the clozapine treatment. It was estimated by approximate calculations that just over 11% of patients with schizophrenia in Iceland were taking clozapine and that around 16% in the cohort had been treated with clozapine at some point.

The onset of schizophrenia in men is usually in the age range 18-25 and in females in the age range 25-35 (Ochoa et al., 2012). Therefore, it should not come as a surprise that females tended to begin clozapine treatment later than males in the cohort, the mean age at the start of clozapine treatment being 36.5 years for males and 41 years for females. Using data from Ochoa et al. (2012) we can estimate the time lag from diagnosis of schizophrenia to clozapine treatment in Iceland to be 13-20 years for males and 6-16 years for females. A study by Demjaha et al. (2017) reported that 84% of patients who were

treatment resistant were so from the onset of the disease. Therefore the delay in prescribing clozapine is far too long for most patients with treatment resistant schizophrenia, considering that one trial with an antipsychotic should only take 6-8 weeks and clozapine is the only evidence based drug of choice after two failed antipsychotic trials (Demjaha et al., 2017).

The majority of patients, 71.2%, who started clozapine treatment, remained on clozapine during the 20 years of follow up in the study. No other study with such a long follow up time was found in the literature to compare to the clozapine continuation ratio long term. In the clozapine cohort 84.4% of patients were still on clozapine after one year of treatment and 81.8% after two years which is higher than reported in the US study where 74% of patients were still taking clozapine one year after the start of treatment and 66% after two years and in the UK where 55% of patients were still on clozapine after two years (Essock et al., 1996; Legge et al., 2016). This high clozapine retention rate in Iceland may have several explanations. These include factors such as a) good access to experienced psychiatrists who are used to prescribing clozapine, b) continuity of contact with nurses in the same outpatient department for years/decades, c) the fact that no other medication is on par with clozapine in the treatment of TRS, d) the fact that over the past two decades patients in Iceland have only paid a fraction of the cost of each blood sample for neutrophil counts, e) that after the first 18 weeks the frequency of blood samples taken has fallen far below once a month and patients have been able to continue receiving the drug despite this as reported in paper II. Other factors may include: f) lower mean dose of clozapine than in some countries, g) the fact that Icelandic patients often only take clozapine in the evenings to minimize daytime sedation, h) treatment always being initiated in a hospital setting to address side effects more quickly, and i) overall continuity of care is probably greater in smaller societies as Iceland than in larger societies.

The mean clozapine daily dose of 304.6 mg is similar or lower than what has been reported in other European studies. The mean dose in a Danish study by Nielsen et al. was 382 mg (Nielsen et al., 2012). In a small Swedish study (n = 33) by Kroken et al. (2014) the mean dose was reported to be 460 mg. In a

review of clozapine trials in Europe and the USA, Fleischhacker et al. (1994) reported a mean dose of 283.7 mg in Europe and 444 mg in the USA. Polypharmacy was roughly the same in the study cohort, 65.6%, as reported in a Danish study where it was 64.2%, and a Spanish study where it was 49-59% (Bernardo et al., 2012; Nielsen et al., 2012). Systematic reviews of polypharmacy with one antipsychotic added to clozapine treatment have only showed small benefits (Barbui et al., 2009; Taylor et al., 2012). Doctors need to monitor carefully clozapine augmentation with other antipsychotics and abandon the augmentation if it does not lead to clinical improvement. In the study cohort 16 different medications were used to augment clozapine treatment which reflects the lack of large positive augmentation studies with specific antipsychotics. The use of long term depot injections was fairly common with 16.9% of patients receiving them which is higher than the 8.2% reported in a Spanish study (Bernardo et al., 2012). A small French study reported that depot injection in combination with clozapine was well tolerated but such combinations are not recommended overall because of possible additional side effects but relatively modest, if any, treatment gains (Souaiby et al., 2017).

We estimate that 16% of patients with schizophrenia in Iceland have ever tried clozapine and that 11.4% of patients are currently on clozapine. This estimate of the current use of clozapine in Iceland is about the same as was estimated by Bachmann et al. (2017), 11.2%, but is lower than the percentage of TRS that is estimated to be in the range of 20-30% (Meltzer, 1997; Picchioni & Murray, 2007). This estimation is based on the assumption that the prevalence of schizophrenia is the same in Iceland as has been previously reported and that total amount of clozapine used for diseases other than TRS and treatment resistant bipolar disorder are negligible (McGrath et al., 2008; Saha et al., 2005). This indicates that psychiatrists in Iceland can and should be more alert to consider clozapine as a treatment option for their patients with TRS.

5.2 Neutropenia and agranulocytosis (Paper II)

In paper II the main aim was to describe the prevalence of neutropenia and agranulocytosis in patients with schizophrenia both on clozapine and never on clozapine and to assess to progression of neutropenia to agranulocytosis. Neutrophil monitoring during clozapine treatment in Iceland was less frequent than guidelines recommend both for the first 18 weeks of treatment but particularly after the first 18 weeks. For the first 18 weeks the median number of days between neutrophil measurements was 18 days whereas Icelandic and FDA guidelines recommend weekly measurements (FDA, 2015; Lyfjastofnun, 2014). After the first 18 weeks the Icelandic guidelines recommend monthly measurements but the median time was 124 days (Lyfjastofnun, 2014). The infrequent measurements did however not lead to more cases of agranulocytosis developing than expected. Only one patient of those around two hundred patients ever on clozapine in the cohort developed agranulocytosis, and that case occurred after taking clozapine for 28 years. It is very uncommon that clozapine induced agranulocytosis occurs so late during the course of therapy, since it occurs in the first five months of treatment in about 80% of cases (Alvir et al., 1993; Lahdelma & Appelberg, 2012). Outpatients with TRS might find it difficult or costly to adhere to the weekly blood tests and this flexible monitoring might have contributed to the higher adherence in the study cohort. Other studies comparing neutrophil monitoring during clozapine treatment to guidelines were not found.

Neutropenia was fairly common both in the clozapine group and in the never-on-clozapine group despite the relatively low frequency of measurements. Mild neutropenia (neutrophils 1500-1900/mm^3) was identified in 12.8% of patients in the clozapine group compared to 7.5% in the never-on-clozapine group ($p = 0.05$). The mild neutropenia was transient and had no clinical consequences in the sample. The frequency of neutrophil measurements was associated with more cases of neutropenia so it's likely that the frequency of mild neutropenia would have been higher if the neutrophil monitoring had been in line with guidelines. Moderate neutropenia (neutrophils 1000-1400/mm^3) occurred in 4.3% of patients taking clozapine and severe

neutropenia (neutrophils 500-900/mm^3) in 0.5% of patients. It was unexpected that these figures were lower than for patients never on clozapine where moderate neutropenia occurred in 5.0% of patients and severe neutropenia in 0.8% of patients. This was true despite the latter group only having about half as many neutrophil measurements done as those on clozapine treatment. There were eight patients in the clozapine group who developed moderate neutropenia, something that leads to a mandatory discontinuation of clozapine treatment in most countries (Nielsen et al., 2016) but only two patients discontinued clozapine treatment in the study sample. The six patients who continued clozapine treatment were still on clozapine one year later without any other episodes of neutropenia. There were two patients with severe neutropenia in the clozapine group and one of them developed agranulocytosis while the other discontinued clozapine treatment.

It is only possible to assess the risk of neutropenia in various stages, mild, moderate to severe, progressing to agranulocytosis if patients have been willing and able to remain on clozapine following a diagnosis of neutropenia. There were 28 patients who had used clozapine for at least one year after neutropenia had developed in the range 500-1900/mm^3 without experiencing any adverse clinical outcomes as well as one patient who had developed agranulocytosis (3.4%). When only looking at patients with neutropenia in the range 500-1400/mm^3 who had used clozapine for at least a year after the neutropenia or being diagnosed with agranulocytosis then one patient out of 7 (14.2)% developed agranulocytosis. This is a higher percentage than for neutropenia in the range 500-1900/mm^3 but the sample size is small. Therefore, replication of such results in larger samples would be a major advantage but this is difficult if not almost impossible at present. Most patients have no option but to stop taking clozapine in most countries after neutropenia below 1500/mm^3 develops because most guidelines recommend stopping clozapine treatment for such a low neutrophil count (Nielsen et al., 2016). This recommendation was though amended in the US in 2015 when neutrophil counts in the 1000-1499/mm^3 range were considered within limits with neutrophil monitoring three times a week (FDA, 2015). A recent study on patients in the VA system in the US

concluded that those changes are likely to increase the number of patients treated with clozapine (Sultan et al., 2017). A study by Hummer et al. (1992) reported that 8 out of 68 patients were diagnosed with neutropenia that resolved without treatment but the mean neutrophil count in the study was in the mild neutropenia range, ($1780/mm^3$). One other small study was found where the rate of neutropenia in schizophrenia patients on clozapine treatment was 11.8% but higher, 17.6%, in schizophrenia patients not on clozapine (Rettenbacher et al., 2010). The results of that study concur with those reported in paper II, suggesting that neutropenia may neither be a good nor a reliable predictor for clozapine induced agranulocytosis.

When agranulocytosis is diagnosed it can be difficult to ascertain its cause and of course there can be a few partial causes that culminate in agranulocytosis as well as one cause like clozapine as is often the deduction when a patient on clozapine treatment develops neutropenia of any type, in particular agranulocytosis. In the study cohort of patients who had never been on clozapine four cases of agranulocytosis were found. In three cases it was possible to identify likely causes but in the fourth case no definite explanation was identified. If that patient had been on clozapine at the time of diagnosis the agranulocytosis would almost certainly have been attributed the clozapine treatment as the sole cause or at least as a partial cause. Neutropenia was just as common in the clozapine group as in the never-on-clozapine group. Therefore, most/many of the neutropenia cases in the clozapine group may have other biological causes, partial, sole or necessary causes, than clozapine treatment.

Females had a higher risk of neutropenia with a hazard ratio of 1.70-2.00 depending on which range of neutropenia was used in the comparisons. It has been reported in a US study that agranulocytosis is more common in females (Alvir et al., 1993). Younger age was also associated with increased likelihood of having neutropenia diagnosed and that is in line with a larger UK study (Munro et al., 1999). Clozapine use was expected to be associated with moderate to severe neutropenia but it was in fact only observed to be associated with mild neutropenia ($p = 0.05$) with a hazard ratio of 1.86.

Clozapine treatment therefore only increased the likelihood of mild neutropenia developing which usually does not have much clinical significance (no progression to agranulocytosis) although such a finding can probably increase the chance of clozapine being discontinued for a particular patient. Such decisions to stop the treatment can be shared of course or taken only by the treating psychiatrist or the patient receiving the treatment.

