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Jani Moilanen

THE USE OF ANTIPSYCHOTIC MEDICATION AND ITS ASSOCIATION WITH OUTCOMES AND BRAIN MORPHOMETRY IN SCHIZOPHRENIA – THE NORTHERN FINLAND BIRTH COHORT 1966 STUDY

UNIVERSITY OF OULU GRADUATE SCHOOL;
UNIVERSITY OF OULU,
FACULTY OF MEDICINE;
MEDICAL RESEARCH CENTER OULU;
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Supervised by
Professor Matti Isohanni
Professor Jouko Miettunen
Professor Hannu Koponen

Reviewed by
Professor Michael Davidson
Docent Jari Haukka

Opponent
Professor Jyrki Korkeila

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University of Oulu, P.O. Box 8000, FI-90014 University of Oulu, Finland

Abstract

Antipsychotic medication forms a cornerstone in the treatment of schizophrenia and its effect on positive symptoms and relapse prevention after the first episode has been shown. After the first episode, the treatment guidelines for schizophrenia recommend the continuation of antipsychotic medication at a minimum from six months to five years. The long-term and life-span benefits and harmful side-effects are not fully known. The aim of this naturalistic study was to analyze long-term use of antipsychotic medication with a special interest in medication tapering and discontinuation in schizophrenia.

Non-medicated subjects were more often males and in remission, less often on a disability pension, and had better clinical outcomes when compared to medicated subjects at age 34 years. No differences were found when comparing relapse rates during the 8.7 years of follow-up after 34 years between non-medicated and medicated subjects. Not having been hospitalized during the previous 5 years before the follow-up predicted long-term successful antipsychotic discontinuation without relapse. In the long-term, use of antipsychotic medication became steadier after the first five years. A favorable outcome was associated with low and steady antipsychotic medication, and unfavorable with high long-term cumulative use and antipsychotic polypharmacy. Subjects with antipsychotic medication had non-significantly lower total gray matter (TGM) volume compared with non-medicated subjects. Time without antipsychotic medication preceding magnetic resonance imaging was associated with increased TGM and with increased regional volume in the right precentral gyrus and right middle frontal gyrus.

This study has a unique description of long-term use of antipsychotics. It provides new information on medication discontinuation and its effect in schizophrenia in the long-term in terms of relapses and brain morphometry.

Keywords: antipsychotics, brain morphometry, outcome, schizophrenia

Moilanen, Jani, Psykoosilääkkeiden käyttö ja käytön yhteys ennusteeseen ja aivojen rakenteeseen skitsofreniassa – Pohjois-Suomen vuoden 1966 syntymäkohortti.

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Tiivistelmä

Psykoosilääkkeet muodostavat perustan skitsofrenian hoidolle, ja niiden on osoitettu tehoavan positiivisiin oireisiin ja relapsin (psykoosin uusiutumisen) estoon ensipsykoosin jälkeen. Skitsofrenian hoitosuosituksissa suositellaan psykoosilääkityksen jatkamista ensipsykoosin jälkeen vähintään puolesta vuodesta viiteen vuoteen. Psykoosilääkityksen pitkäaikaiset ja elämänkestoiset hyödyt ja haittavaikutukset eivät ole täysin tiedossa. Tämän naturalistisen tutkimuksen tavoitteena oli analysoida antipsykoottisen lääkityksen pitkäaikaiskäyttöä ja erityisesti lääkityksen lopettamista skitsofreniassa.

Lääkkeettömät tutkittavat olivat 34-vuotiaina useammin miehiä sekä remissiossa (elpymävaiheessa), harvemmin työkyvyttömyyseläkkeellä, ja heillä oli parempi toimintakyky verrattuna lääkkeitä käyttäviin. Lääkkeettömien ja lääkkeitä käyttävien välillä ei havaittu 8,7 vuoden seurannassa eroa relapsien määrissä 34 ikävuoden jälkeen. Psykoosilääkkeiden onnistunutta, pitkäaikaista lopettamista ilman relapsia ennusti seurannassa se, ettei tutkittava ollut ollut sairaalahoidossa seurantaa edeltävien viiden vuoden aikana. Pitkällä aikavälillä psykoosilääkityksen käyttö tasaantui ensimmäisten viiden vuoden jälkeen. Suotuisa ennuste liittyi vähäiseen ja jatkuvaan lääkitykseen. Epäsuotuisa ennuste puolestaan liittyi korkeaan kumulatiiviseen lääkemäärään ja useamman psykoosilääkkeen yhtäaikaiskäyttöön. Lääkkeitä käyttävien tutkittavien harmaan aineen kokonaistilavuus oli ei-merkitsevästi pienempi kuin lääkkeettömien tutkittavien. Psykoosilääkityksetön aika ennen magneettikuvausta oli yhteydessä suurempaan harmaan aineen kokonaistilavuuteen sekä paikallisesti suurempaan tilavuuteen oikeassa etukeskipoimussa ja keskiotsapoimussa.