Neutropenia is one of the reasons why patients stop clozapine treatment (Legge et al., 2016) despite the low risk of progression to agranulocytosis for mild to moderate neutropenia. According to paper II, patients with mild neutropenia who remain on clozapine have a very low risk of developing agranulocytosis and most patients with moderate neutropenia will not develop agranulocytosis. Caution must though be exercised until replications of these results are published in the literature. Clozapine rechallenges should be considered for patients who have had a good response to clozapine earlier and have stopped the treatment due to mild to moderate neutropenia. The case is stronger if no other treatment has shown a clinical response comparable to that seen on clozapine. The low risk of agranulocytosis in mild to moderate neutropenia should be placed in the context of severity of the illness, schizophrenia, which is associated with a decreased lifespan of 22.5 – 25 years and the reduced mortality associated with clozapine treatment which probably outweighs the small risk of dying from agranulocytosis (Hayes et al., 2014; Tiihonen et al., 2009). The risk of dying from agranulocytosis has been estimated to be 0.02% (Alvir et al., 1993; Lahdelma & Appelberg, 2012; Munro et al., 1999; Schulte, 2006). In a study from Finland it was reported that 40% of patients with agranulocytosis and 80% of the mortality from agranulocytosis during clozapine treatment was observed for patients who used clozapine with other medication which have been associated with agranulocytosis (Lahdelma & Appelberg, 2012). Accordingly, the absolute risk of dying from agranulocytosis is in all probability less than 0.02% for patients who are not on any other medications that have been associated with agranulocytosis.

5.3 Risk of diabetes and dyslipidemia (Paper III)

In paper III the main aims were to assess the prevalence of T2D and dyslipidemia and to compare the proportions of patients with schizophrenia ever or never on clozapine to a standard Icelandic population. The observed prevalence of T2D was 14.3% in the clozapine group and 13.7% in the never-on-clozapine group. The standardized morbidity ratio for T2D for females on clozapine was 4.4 and 2.3 for males, respectively. For patients with schizophrenia never on clozapine the standardized morbidity ratio for T2D for females was 2.6 and 1.5 for males, respectively. Clozapine use was not associated with high blood sugar (over 13 mmol/l) after correcting for age and T2D. Only one case of ketoacidosis was identified in the study cohort of 583 patients during mean follow up of 9.2 years for patients on clozapine and 13.8 years for patients never on clozapine. There was no significant difference observed for LDL or total cholesterol in the clozapine and the never-on-clozapine cohorts compared to the Icelandic standard population. HDL was lower in the clozapine group compared to the Icelandic standard population but the difference was only significant for males. The greatest difference observed for the various blood lipids was in the triglyceride levels that were significantly higher both in the clozapine group and in the never-on-clozapine group compared to the Icelandic standard population.

In a large Medicaid study clozapine has been reported to be significantly more often associated with T2D than other antipsychotics which is in line with the results of paper III (Stroup et al., 2016). Similar results were found in a smaller Dutch study that compared the incidence of T2D over a 5 year period in patients with schizophrenia on clozapine versus patients with schizophrenia not on clozapine where the incidence of T2D was 22.3% in the clozapine group and 16% in the never-on-clozapine group (Schulte et al., 2016). It has been suggested, but is debatable, that patients treated with clozapine may be at greater risk of T2D because they are the most severely afflicted schizophrenia patients and their lifestyles may place them at a greater risk of T2D than other patients with schizophrenia (Sharpe et al., 2006).

Standardized morbidity ratios for T2D was higher for females than males in the cohort. The higher ratios of T2D in females have also been reported in a large US study in the Medicare and Medicaid systems in patients with schizophrenia (L. Dixon et al., 2000). The mean clozapine blood levels have also been reported to be 17% higher in females than in males and that could possibly account, at least to some degree, for higher rates of T2D found in females treated with clozapine (Anderson et al., 2015).

Of the 27 patients in the clozapine group diagnosed with T2D, 7 (26%) were diagnosed with T2D before starting clozapine treatment, 16 (59%) during clozapine treatment and 4 (15%) after discontinuation of clozapine. Paper I reported that two thirds of patients on clozapine are taking other antipsychotic medications in addition to clozapine and the mean DDD was rather high, 1.67 which can further have added to the risk of T2D in this cohort. These proportions indicate how complicated it can be to assess the causality of clozapine induced T2D in patients with schizophrenia.

Patients with a high risk of developing T2D as defined by HbA1c within the range 6-6.4% were about twice as common in the clozapine group (11.7%) as in the never-on-clozapine group (5.8%). One possible explanation is measurement bias, namely that patients on clozapine are more often in contact with LUH due to the neutrophil monitoring and as a result are more likely to have had more frequent HbA1c measurements, including some in this intermediate range between normal levels and T2D levels of HbA1c as a marker for long-term blood sugar. In the clozapine group 147 patients out of 188 (72.2%) had at least one measurement while in the never-on-clozapine group there were 205 patients out of 395 (51.9%) who had at least one measurement of HbA1c. There were 9 patients (2.3%) in the never-on-clozapine group that probably had an increased risk of T2D since they had a glucose measurement between 13-15 mmol/l without meeting the criteria for high risk of diabetes or receiving a diagnosis of T2D.

It has been reported that metformin can be used in patients without T2D to counteract weight gain that is often observed in patients treated with clozapine (Chen et al., 2013). In the clozapine group there were 10 patients using

metformin without a diabetes diagnosis and five of them had a high risk of developing T2D. These results indicate that the use of metformin and related medications cannot be used reliably in Iceland and probably in some other countries as a proxy for the T2D diagnosis in clinical samples.

Only one case of ketoacidosis (0.2%) was identified in the cohort and this condition was most likely caused by T1D but not the use of antipsychotic medication. Other studies on larger samples in the US, studies with more power to detect rare events, have reported higher incidence rates of 1.2.-3.1% during treatment with clozapine (Cohen et al., 2012). In a large study from the US Veterans Affairs, overall 0.2% patients on any antipsychotic were hospitalized because of ketoacidosis but the observed risk was higher for clozapine or 2% (Leslie & Rosenheck, 2004). One possible reason for lower risk in Iceland is that the Icelandic health care system is very different from the US system and offers good access to universal primary health care for all citizens, thus diabetic illness in this group might be more likely to be treated there before it progresses to ketoacidosis.

The medical health records did not have sufficient data on patients' weight progression to allow for a meaningful analysis. That was unfortunate and probably reflects the fact that too little attention has been on measuring and registering patients´ weight gain both for inpatients and outpatients during antipsychotic treatment. That seems to be changing though in recent years in our practice and over the last couple of years more commonly patients weight is recorded regularly in the EHR.

In the study cohort antipsychotics, and notably clozapine, had more adverse effects on triglycerides than on cholesterol which is in line with previous studies (Henderson et al., 2000; Newcomer, 2005). A negative effect on HDL was observed that only reached statistical significance for the clozapine group. Cholesterol levels were higher in the clozapine group for females but this did neither reach statistical significance nor were any other significant effects on cholesterol observed. The risk of antipsychotics raising triglyceride levels is better established in the literature than their more complex effects on cholesterol where some studies have shown total cholesterol to be higher and

HDL to be lower while other studies have not shown any such effects (Newcomer, 2005; Wirshing et al., 2002; Wu et al., 2006). Most guidelines on metabolic monitoring during antipsychotic treatment recommend that patients should have blood lipids done regularly (De Hert et al., 2011). In the clozapine group a blood lipid measurement could be found for 144 patients out of 188 (77%) reflecting that there is a definite room for improvement in the blood lipid monitoring for patients in this cohort. Guidelines on statin use only recommend statins for very high levels of LDL (over 4.9 mmol/l) if the patient does not have atherosclerotic cardiovascular disease, T2D or at least a 7.5% risk of developing atherosclerotic cardiovascular disease in the next 10 years (Stone et al., 2014). Only 5% of patients in the study had such high LDL levels and 10% in the clozapine group were using statins which was the same as in a Danish study from 2007 (Nielsen et al., 2012). There were similar levels of total cholesterol and LDL in the study cohorts as in the age and sex matched Icelandic population controls. Therefore it is likely that screening in the study cohorts would not lead to more treatment with statins than screening in general in the Icelandic population. It is very unlikely that a young patient with schizophrenia who does not have T2D or cardiovascular disease would be prescribed statins following blood lipid screening. Even though statins are not recommended in primary prevention there are recent meta-analyses that show reduced total mortality in primary prevention (Mihaylova et al., 2012; Taylor et al., 2013). No studies on statin treatment for primary prevention in patients with schizophrenia were found in the literature but it would be interesting to know if statin treatment would be more beneficial in those patients who have a higher prevalence of metabolic disorders.

5.4 Limitations of papers I-III

There are some limitations in the dataset that may have influenced the findings reported in papers I-III. This thesis is based on a retrospective analysis of EHR and paper records of patients at LUH. Therefore, it is possible that some results cannot be fully generalized to patients with less severe forms of schizophrenia who have not been in contact with mental health services of LUH. When comparing patients ever on clozapine versus patients never on clozapine

there weren't complete medical data available to correct fully for various possible confounders including family history, BMI, medication use other than clozapine, physical activity, diet, etc. Patients never on clozapine were also on average 7 years older than those ever on clozapine. Patients on clozapine are or should by definition be patients with TRS so the use of clozapine may not be the only difference between them and those patients with schizophrenia who have never been on clozapine. Although we had full access to the LUH EHR and the electronic regional databases for neutrophil counts, blood sugar measurements and blood lipid measurements, we could not get access to data in two private blood testing facilities in Reykjavik. It is possible that some blood measurements for patients in the cohort may have been done there. However, the vast majority of patients with schizophrenia and almost every TRS-patient on clozapine is followed up from LUH so it is highly unlikely that this should have affected the main results and conclusions. Some neutrophil measurements in the database may not have been requested because of neutrophil monitoring during clozapine treatment but for other medical reasons, most frequently infections in all probability that commonly lead to a rising number of neutrophils, not neutropenia. The strengths of the study include full access to electronic medical records at LUH for two decades and full access to patients´ medical journals for older medical records on paper. We estimate that over 90% of Icelandic patients with schizophrenia, in particular the more severe forms, have been treated and followed up at LUH over the past four decades.

5.5 EBP, VBP and risk assessment in clozapine treatment

With clozapine being so underutilized in most countries EBP is apparently often not being applied in the treatment of TRS where clozapine is the only drug with that indication (Kane et al., 1988; Picchioni & Murray, 2007). Clozapine should be offered to about 20-30% of patients with schizophrenia but the reality is that it is only prescribed on average for 9.2% of such patients with wide differences observed between countries (Bachmann et al., 2017). The risk of agranulocytosis and the recommended and sometimes mandatory blood neutrophil monitoring may be two of the major reasons why clozapine is not being used more commonly along with some common side effects (Kane, 2012;

Nielsen et al., 2010). A UK study of patients on clozapine reported that 64% of patients claimed that the blood monitoring was "OK - a necessary part of treatment" but 28% claimed that they did not like the blood test (Taylor et al., 2000). Each individual patient has his or her own values regarding clozapine treatment and the blood monitoring which are not necessarily the same values as the patient´s family might have or the prescribing doctor. Shared decision-making refers to a structured process that encourages full participation by patient and provider in treatment decisions and it has been shown that it can improve the participation of mental health patients in their care and the quality of decisions taken in terms of knowledge and values (Drake et al., 2009). Both patients and providers acknowledge the desirability of shared decision making in schizophrenia but it occurs less often in real life mental health settings than desired by patients (Beitinger et al., 2014).

It is well established that most people have difficulty in working with and understanding very low figures and risks (Kahneman, 2011). In making treatment decisions in TRS the exceedingly low risk of dying from agranulocytosis must be put into perspective for patients, families and doctors alike to facilitate a better understanding and ability to work with the low risk in the context of other equally likely or more probable adverse outcomes. The risk of developing agranulocytosis is around 0.7% and in 3% of cases it has a lethal outcome which translates to 0.02% or 2 out of every 10.000 patients overall but a lethal outcome is as low as 0.004% or 4 out of every 100.000 treated patients after the first 5 months of treatment (Alvir et al., 1993; Lahdelma & Appelberg, 2012). That risk can drop even further for patients who are not simultaneously on other medications associated with agranulocytosis (Lahdelma & Appelberg, 2012). To put the risk of dying from agranulocytosis during clozapine treatment into perspective it is possible to compare it to the risk of dying in a road traffic accident in Europe. The risk of dying in a road traffic accident in Europe has been estimated to be 0.37% over a 40 year period $(1- (1 - 9.3/100.000)^{40})$ or 3-4 subjects per 1.000; 40 years is a period comparable to that if a patient takes clozapine during his adulthood years (WHO, 2015). A patient taking clozapine for 40 years and residing in Europe therefore has an 18.5 times higher risk of

dying in a road traffic accident than dying from agranulocytosis. This low risk must also be balanced against risks like self-harm and suicide and a lowered-life expectancy of 22.5-25 years among patients who develop schizophrenia because clozapine has been shown to reduce the mortality of such patients (Tiihonen et al., 2009; Wimberley et al., 2017).

Methods for cost effectiveness analysis are well established and often used when assessing which intervention to use in disease intervention (Hill, 2012). Clozapine blood monitoring is far from being cost effective with 1 quality adjusted life year costing at least 970.000 USD where the NHS cost effectiveness threshold for treatment is 20.000 – 30.000 GBP or 26.000-39.000 USD (Girardin et al., 2014; McCabe et al., 2008). Resources used for blood monitoring after the first 6 months for example might therefore be used more efficiently for other health interventions for patients with TRS. Clozapine use in itself is also associated with significant savings in hospital care as shown by a recent meta-analysis (Land et al., 2017).

When assessing if long term blood monitoring is necessary during clozapine treatment it can be helpful to compare the risk associated with other medications where long term monitoring is at present neither deemed necessary nor mandatory. After the first 5 months of treatment with clozapine the risk of agranulocytosis drops from around 0.7% to about 0.14% which is lower than with ticlopidine (0.8%) and dapsone (0.24-0.42%), about the same as chlorpromazine (0.13%) which has been widely used for half a century and is still in use, and slightly higher than sulfasalazine (0.06%).

In paper II the progression rate from neutropenia to agranulocytosis was observed to be very low and only mild neutropenia was found to be more common in the clozapine group which could reflect the higher frequency of blood measurements if temporary mild neutropenia is commonly a fluctuating phenomenon that some people experience on occasions without any associated adverse outcomes. The findings from paper II obviously require replication but one relatively small study has reported similar findings, namely neutropenia being more common among patients with schizophrenia not on clozapine than those on clozapine (Rettenbacher et al., 2010). If the results are

replicated by others in large samples that would indicate that neutropenia is a poor indicator for agranulocytosis and that many patients may as a result of current guidelines stop clozapine treatment unnecessarily thereby increasing their risk of dying prematurely (Tiihonen et al., 2009; Wimberley et al., 2017).

All of the above, accepting though that replications are urgently needed, really begs the question if clozapine long term monitoring is really necessary because it may unnecessarily bar patients with TRS from receiving the treatment which is most likely to keep their symptoms in check and reduce their overall mortality. Denying a patient who has been on stable long-term clozapine treatment for 6 months or more the medication if the patient does not show up for blood monitoring ("No blood, no drug" policy) may not at all be in the patient´s best interest. When assessing if to use clozapine in TRS the focus should not be on agranulocytosis and blood monitoring beyond 6 months which has a debatable risk/benefit ratio. Patient's values regarding the blood monitoring and the small risks involved should be explained in laymen terms to the patient and/or his spouse or closest relatives and discussed. The outcome of these discussion should assist a shared decision making process in order to decide whether further long term blood monitoring is indicated or not. The exceedingly small risk of lethal agranulocytosis should not prevent the bulk of patients with TRS from trying clozapine or from remaining on clozapine treatment if they fail to comply with long-term blood monitoring.

5.6 Conclusions

Clozapine could and should be prescribed earlier following diagnosis and for more patients with TRS than is done at present in most countries. Psychiatrists and pharmacists in hospitals need to be more alert when assessing if a patient is a candidate for clozapine treatment. Most patients, 71.2%, who start clozapine treatment stay on the medication for at least two decades in Iceland. A diagnosis of mild to moderate neutropenia did not result in a higher discontinuation rate in the study cohort but neutropenia is often cited as major problem in clozapine treatment. Neutropenia is common in both patients on clozapine and never on clozapine so there is a large proportion of neutropenia

cases among patients treated with clozapine that may not at all be related to the clozapine treatment. Patients who have previously responded to clozapine and discontinued due to neutropenia, especially in the 1000-1500/mm^3 range, should be rechallenged with clozapine, provided that clozapine is the medication that seems to have provided the best treatment response, since there is usually no other equally effective treatment for TRS available. Antipsychotic polypharmacy with clozapine is very common despite lack of good evidence supporting such practice. Doctors need to evaluate thoroughly the clinical benefit versus the risk of more side effects, in the short and long term, if they add other antipsychotic medications to clozapine and aim to actively discontinue medications that do not show a clinically meaningful response. The DDD increased as more antipsychotics were used alongside clozapine treatment exposing the patients to a greater risk of more ADRs. The metabolic side effects are especially problematic in this regard in the long term. Clozapine use is clearly associated with T2D and females seem to be especially vulnerable with a standardized morbidity ratio for T2D of 4.4. Monitoring of blood glucose and HbA1c for patients with schizophrenia needs to be improved in Iceland and should be done at least once a year. Guidelines also state that blood lipids should be assessed once every year but there is less evidence supporting this, especially for young patients. In practice blood lipid measurements are inexpensive and it's probably easiest to do them annually when T2D monitoring is done. Neutrophil monitoring should not be mandatory after the first half year of treatment. Doctors and patients should discuss the risk of agranulocytosis to enable a shared decision-making process and decide in due course on appropriate monitoring based on the patients´ values and an informed written consent on how they want to proceed.

5.7 Future directions

We need more studies to assess the prevalence and significance of neutropenia in patients with schizophrenia on clozapine compared to patients never on clozapine. Moreover further studies are called for that assess the risk of progression of neutropenia to agranulocytosis. This should become easier in most countries as EHR and databases have become more widely used in

routine clinical care in recent years. In paper II neutropenia was observed to be just as prevalent in patients on clozapine as in patients who had never been on clozapine and the risk of progression from neutropenia to agranulocytosis was very low since only one patient developed agranulocytosis following severe neutropenia. The findings of paper II, if true, would support that the current European guidelines on discontinuing clozapine for patients in the 1000-1500/mm^3 range should be reevaluated and that more frequent neutrophil monitoring would be a more logical and prudent response during periods of low neutrophil counts as the FDA has recommended in the US since 2015. This could lower the discontinuation rate of clozapine treatment and thereby improve treatment and mortality rates in TRS, including reducing suicides and acts of repeated self-harm.

Larger collaborative studies are needed to access the genetic risks of antipsychotics induced weight gain and T2D. Identifying genetic risk factors may help to find methods to guide which medications to avoid for patients at high risk of certain side effects. This seems to be especially important for female patients and their risk for T2D.

The results indicate that there is a need to address treatment for higher triglycerides during antipsychotic treatment. More research is though needed to assess if primary prevention with statins is indicated in patients with schizophrenia because they have in general a higher risk of developing cardiovascular disease and a lifespan which is 22.5-25 years shorter than that of the general population.

In years to come patients in this cohort will get older and as a result there will be more power to assess whether and how early on a mortality gap develops between patients with schizophrenia ever on clozapine and those never on clozapine, contrasting each group with matched controls from the Icelandic population.

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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.

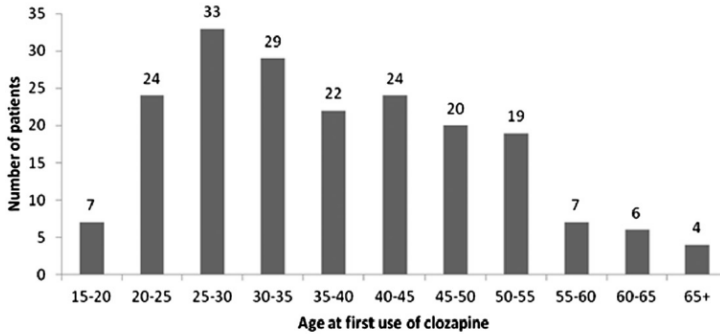

Figure 1. Age of patients when clozapine treatment was first used (n = 195).

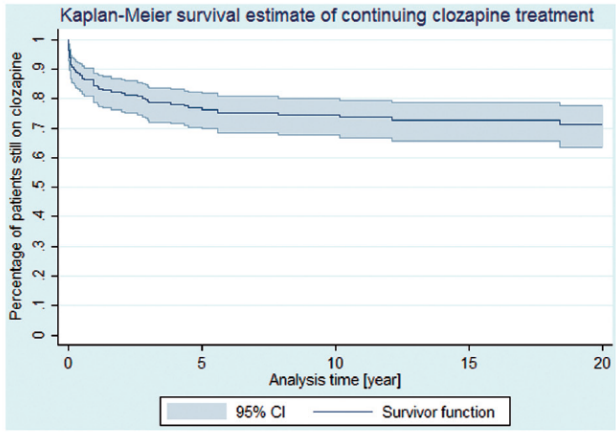

Figure 2. Proportion of patients who stay on clozapine after the latest start of clozapine treatment (n = 201).

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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The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Paper II

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RESEARCH ARTICLE Open Access

Neutropenia and agranulocytosis during treatment of schizophrenia with clozapine versus other antipsychotics: an observational study in Iceland

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Abstract

Background: Data on the haematological outcomes of patients who continue clozapine treatment following neutropenia are very rare as even mild neutropenia results in mandatory discontinuation of clozapine in most countries. However, in Iceland where clozapine monitoring is less stringent allows an observational study to be done on the risk of agranulocytosis and neutropenia during treatment with clozapine compared with other antipsychotics among patients with schizophrenia.

Methods: The present study is a part of a wider ongoing longitudinal study of schizophrenia in Iceland. We identified 201 patients with schizophrenia treated with clozapine and 410 patients with schizophrenia who had never been on clozapine by searching the electronic health records of Landspitali, the National University Hospital. Neutrophil counts were searched in electronic databases to identify patients who developed neutropenia/agranulocytosis and the frequency of neutrophil measurements was examined as well.

Results: The median number of days between neutrophil measurements during the first 18 weeks of clozapine treatment was 25 days but after the first 18 weeks on the drug the median became 124 days. Thirty four cases of neutropenia were identified during clozapine treatment with an average follow up time of 9.2 years. The majority, 24 individuals developed mild neutropenia (1500–1900 neutrophils/mm^3). None of these progressed to agranulocytosis. The remaining 10 patients developed neutropenia in the range 500–1400 /mm^3 of whom one developed agranulocytosis, three stopped clozapine use and 6 patients continued on clozapine for at least a year without developing agranulocytosis. Unexpectedly, schizophrenia patients on other antipsychotics had an equal risk of developing neutropenia as those on clozapine.

Conclusions: Neutropenia is common both in patients with schizophrenia on clozapine treatment and in those never on clozapine. Therefore a large part of neutropenia during clozapine treatment is probably not caused by clozapine. These findings have implications in assessing the balance between the risk of progression from neutropenia to agranulocytosis against the morbidity resulting from the premature discontinuation of clozapine under the current monitoring regulations in the US and in most of Europe.

Keywords: Schizophrenia, Clozapine, Antipsychotics, Neutropenia, Agranulocytosis

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Background

Around 20–30% of patients with schizophrenia prove to be treatment resistant, defined as failure to respond to two or more antipsychotics (one of which should be an atypical) when given an adequate dose for at least six to eight weeks [1, 2]. Clozapine has been demonstrated to be the drug of choice for these patients [3, 4].

Some physicians are reluctant to prescribe clozapine, probably because of the relatively high burden of adverse side effects, especially the rare but potentially life-threatening agranulocytosis [4]. Even though clozapine has a high burden of various adverse side effects we have reported that over 70% of patients that commence clozapine treatment in Iceland remain on it long term [5]. A pharmacogenetic test for agranulocytosis with adequate predictive validity is unlikely and would likely present ethical challenges [6, 7]. The risk of agranulocytosis is managed in most developed countries by mandatory blood monitoring for patients on clozapine [8]. In the UK patients taking clozapine must enrol in a clozapine monitoring service where it is obligatory to be monitored weekly for the first 18 weeks of treatment. During the next 34 weeks neutrophil monitoring is done every other week and then monthly after the first year of monitoring has passed [9]. The risk of agranulocytosis is estimated to be 0.68% but after the first year this risk drops by a factor of 10 [10, 11]. The mortality when agranulocytosis develops has been estimated to be 2.7–3.1% [12, 13]. Therefore the absolute mortality of patients on clozapine due to agranulocytosis is very low or around 0.02% or two out of ten thousand patients. Regular blood monitoring has been reported to be effective in reducing this risk [14] but it also places limitations on the use of clozapine in three ways: firstly, by excluding patients living in areas where clozapine monitoring systems are not in place, secondly by making physicians reluctant to prescribe it, thirdly by placing an additional burden on patients, and lastly by requiring that any patient whose neutrophil count drops below 1500/mm3 discontinues clozapine permanently [15]. There is growing evidence that clozapine treatment is associated with

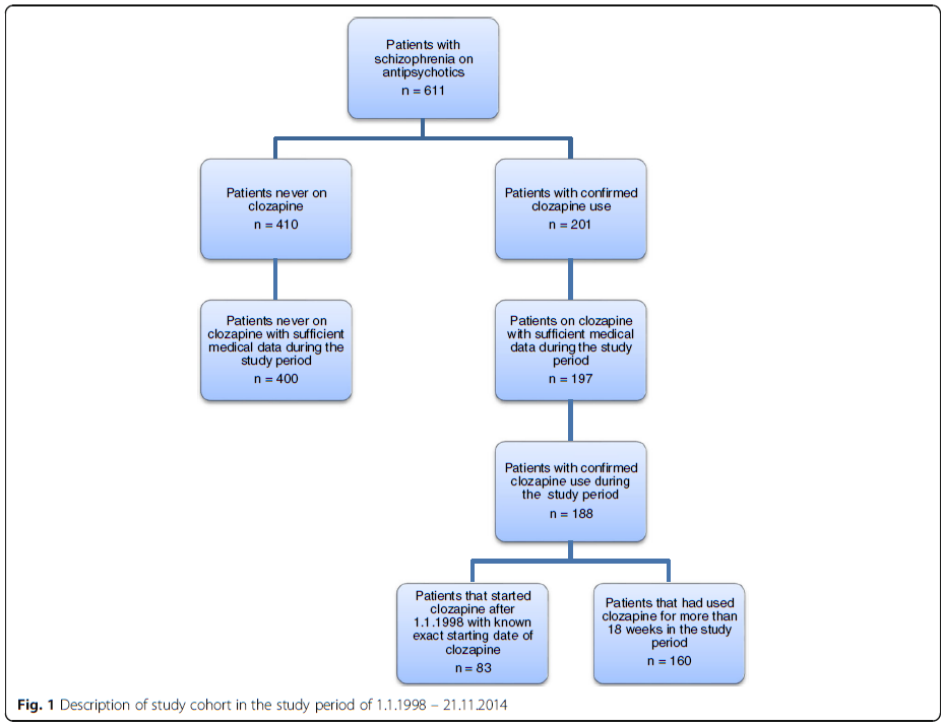

Fig. 1 Description of study cohort in the study period of 1.1.1998 – 21.11.2014

reduced mortality compared to treatment with other antipsychotics [16].

Monitoring systems are in place in the United States and in most European countries but the regulation of clozapine use varies substantially between countries [8]. Some countries, including Iceland, have taken a more flexible stance and not enforced such regulations for clozapine prescriptions in view of the fact that there is no other alternative drug available with similar efficacy for treatment resistant schizophrenia, as well as the practical difficulties of regular monitoring in remote areas.

People of certain ethnic groups, such as Yemenite Jews and 25–50% of black Africans, commonly have an intrinsic low neutrophil count in the range of 1.0 – 1.5 without any observed adverse clinical effects such as more frequent bacterial infections. These individuals are said to have benign ethnic neutropenia (BEN) [17]. According to the UK guidelines, clozapine treatment is stopped when neutrophil count falls below 1500/mm^3. By following this recommendation it can be quite challenging to provide clozapine to these patients. This reality was acknowledged in the USA in the recent change of recommendations in October 2015 by the Food and Drug Administration (FDA) with a relaxation of the requirement to stop clozapine treatment when the neutrophil count falls below 1000/mm^3 [18]. Prescribers can now continue to prescribe clozapine treatment for patients with an neutrophil count less than 1000/mm^3 if the prescriber's evaluation is that the benefits of clozapine therapy outweigh the risk of severe neutropenia [18].

The risks and benefits of changing or abolishing clozapine monitoring are difficult to quantify owing to a lack of evidence on the natural course of neutrophil counts in the absence of a monitoring programme.

The aim of this study

To analyze the risk of neutropenia and further the progression to agranulocytosis in a sample of patients with schizophrenia in Iceland, where it is not mandatory to provide blood samples at certain intervals in order to get clozapine dispensed.

Methods

Study population

The present study is a part of a wider ongoing longitudinal study of psychotic disorders in the Landspitali University Hospital (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 have been invited to take part in the study. Almost all the patients in study have been admitted to LUH. Most of the patients were recruited in 2000–2004. In this study we looked at patients in the LUH cohort who were alive on the 1.1.2003 and who had a confirmed diagnosis of schizophrenia according to the Research Diagnostic Criteria, assessed using the "Schedules for Affective Disorder and Schizophrenia-Lifetime version" (SADS-L) [19]. In total there were 611 patients who met the criteria (Fig. 1).

LUH introduced electronic health records (EHR) in 1998 but older health records are available on paper. Subsequently the proportion of medical, psychology and nursing data in the EHR has been steadily growing and currently includes almost all patient data in LUH.

LUH is the only tertiary hospital for mental health services in Iceland. LUH also provides secondary psychiatric services and psychiatric inpatient beds for over 90% of the population, the proportion being even higher for treatment resistant patients. Therefore the overwhelming majority of all Icelandic patients with schizophrenia who have ever taken clozapine have been in regular contact with mental health services or other services at LUH.

Case identification

To identify patients that have used clozapine we used a keyword search in the EHR for the words "clozapin", "closapin" and "Leponex". The "e" at the end of clozapin was skipped because of possible spelling errors in the EMR but a keyword search of "clozapin" will find both "clozapin" and "Clozapine". Leponex was the only brand name of clozapine in Iceland during the study period. All medical notes with the clozapine keywords were reviewed to confirm clozapine use. Wherever insufficient documentation of prior psychotic disorder and medication use was present in the EHR, the paper medical records were reviewed. We identified 201 patients with schizophrenia. The remaining 410 patients with schizophrenia who had never used clozapine but had been treated with other antipsychotics comprised the comparison group. Information on the first period of clozapine treatment for patients with schizophrenia was available for 195 patients out of 201.

Frequency of blood tests

The frequency of blood measurements was analyzed for patients treated with clozapine from 1.1.1998 until 21.11 2014. The frequency of measurements was calculated by dividing the total time on clozapine treatment by the number of neutrophil measurements. The frequency of measurements during the first 18 weeks was analyzed separately from the subsequent time-period. The frequency analysis for neutrophil measurements only included patients who were using clozapine for the first time. Eighteen patients for whom the clozapine start date was not known to an exact date and four patients

who did not live in the Reykjavik metropolitan area, where LUH is situated, were excluded from the blood monitoring analyzes for the first 18 weeks.

Identification of neutropenia or agranulocytosis

We searched electronically all available results of blood measurements at LUH for neutrophil counts. The LUH database is linked to regional laboratory databases in Iceland using the Icelandic social security number (kennitala) which is a unique personal identifier for each Icelander. Among these is the database in the regional hospital in Akureyri where Iceland's only other department of psychiatry is located in Iceland's second largest hospital. This department provides mental health services for the remaining 10% of Iceland's population. We also used a keyword search in the EHR to identify additional cases with the following keywords to find medical notes where neutropenia or agranulocytosis were mentioned; "Neutropaenia", "neutropaenia", "neutropenia", "leucopaenia", "leucopenia", "kyrningafæ", "hvítkornafæ". The complete medical notes, electronic as well as on paper, were reviewed in order to confirm the diagnosis.

Neutrophil count in the range of 1500/mm^3 – 1900/mm^3 was defined as mild neutropenia. Icelandic guidelines recommend that if neutrophils counts are 1500/mm^3-1900/mm^3 then neutrophil monitoring should be increased to twice every week until the neutrophil count rises to 2000/mm^3 or above, whereas if neutrophils fall below 1500/mm^3 treatment should be stopped [15, 20]. Neutrophil count in the range 1000/mm^3-1400/mm^3 was defined as moderate neutropenia and neutrophil count in the range of 500/mm^3-900/mm^3 as severe neutropenia [20]. Agranulocytosis literally means the absence of circulating granulocytes but the term is used in clinical practice in psychiatry when the neutrophil count falls below 500/mm^3 [20]. Neutrophil counts in Iceland are rounded to the nearest 100/mm^3.

The STROBE guidelines for reporting the results of observational studies were followed. Statistical analyses were performed with STATA, version 13. A Cox proportional hazard model was used to assess factors associated with neutropenia. One patient was excluded from the Cox proportional hazards model because he used clozapine only for one day.

Results

Neutrophil monitoring

In Iceland the guidelines for neutrophil monitoring recommend weekly neutrophil counts for the first 18 weeks and monthly subsequently, but these guidelines are not enforced in a mandatory way [15]. Table 1 describes the frequency of neutrophil measurements after clozapine treatment was started. During the first 18 weeks of treatment a total of 16 out of 83 patients discontinued clozapine. Neutrophils were measured weekly or more often for only 12 out of 83 patients (14.4%). Neutrophil measurements were performed every 5 weeks or less for 22 patients (26.5%) and 7 patients had no neutrophil measurements done. The mean number of days between neutrophil measurements was 25 days (SD = 28) and the median number of days between blood tests was 18 days.

Table 1 Frequency of neutrophil measurements during clozapine treatment

Measurements	n	%
First 18 weeks ($n = 83$)		
Weekly	12	14.5
Every 1–2 weeks	22	26.5
Every 2–3 weeks	15	18.1
Every 3–4 weeks	6	7.2
Every 4–5 weeks	6	7.2
Less than every 5 weeks	22	26.5
After 18 weeks ($n = 160$)		
Monthly	6	3.8
Every 1–2 months	33	20.6
Every 2–3 months	25	15.0
Every 3–6 months	31	19.4
Every 6-12months	37	21.3
Less than every year	31	20.0

Only 6 out of 160 patients (3.8%) had at least monthly measurements of neutrophils carried out in line with guidelines. The median number of days between neutrophil measurements was 124 days. If the 7 patients who had no neutrophil measurements done are excluded the mean number of days between measurements is 229 (SD = 329).

Progression from neutropenia to agranulocytosis

Table 2 shows how frequently neutropenia progressed to agranulocytosis in our sample. For mild to moderate neutropenia (1000-1900/mm3) no progression to agranulocytosis was observed for 32 cases. If we only include patients that stayed on clozapine for at least one year following mild to moderate neutropenia then none of 28 patients developed agranulocytosis. For patients with moderate to severe neutropenia (<1500/mm3) one patient out of 10 developed agranulocytosis. It is worth noting that only 2 out of 8 (25%) patients with moderate neutropenia discontinued clozapine compared with 28.8% discontinuation for all patients ever prescribed clozapine for treatment resistant schizophrenia in our sample.

Neutropenia in patients with schizophrenia

Table 3 describes the results of neutrophil measurements with regard to low neutrophil count in the period 1.1.1998 – 21.11.2014. We found only one 56 year old

Table 2 Progression of lowest neutrophil count to agranulocytosis

Lowest neutrophil count (excluding counts taken during episode of agranulocytosis)	Amber: Mild neutropenia 1500-1900/mm3	Red: Moderate neutropenia 1000-1400/mm3	Severe neutropenia 500-900/mm3
	n = 24	*n* = 8	*n* = 2
One year after lowest level of neutropenia			
Still on Clozapine	22	6	0
Clozapine discontinued	2	2	1
Developed agranulocytosis (and then discontinued)	0	0	1
Clozapine and agranulocytosis status unknown	0	0	0
Three years after lowest level of neutropenia			
Still on Clozapine	18	4	0
Clozapine discontinued	3	2	1
Developed agranulocytosis (and then discontinued)	0	0	1
Clozapine and agranulocytosis status unknown	3	2	0

patient on clozapine whose neutrophils dropped below 500/mm^3, a count clinically defined as agranulocytosis. Clozapine was identified as the most likely contributing factor. Since this patient had been on clozapine for 28 years when the agranulocytosis developed it cannot be excluded that unknown age-related causes were at play [11, 12]. Neutrophil measurements in the moderate to severe range of 500-1400/mm^3 were found in 9 patients in the clozapine group or 4.8% of the cohort, on all occasions these were 900/mm^3 and above. Moderate to severe neutropenia in the never-on-clozapine group was found in 23 patients or 5.8% of the cohort, and all the neutrophil counts were 800/mm^3 and above.

Patients in the never-on-clozapine group proved to have a similar risk of developing agranulocytosis in the long term since four patients out of 400 (1%) developed agranulocytosis during the same period of observation. However, two out of four did develop agranulocytosis while on cytotoxic treatment due to cancer. The third case was clinically thought to have been caused by interferon treatment for hepatitis C. A likely cause could not be identified in the fourth case but possible contributing factors were alcohol abuse, malnutrition and hepatitis C.

Table 3 Lowest neutrophil count in the clozapine group and never-on-clozapine group

	On clozapine		Never-on-clozapine	
Average age at follow up [Years]	51.2		58.1	
Average number of neutrophil measurements per patient	32.4		15.8	
Average time of follow up [Years]	9.2		13.8	
	n = 188	%	*n* = 400	%
No neutrophil measurements performed in time period	6	3.2	8	2.0
Never neutropenia, neutrophils 2000/mm3 or higher	148	78.7	335	83.8
Mild neutropenia, neutrophils 1500-1900/mm3	24	12.8	30	7.5
Moderate neutropenia, neutrophils 1000-1400/mm3	8	4.3	20	5.0
Severe neutropenia, neutrophils 500-900/mm3	1	0.5	3	0.8
Agranulocytosis, neutrophils 0-400/mm3	1	0.5	4	1.0

Table 4 shows Cox proportional hazards models exploring the factors associated with detecting various degrees of neutropenia. When the outcome under scrutiny was neutrophils in the range of 0-1900/mm^3 then neutropenia was associated with more frequent testing, younger age and female sex. Being on clozapine was not significantly associated with risk for developing neutropenia.

Discussion

Neutrophil monitoring in Iceland was far less frequent than guidelines recommend. Neutropenia was equally commonly observed in the clozapine group as in the group that had never used clozapine, although mild neutropenia was more common in patients on clozapine. Of the eight patients on clozapine who developed a moderate neutropenia (neutrophils 1000 – 1400/mm^3), which would have resulted in mandatory cessation of clozapine in the UK, only two discontinued clozapine. The other six remained on clozapine a year later and none of these six suffered a further episode of neutropenia. Of two patients whose neutrophil count fell below 1000/mm^3, one went on to develop agranulocytosis, having been of clozapine for 28 years.

The occurrence of mild (12.8%), moderate (4.3%) and severe neutropenia (0.5%) was fairly commonly identified in patients on clozapine despite the low frequency of measurements. Since more frequent measurements were significantly associated with neutropenia, it is likely that the occurrence of mild to moderate neutropenia would

Table 4 Cox proportional hazards model with possible factors associated with detecting moderate to severe neutropenia and agranulocytosis

	Hazard Ratio	Standard Error	Z-Score	95% CI	*P*-value
A. Neutrophils 0 - 1900/mm3					
Patient on clozapine	1.33	0.33	1.14	0.81-2.18	0.25
Sex (female)	1.82	0.40	2.76	1.19-2.80	0.01
Average age at risk	0.97	0.01	−3.75	0.96-0.99	<0.001
Measurements per year	1.14	0.02	6.32	1.09-1.18	<0.001
B. Neutrophils 0 – 1400/mm3 (equivalent to red result)					
Patient on clozapine	0.74	0.33	−0.68	0.31-1.76	0.50
Sex (female)	2.00	0.67	2.08	1.04-3.88	0.04
Average age at risk	0.98	0.01	−1.47	0.96-1.00	0.14
Measurements per year	1.17	0.04	4.66	1.10-1.26	<0.001
C. Neutrophils 1000 - 1900/mm3					
Patient on clozapine	1.44	0.37	1.39	0.86-2.40	0.18
Sex (female)	1.76	0.41	2.46	1.12-2.77	0.03
Average age at risk	0.97	0.01	−3.85	0.95-0.98	<0.001
Measurements per year	1.13	0.02	5.98	1.09-1.18	<0.001
D. Neutrophils 1500 – 1900/mm3 (equivalent to amber result)					
Patient on clozapine	1.86	0.58	1.99	1.00-3.43	0.05
Sex (female)	1.70	0.49	1.85	0.97-3.00	0.09
Average age at risk	0.96	0.01	−3.70	0.94-0.98	<0.001
Measurements per year	1.12	0.03	4.62	1.06-1.17	<0.001

A) $n = 587$, 89 cases. B) $n = 587$, 37 cases. C) $n = 587$, 80 cases. D) $n = 587$, 52 cases

have been higher if the frequency of measurements had been in line with guidelines.

Moderate (5%) and severe neutropenia (0.8%) was more common in patients with schizophrenia who had never been on clozapine despite having neutrophil counts done around half as frequently as those on clozapine. Only mild neutropenia was found more frequently in clozapine-treated patients than in those never on clozapine.

It came as a surprise that being on clozapine was not associated with neutropenia in the range of 0-1400/mm^3. For mild neutropenia in the range 1500-1900/mm^3 being on clozapine was, on the other hand, significantly associated with almost doubling of the risk for neutropenia (hazard ratio of 1.86). Therefore, treatment with clozapine seemed to predict mild neutropenia, a phenomenon which is usually clinically insignificant but that can probably increase the likelihood of clozapine treatment being discontinued. Females had a higher risk of developing neutropenia with a hazard ratio ranging from 1.70-2.00, depending on the neutropenia range under observation. It has been reported that agranulocytosis during clozapine treatment is more common among females [12]. Neutropenia was also significantly more common with lower age which is in line with what has been shown in larger studies [11].

It can be concluded that most of the neutropenic episodes in our sample were transient and of no observable clinical significance. However, of those developing mild neutropenia (neutrophils 1500 – 1900/mm^3), none subsequently developed agranulocytosis. One study has reported that the rate of neutropenia during clozapine treatment was 11.8% as compared to 17.6% for those on second generation antipsychotics [21]. These results concur with ours and indicate that mild to moderate neutropenia is not a good predictor for clozapine induced agranulocytosis.

In our never-on-clozapine group four cases of agranulocytosis were identified and in three cases a plausible explanation was identified but the main cause was speculative in the fourth case. If that patient had been on clozapine then the agranulocytosis would almost certainly have been attributed to clozapine treatment because no other probable causes were found. The risk of neutropenia in the clozapine group was similar to that in the never-on-clozapine group, indicating that in many if not most instances of neutropenia during clozapine

treatment observed neutropenia may in fact not be caused by the clozapine treatment.

The progression from neutropenia to agranulocytosis was low in our sample. When we look at patients that had ever developed neutropenia in the range of 500–1900/mm^3 and had used clozapine for at least a year after developing neutropenia or agranulocytosis, then only one patient out of 29 (3.4%) progressed to agranulocytosis. These results should though be interpreted with caution because the sample is small and we note that a 95% confidence interval for one event in 32 cases is 0 to 9.5%. The progression rate of neutropenia to agranulocytosis for patients with neutropenia in the more restrictive range of 500-1400/mm^3 who continued to take clozapine for at least a year after developing neutropenia, was 1 out 7 (14.2%). Most guidelines recommend stopping clozapine treatment when neutrophils fall below 1500/mm^3 so such data on patients who continue on clozapine following a "red result" is not often available. In a study by Hummer et al. 8 out of 68 patients were diagnosed with transient neutropenia that resolved without any change in treatment but the average neutrophil count was in the mild neutropenia range, 1780/mm^3 [22].

The frequency of neutrophil measurements in Iceland during the first 18 weeks of treatment proved to be far lower than guidelines recommend, the median time between measurements being 18 days instead of weekly. The frequency of neutrophil measurements after the first 18 weeks were also far from what guidelines suggest, the median time between measurements being 124 days instead of monthly. The infrequent neutrophil measurements did, however, not lead to more frequent agranulocytosis than expected, and the only patient who developed agranulocytosis did so after being on clozapine for over 28 years and recovered fully. It is possible that the inclination to accept flexible neutrophil monitoring, accepting that many treatment resistant patients find it difficult, unpleasant or costly to turn up weekly for blood tests as outpatients, may have contributed to a higher proportion of patients staying on clozapine long term in Iceland than reported in some other studies [23, 24].

There are some limitations in our dataset. When analyzing the neutrophil monitoring data we had access to the blood test databases in LUH and the regional hospital in Akureyri. There are two private blood test facilities that we did not have access to and it is possible that some blood measurements were done there. However most patients with schizophrenia and nearly all those on clozapine are followed up from the LUH. Some neutrophil measurements in the database may not have been requested for the purpose of clozapine blood monitoring but for other medical reasons. Therefore the true neutrophil monitoring associated with clozapine may be a little bit more or less than we state in the results. The true prevalence of neutropenia might also be underestimated if it had been diagnosed in the private blood test facilities.

It is likely that many patients stop clozapine treatment because of low neutrophil measurements despite the risk of agranulocytosis being small in mild to moderate neutropenia. Our data suggest that the majority of patients who stop clozapine treatment after falling into the "red zone" (neutrophils < 1500/mm^3) would probably not develop agranulocytosis were they to remain on treatment, particularly if their neutropenia is in the 1000-1500/mm^3 range. Clozapine rechallenge should be assessed as an option in those patients if no other treatment has had the same observed clinical treatment effect as clozapine. The reduced mortality associated with clozapine treatment is substantial [16] and this is likely to outweigh the small risk of agranulocytosis in patients who continue clozapine treatment despite mild to moderate neutropenia. The risk of dying from agranulocytosis on clozapine has been estimated to be 0.02% [10–13]. We can contrast that risk to the risk of dying in a road traffic accident in Europe over a 40 year period which has been reported to be 0.37% (1- $(1–9.3/100.000)^{40}$) [25]. Therefore, in Europe a patient on clozapine for 40 years has an 18.5 times (0.37%/0.02%) higher risk of dying in a road traffic accident than of dying from agranulocytosis.

There is a large population of schizophrenia patients who are currently suboptimally treated; having previously made a response to clozapine that was subsequently discontinued due to neutropenia. Particularly where the neutropenia was in the 1000–1500 range, consideration should be given for clozapine rechallenge in these cases, bearing in mind that 80% of patients can be successfully challenged with careful patient selection and monitoring [26]. There is a strong case for actively seeking out such patients for clozapine rechallenge, and this approach has been shown to be successful [27].

Conclusions

Our data would support revisions to current European guidelines, as those called for by Cohen [28]. Specifically, our results suggest that consideration could be given to reducing the lower limit of the amber range, whereby clozapine can be continued with additional monitoring, from 1500 to 1000. This change would result in a much lower rate of clozapine discontinuation, and our findings suggest that the progression to agranulocytosis would remain a rare event. Such a limit has been introduced in the UK for patients with benign ethnic neutropenia [29] and is in line with the new FDA guidelines regarding clozapine monitoring [18].

Abbreviations

CI: Confidence interval; EHR: Electronic health records; FDA: Food and drug administration; LUH: Landspitali University Hospital; NIHR: National Institute for Health Research

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Availability of data and materials
Data sets are not available to readers due to ethical considerations.

Authors' contributions
Authors OI and ES designed the study and wrote the protocol. Authors OI, ES, HJ and MH were involved in the data collection. Author OI wrote the first draft of the manuscript and undertook the statistical analysis. Authors OI, JHM and ES managed the literature searches and analyses. All authors contributed to writing the manuscript. All authors reviewed and approved the final draft of the manuscript.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Not applicable.

Ethics approval and consent to participate
The study has been approved by the National Bioethics Committee (FS-02-041(03–030)) and the Data Protection Authority (2009090737ÞS). All participants gave written informed consent.

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ORIGINAL ARTICLE

Risk of diabetes and dyslipidemia during clozapine and other antipsychotic drug treatment of schizophrenia in Iceland

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ABSTRACT

Background: Type 2 diabetes (T2D) and raised blood lipids are associated with the use of antipsychotics, not least clozapine.

Aims: To describe the prevalence of high blood glucose levels, T2D, and dyslipidemia, in association with the use of clozapine or other antipsychotics in patients with schizophrenia in Iceland.

Method: This study identified 188 patients treated with clozapine and 395 patients never treated with clozapine by searching the electronic health records of Landspitali, the National University Hospital. The comparison group consisted of Icelandic population controls. Data were obtained on blood glucose, HbA1c, and blood lipid levels from these health records.

Results: The prevalence of T2D was 14.3% in the clozapine group, where the mean age was 51.2 years, and 13.7% in the never-on-clozapine group, where the mean age was 58.6 years. Males on clozapine were 2.3-times more likely and females 4.4-times more likely to have developed T2D than controls from an age-adjusted Icelandic cohort, while males on other antipsychotics were 1.5-times more likely and females 2.3-times as likely to have T2D than controls. Only one case of ketoacidosis was identified. Triglyceride levels were significantly higher in both treatment groups compared to controls in the age-adjusted Icelandic cohort.

Conclusions: Clinicians must take active steps to reduce the risk of T2D and raised triglycerides in patients with schizophrenia. Antipsychotics were associated with a greater risk of T2D developing in females compared to males.

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Schizophrenia; clozapine; diabetes; dyslipidemia; metabolic

Background

Second generation antipsychotics (SGA) have been widely reported to increase the risk of T2D, obesity, and dyslipidemia during the treatment of psychotic disorders such as schizophrenia (1). Metabolic syndrome has been shown to be more common with patients treated with clozapine (51.9%) than with other antipsychotics in schizophrenia (32.5%) (2). In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, the proportion of males with metabolic syndrome was 36.6%, but 54.2% for females (3). In an Icelandic study of patients with schizophrenia with a mean age of 50 years the prevalence of metabolic syndrome was found to be 57%, compared to 14% in the general population (4). In the same study the prevalence of T2D was 15%.

Most antipsychotics have been associated with weight gain, at least in some patient populations. Olanzapine and clozapine have the highest risk of weight gain (1,5). Ziprasidone, aripiprazole, and amisulpride have the lowest reported risk of weight gain, but risperidone and quetiapine are intermediate in this regard (1). Females may be at higher risk for antipsychotic induced weight gain than males (6). Variants in the genes for the melanocortin 4 receptor (MC4R), the serotonin 2C receptor (HTR2C), the leptin, the neuropeptide Y (NPY) receptor, as well as the cannabinoid receptor 1 (CNR1) genes have been reported to be associated with increased antipsychotic induced weight gain (7). Obesity is the main modifiable risk factor for T2D and 80% of patients are overweight at diagnosis (8). It is important to assess preventive measures for T2D early in the disease course. A lifestyle and life skill intervention for weight gain has been reported to be effective in first episode psychosis (9). It has also been reported that, when switching from an antipsychotic with high risk for weight gain to an antipsychotic with less risk for weight gain, patients find it easier to lose weight in due course (10).

Clozapine has been found to increase the risk of T2D more than other antipsychotics (11). In addition to increasing the risk of T2D through weight gain, clozapine has been reported to suppress glucose-stimulated insulin secretion in rodent pancreatic islets (12). Aripiprazole and ziprasidone are associated with the lowest risk, and some studies report no added risk for patients on these drugs (13–15). The risk for T2D has been reported to be dose-dependent for some antipsychotics such as olanzapine, risperidone, and quetiapine (14).

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Apart from genetics and obesity, other risk factors for T2D include: age, unhealthy diet, physical inactivity, smoking, alcohol consumption, and obstructive sleep apnea (16).

Patients treated with antipsychotics have an estimated 10-times the risk of developing ketoacidosis compared to the normal population (17). The incidence of ketoacidosis during clozapine treatment in the US has been estimated to be 1.2–3.1% (18).

Dyslipidemia, a well-known risk factor for coronary artery disease, is characterized by elevated triglycerides, high total cholesterol, high levels of low density lipoprotein (LDL), and low levels of high density lipoprotein (HDL) (19). Clozapine and olanzapine have been associated with an increase in triglyceride levels in patients with schizophrenia (1,20,21). Risperidone has also been associated with increased triglyceride levels (21). Some studies have shown an increase in total cholesterol and lowering of HDL during treatment with olanzapine and clozapine, while other studies have not detected such changes (1,20,21). Other antipsychotics like amisulpride and ziprasidone have been reported to have a more favorable effect on blood lipid profiles and may, therefore, be preferable for patients who have developed the metabolic syndrome (22).

Life expectancy in schizophrenia is reduced by more than 20 years, mainly due to relatively poor physical health, although a high risk for suicide also has an impact (23). Antipsychotic drug use in schizophrenia is associated with higher life expectancy, even though antipsychotics are associated with metabolic side-effects (23). Clozapine has been reported to have more adverse effects than other antipsychotics, but there is evidence that clozapine reduces the risk of suicide as well as overall mortality compared to other antipsychotics (23). A study in the US reported the rate of death from cardiovascular disease in Hispanic and African-American patients receiving clozapine to be 4.3- and 11.5-times the rate in Caucasian patients, so the risk of death from cardiovascular disease for patients on clozapine may depend on genetic makeup, as well as diet and social factors (24).

Aims

The aim of this study is to analyze the prevalence of diabetes and dyslipidemia in a well-described sample of Icelandic schizophrenia patients on clozapine, as well as patients with schizophrenia who have never been on clozapine. In order to assess the standardized morbidity ratio of diabetes and dyslipidemia for both groups, the results will be contrasted with prevalence figures based on Icelandic population cohorts.

Methods

Study population

The study population has been described in a previous article by the same authors (25). The study is a part of an ongoing study of psychotic disorders in the Department of Psychiatry at Landspitali University Hospital (LUH), focusing on patients with schizophrenia and bipolar disorder. In this study we looked at patients in the LUH cohort who were alive on 1 January 2003 and who had a confirmed diagnosis of schizophrenia according to the 'Schedules for Affective Disorder and Schizophrenia-Lifetime version' (SADS-L) (26). In total, there were 611 patients who met the criteria. All participants gave written informed consent. We identified in this way 201 patients with schizophrenia who had used clozapine and 410 patients with schizophrenia who had never used clozapine but had been treated with other antipsychotics. To identify patients that had used clozapine, we did a keyword search in the electronic health records for 'clozapin', 'closapin', and 'Leponex'. All medical notes with the clozapine keywords were reviewed to assess both whether clozapine had been used and the time frame of use. For patients that had insufficient documentation of prior psychiatric illness and medication use in the her, the paper medical records were reviewed for clozapine use.

Figure 1 shows that there were 188 patients in the clozapine group older than 25 years with sufficient medical data. Of them, 33 died between 1 January 2003–21 November 2014. Of the 400 patients in the non-clozapine group for whom we had sufficient medical data, 114 patients died between 1 January 2003–21 November 2014.

Mean age was calculated using the lowest age observed at the following three potential end-points: Age at the end

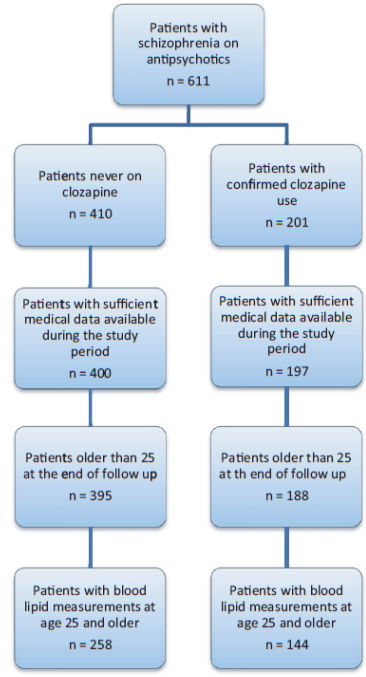

Figure 1. Description of study cohort in the study period of 1 January 1998–21 November 2014.

of the study (21 November 2014), age when a patient died, or age when no further medical data was available on a patient in our database.

Metabolic disorders

T2D was diagnosed if the patients had a formal diagnosis of T2D, HbA1C $\geq$ 6.5% on two separate occasions or two measurements of fasting plasma glucose over 12.6 mg/l (7.0 mmol/l). The patient's primary physician was contacted if additional blood samples were needed to assess if the patients had developed T2D. High risk of T2D was labelled if the last measurement of HbA1c was in the range 6.0–6.4%. Ketoacidosis was diagnosed if a clinical diagnosis of ketoacidosis could be confirmed. In accordance with the ATP-III guidelines we defined LDL in the range 160–189 mg/dl (4.13–4.89 mmol/l) as high LDL, and LDL over 190 mg/dl (4.90 mmol/l) as very high (19). Total cholesterol over 200 mm/dl (5.17 mmol/l) was defined as high. Triglycerides between 200–499 mg/dl (2.56–5.63 mmol/l) were defined as high, and triglycerides over 500 mg/dl (5.65 mmol/l) as very high. When analysing statin use while patients were taking clozapine, we used the last known medication regimen stated in the medical notes before the end of follow-up, or the date when the patient discontinued clozapine.

A keyword search in the electronic health records was done, to find medical notes where the metabolic disorders were mentioned. For diabetes, we looked for 'diabetes', 'sykursýki', 'metformin', 'glucophage' and 'T2D'. For ketoacidosis, we looked for 'ketoacidos' and 'ketona'. For dyslipidemia, the blood lipid measurements in the blood test database were analysed. All blood measurements of: HbA1c, glucose, total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides were collected electronically via the electronic health records. When assessing blood lipids, the latest measurements of blood lipids were used. For patients on clozapine we used the latest blood measurements while the patient had been receiving clozapine.

Statistical analysis

Statistical analyses were performed with STATA, version 13. A Cox proportional hazard model was used to assess the association of blood sugar values over 13 mm/l with 'average time at risk', 'clozapine ever used', and 'T2D at the end of follow-up'. Time at risk for patients on clozapine was defined as the start of clozapine treatment or the start of the study period if the patients had commenced clozapine treatment before the onset of the study period, until one of the following end-points was reached: a measurement of blood sugar value over 13 mm/l, end of the study period, patient died or when the patient discontinued clozapine treatment. Time at risk for patients never on clozapine was defined as the onset of the study period, until one of the following end-points was reached: a measurement of blood sugar over 13 mm/l, end of the study period, or when the patient died. We tested for the proportional hazards assumption using the estat phtest in STATA.

The prevalence of T2D and blood lipid levels were compared to a population of Icelanders using data from the Icelandic National Heart Association, making use both of data from the AGES (27) and the REFINE (Risk Evaluation For INfarct Estimates) studies. The prevalence of T2D and blood lipid levels were calculated for men and women by age ranges of 5 years from 25–90. The prevalence of T2D and blood lipid levels in different age ranges of the Icelandic population controls was used to calculate the expected prevalence of T2D and blood lipid levels. This comparison indicated what prevalence of T2D and lipid levels could be expected if comparable age groups were examined in the general population.

Results

Prevalence of diabetes in patients with schizophrenia

The observed prevalence of T2D was 14.3% in the clozapine group, where the mean age was 51.2 years, whereas the observed prevalence of T2D was 13.7% in the never-on-clozapine group, where the mean age was 58.6 years. Table 1 describes the prevalence of diabetes in the cohort in more detail. The age-adjusted difference of T2D for the groups is shown in Table 2.

In the clozapine group the prevalence of T2D for females was 16.1%, which was higher than for males where the

Table 1. Diabetes in patients with schizophrenia treated with clozapine and those never treated with clozapine.

	Clozapine		Never-on-clozapine	
	Male ($n = 132$)	Female ($n = 56$)	Male ($n = 245$)	Female ($n = 150$)
Patients with type 2 diabetes (T2D)	18	9	31	23
T2D diagnosed before clozapine treatment	4	3	—	—
T2D diagnosed during clozapine treatment	11	5	—	—
T2D diagnosed after discontinuation of clozapine treatment	3	1	—	—
Patients with type 1 diabetes (T1D)	1	0	2	0
Patients with of T1D and T2D	19	9	33	23
Patients with a high risk of T2D (HbA1c in range of 6.0–6.4%)	13	9	15	8
Patients with T1D, T2D, or a high risk of T2D	32	18	48	31
Prevalence of T2D	13.6%	16.1%	12.7%	15.3%
Prevalence of T1D, T2D, or a high risk of T2D	23.5%	32.1%	18.8%	20.7%
Patients on metformin without a diagnosis of T2D or T1D	5	5	—	—
Mean age at end of follow-up	50.0 (11.9)[a]	54.3 (11.4)[a]	56.7 (14.2)[a]	61.5 (16.1)[a]
Mean follow-up period during clozapine treatment in years	9.3 (5.9)[a]	8.9 (5.6)[a]		
Mean follow up period in years			14.0 (3.9)[a]	13.5 (3.8)[a]

[a]Standard deviation.

proportion of T2D was 13.6%, but the difference was not significant ($p = 0.32$).

Prevalence of T2D in patients with schizophrenia compared to Icelandic population controls

Table 2 shows that T2D was more common in patients with schizophrenia than in Icelandic population controls adjusted for sex and age. The standardized morbidity ratio for T2D was highest for females on clozapine, 4.4.

Time from onset of clozapine treatment to diabetes

For patients diagnosed with T2D during clozapine treatment, the mean time from initiation of clozapine treatment to diagnosis of T2D was 7.7 years (SD = 6.7) and the median time was 7.3 years. The range of T2D diagnosis was from 43 days to 25.3 years. The four patients that were diagnosed with T2D diabetes after clozapine discontinuation were diagnosed with T2D 69 days, 3.2 years, 5.6 years, and 7.8 years following discontinuation.

Ketoacidosis and high blood sugar

Table 3 demonstrates that not a single case of ketoacidosis was identified in the group of patients on clozapine, and only a single case in the never-on-clozapine group. Therefore, the proportion of ketoacidosis in the whole group was only 0.2% (1/583). The highest glucose measurement found in the group of patients without T1D or T2D was 15.0 mmol/l.

We used a Cox proportional hazards model to assess whether clozapine, age and gender were associated with blood glucose values above 13 mmol/l. While clozapine use was not associated with such blood sugar values, lower age was significantly associated with blood glucose over 13 mmol/l in males but not females.

Table 2. Type 2 diabetes in patients with schizophrenia compared to Icelandic population controls, age- and sex-adjusted.

	Clozapine	Never-on-clozapine
Male		
T2D	13.6%	12.7%
Expected T2D from Icelandic population	5.8%	8.5%
Standardized morbidity ratio	2.3	1.5
Confidence interval (95%)	1.4–3.5	1.0–2.0
p-value	<0.001	0.029
Female		
T2D	16.0%	15.3%
Expected T2D from Icelandic population	3.6%	5.5%
Standardized morbidity ratio	4.4	2.6
Confidence interval (95%)	2.1–7.8	1.7–3.7
p-value	<0.001	<0.001

Blood lipids

In Table 4, the results of blood lipid measurements are presented for 144 patients in the clozapine group and 258 patients in the never-on-clozapine group. In the clozapine group, nine patients (6%) had very high levels of LDL (over 4.9 mmol/l), and a similar proportion was observed in the never-on-clozapine group, where 13 patients were identified (5%). In the clozapine group, 89 patients (62%) had high levels of total cholesterol (over 5.2 mmol/l) and 133 (52%) in the never-on-clozapine group. In the clozapine group, 11 patients (8%) had total cholesterol below 4 mmol/l, but 34 (13%) in the never-on-clozapine group. No patient in the never-on-clozapine group had very high levels of triglycerides (over 5.65 mmol/l), but five patients (3%) in the clozapine group were observed to have such high levels.

In the clozapine group, we had detailed information on drug use for 154 patients and, of these, 16 were using statins (10%) for high cholesterol and one patient (1%) was on a fibrate drug to lower triglyceride levels.

Conclusions

The results of this study indicate that treatment with clozapine increases the risk of T2D 4.4-fold for females and 2.3-fold for males in patients with schizophrenia. The risk of T2D among patients who had never been treated with clozapine was also higher for females than males (2.6- vs 1.5-fold). High blood sugar (over 13 mmol/l) was not associated with clozapine use after correcting for TD2 and age in our sample. Only one case of ketoacidosis was identified among 583 patients during follow-up, lasting, on average, 9.2 years for those on clozapine and 13.8 years for those never on clozapine. Triglyceride levels were elevated both in the clozapine group and in the never-on-clozapine group compared to the standard population. HDL was lower in the clozapine group than in the Icelandic population, but the difference was only significant for males. No significant differences were observed for LDL or total cholesterol.

In line with our findings, a large Medicaid study reported clozapine to be significantly more often associated with higher rates of T2D than other antipsychotics (11). A Dutch study compared the incidence of diabetes in 94 patients with schizophrenia on clozapine to 94 matched patients with schizophrenia that had never been on clozapine over a 5-year period (28). The observed cumulative increase of

Table 3. High blood sugar and ketoacidosis in patients with schizophrenia.

	Clozapine ($n = 188$)					Never-on-clozapine ($n = 395$)				
Highest glucose measurement (mmol/l)	13–20	20–30	30–40	40+	Ketoacidosis	13–20	20–30	30–40	40+	Ketoacidosis
Diabetes status										
Type 2 diabetes ($n = 81$)	7	1	2	0	0	14	12	0	3	0
Type 1 diabetes ($n = 3$)	0	1	0	0	0	1	0	0	0	1
High risk of type 2 diabetes ($n = 45$)	1	0	0	0	0	0	0	0	0	0
No glucose dysregulation ($n = 454$)	0	0	0	0	0	9	0	0	0	0

Table 4. Blood lipids in patients with schizophrenia, both on clozapine and never-on-clozapine vs expected values from Icelandic population controls.

	Clozapine	Expected from Icelandic population	*p*-value	Never-on-clozapine	Expected from Icelandic population	*p*-value
Male (*n*)	99			175		
Mean age at last blood lipid test	47.7	—	—	54.4	—	—
Mean total cholesterol (mmol/l)	5.43	5.23	0.28	5.17	5.25	0.58
Mean LDL (mmol/l)	3.15	3.31	0.27	3.19	3.31	0.36
Mean total HDL (mmol/l)	1.21	1.31	0.04	1.26	1.33	0.10
Mean total triglycerides (mmol/l)	2.34	1.36	<0.01	1.58	1.35	0.04
Female (*n*)	45			83		
Mean age at last blood lipid test	51.9	—	—	58.0	—	—
Mean total cholesterol (mmol/l)	5.84	5.35	0.16	5.39	5.49	0.89
Mean LDL (mmol/l)	3.55	3.22	0.15	3.25	3.32	0.90
Mean total HDL (mmol/l)	1.40	1.65	0.01	1.40	1.66	0.34
Mean total triglycerides (mmol/l)	1.95	1.07	<0.01	1.64	1.13	0.03

diabetes was 22.3% in the clozapine group, but 16% in the non-clozapine group. In this study, the combined prevalence of T1D, T2D, and high risk of T2D was 23.5% for males and 32.1% for females. One possible explanation for this sex difference is that clozapine plasma concentration in females has been reported to be on average 17% higher in females than in males (29). This difference between the sexes has also been reported in a large US study for patients with schizophrenia in the Medicare and Medicaid systems (30).

The proportion of patients at a high risk of developing T2D was twice as high in the clozapine group as in the never-on-clozapine group, 11.7% compared to 5.8%. As one would expect due to neutrophil monitoring requirements, patients on clozapine were more often in contact with LUH and had more frequent measurements of HbA1c (147 out of 188 patients had a least one measurement) than patients never on clozapine (205 out of 395 patients had a least one measurement). We had nine patients in the never-on-clozapine group who had only a single glucose measurement between 13–20 mmol/l without receiving a diagnosis of diabetes or meeting criteria for high risk of diabetes, but those patients are at enhanced risk to be diagnosed with T2D later on. That could possibly explain a part of the differences observed between the groups.

In total, there were 27 patients ever treated with clozapine diagnosed with T2D, and 16 (59%) of these were diagnosed with T2D during clozapine treatment. Of the other 11 patients, seven (26%) were diagnosed before clozapine treatment started and four (15%) after clozapine treatment had been discontinued. This indicates how complicated it is to assess the causality of clozapine-induced T2D in patients with schizophrenia. In a previous study, we reported that two thirds of patients taking clozapine were taking more than one antipsychotic, and used a relatively high WHO defined daily dose (DDD), 1.67, which could also add to the risk of T2D (25). Patients treated with clozapine are the most severely afflicted patients with schizophrenia, and their lifestyle may possibly place them at greater risk of T2D than the lifestyle of other patients with the same diagnosis (31). It is very difficult to control fully for these factors, so treatment resistance itself might be an important risk factor for T2D.

We found 10 patients in the clozapine group who had used metformin but were not diagnosed with diabetes and, of these, five met criteria for high risk of developing T2D. That constitutes 5.3% of all patients on clozapine. Metformin can be used in patients without a diagnosis of diabetes or those at high risk of developing diabetes to counteract the metabolic side-effects of clozapine, including weight gain (32). The use of metformin in our cohort indicates that use of metformin and related drugs cannot be a reliable proxy for the diagnosis of T2D in clinical samples.

Ketoacidosis was a very rare event in our cohort, since only one patient out of 583 developed ketoacidosis, and that condition was probably caused by the patient's T1D, not antipsychotic use. That is much lower than the reported incidence rates of 1.2–3.1% during clozapine treatment in the US (18). However, our sample is smaller than the samples in most US studies, with less power to detect very rare events and, further, in such comparisons it must be borne in mind that the US healthcare system is very different from the Icelandic healthcare system, where access to primary healthcare is universally available to all citizens. We analysed with a Cox proportional hazards model if high blood glucose (over 13 mmol/l) was associated with clozapine treatment using patients with schizophrenia who had never been treated with clozapine for comparison. Clozapine as such was in fact not associated with high blood glucose in all the available blood samples, and the main risk factor for high blood glucose was a diagnosis of diabetes. Accordingly, the risk of ketoacidosis during antipsychotic treatment seems very small, especially if the patients do not have T1D. In a large study from the US Veterans Affairs, 0.2% of patients on antipsychotics were hospitalized because of ketoacidosis, which is comparable to our findings, but in that study the risk was highest for patients on clozapine, 2%, which is higher than we observed in our study (33).

Our results show that antipsychotics, especially clozapine, have more adverse effects on triglyceride values than on cholesterol levels, as has previously been reported (1,34). HDL cholesterol was lower both in the clozapine group and in the never-on-clozapine group than among controls, but the difference only reached statistical significance in the clozapine group. The effects of clozapine on cholesterol levels are not as well established in the literature as the effects on triglycerides. While some studies have reported total cholesterol to be higher and HDL to be lowered, other studies have not replicated such findings (1,20,21). In the clozapine group, 144 out of 188 patients (77%) had at least one measurement of blood lipids done during clozapine treatment. Most guidelines on metabolic monitoring for patients on antipsychotics

recommend that all patients receiving antipsychotic treatment should have blood lipids measured regularly (35). It has been reported that the impact of clinical guidelines on screening and monitoring is minimal-to-poor (35). One of the issues with the lipid monitoring might be that recent guidelines only support statin treatment to lower blood lipids for very high levels of LDL (over 4.90 mmol/l), that is if the patients do not have a diagnosis of T2D, atherosclerotic cardiovascular disease, or at least a 7.5% risk of developing atherosclerotic cardiovascular disease in the next 10 years (19). In our sample of patients on clozapine, where the average age was 51.2 years, only 6% of patients had LDL levels over 4.9 mmol/l. Recent meta-analyses for statin use in primary prevention do report reduced total mortality (36,37). The proportion of patients using statins in our clozapine group was 10%, which is the same ratio as in a Danish cohort study from 2007 on patients with schizophrenia treated with clozapine (38). In our sample, the LDL and total cholesterol levels were very similar in the clozapine group, the never-on-clozapine group, and in the age- and sex-matched Icelandic population controls. Screening in the schizophrenia groups would, therefore, probably not support more statin treatment than screening in the Icelandic population. It is, therefore, unlikely that a young patient diagnosed with schizophrenia, who has neither diabetes nor atherosclerotic cardiovascular disease, would have statins prescribed.

There are some limitations to this study. It is a retrospective comparative analysis of patients that have been treated at a national university hospital, so the results may not generalize fully to patients with less severe forms of schizophrenia who are not in contact with mental health services. The medical records used to gather clinical information for this study did not include complete data on all risk factors for diabetes (family history, BMI, medication, smoking, physical activity, diet, etc.). The patients on clozapine were significantly younger (51.2 years) than those never treated with clozapine (58.1 years). By definition, patients treated with clozapine are suffering from a more severe and a more treatment-resistant form of schizophrenia and, therefore, the use of clozapine is not the only difference between these two groups. The strengths of the study include the availability to screen electronic health records over long periods and full access to all patient records at LUH over two decades in a national university hospital where over 90% of all patients with schizophrenia in Iceland have been treated for the past decades.

Clinicians need to be aware of the risk of T2D developing for patients with schizophrenia, in particular for females on clozapine treatment. Regular measurements of fasting glucose and HbA1c should be done, at least once a year. There is less evidence available to support annual measurements of blood lipids, especially for patients that are on a stable antipsychotic treatment unless blood lipids are elevated or the patient has a diagnosis of atherosclerotic cardiovascular disease or T2D. Since patients with schizophrenia are at a very high risk of developing atherosclerotic cardiovascular disease (39), more research is needed to assess whether statins should be used more for primary prevention during long-term follow-up.

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