Tämä tutkimus kuvaa ainutlaatuisesti pitkäaikaista psykoosilääkkeiden käyttöä. Se tarjoaa uutta tietoa lääkityksen lopettamisesta ja sen pitkän aikavälin vaikutuksista relapseihin ja aivojen rakenteeseen skitsofreniassa.

Asiasanat: aivomorfometria, ennuste, psykoosilääke, skitsofrenia

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Oulu, April 2016 Jani Moilanen

Abbreviations

APP	Antipsychotic polypharmacy
APA	American Psychiatric Association
CGI	Clinical Global Impression
DSM	Diagnostic and Statistical Manual of Mental Disorders
EPS	Extrapyramidal Symptoms
FHDR	Finnish Hospital Discharge Register (currently Care Register for Health Care)
ICD	International Classification of Diseases
MRI	Magnetic Resonance Imaging
NFBC	Northern Finland Birth Cohort
NMDA	N-methyl-D-aspartate
NICE	National Institute of Clinical Excellence
PANSS	Positive and Negative Syndrome Scale
SOFAS	Social and Occupational Functioning Assessment Scale
TGM	Total gray matter
VBM	Voxel-based morphometry
WHO	World Health Organization

Main definitions

Adherence	The extent to which a patient's behavior matches a prescriber’s recommendations agreed by both the patient and prescriber.
Antipsychotic polypharmacy	The use of more than one antipsychotic.
Antipsychotics	A class of drugs used to treat psychotic symptoms in patients with psychotic disorders.
Antipsychotic withdrawal	Gradual discontinuation of antipsychotics.
Atypical antipsychotics	Antipsychotic agents with serotonin-dopamine antagonism, having a clinical profile of equal positive symptom antipsychotic actions but low extra pyramidal symptoms and less hyperprolactinemia compared to typical cases.
Chlorpromazine equivalent	Dose that equals 100 mg of chlorpromazine.
Compliance	The extent to which a patient's behavior matches a prescriber’s recommendations.
Daily dose	A dose used each day.
Dose tapering	A gradual discontinuation or reduction of a therapeutic dose of a particular drug required by a patient over prolonged period of time.
Dose-years	A cumulative value of antipsychotic use in the form of (chlorpromazine equivalent in mg) x (time on dose measured in years).
Long-term	At least two years of follow-up of antipsychotic use; within this study the follow-up was longer (mainly at least ten years).
Maintenance treatment	Within this study meaning long-term treatment with antipsychotics.
Non-medication	Not using antipsychotics.
Outcome	The measure of a patient’s status as defined by symptomatology and functioning. When assessing outcomes within this study, remission status, number of psychiatric treatments, and assessment scales were used.

Remission	The period of time when the severity of core symptoms is mostly mild. Within this study, the remission criteria of Andreasen *et al*. (2005) were used, with the exception that the duration of remission criterion of six months was not applied.
Typical antipsychotics	Antipsychotic agents sharing the property of dopamine$_2$ antagonism, which besides antipsychotic effects causes many side effects, presumably by blocking the same number of dopamine$_2$ receptors in all brain areas.

List of original publications

This thesis is based on the following publications, which are referred to throughout the text by their Roman numerals I-III:

I Moilanen J, Haapea M, Miettunen J, Jääskeläinen E, Veijola J, Isohanni M & Koponen H (2013) Characteristics of subjects with schizophrenia spectrum disorder with and without antipsychotic medication - A ten-year follow-up of the Northern Finland 1966 Birth Cohort Study. Eur Psychiatry 28(1): 53-58.

II Moilanen J, Haapea M, Jääskeläinen E, Veijola J, Isohanni M, Koponen H & Miettunen J Long-term antipsychotic use and its association with outcomes in schizophrenia - the Northern Finland Birth Cohort 1966. Eur Psychiatry, in press.

III Moilanen J, Huhtaniska S, Haapea M, Jääskeläinen E, Veijola J, Isohanni M, Koponen H & Miettunen J (2015) Brain morphometry of individuals with schizophrenia with and without antipsychotic medication - The Northern Finland Birth Cohort 1966 study. Eur Psychiatry 30(5): 598-605.

Contents

1 Introduction

Schizophrenic psychoses present a major public health problem affecting about 1% of the population. They cause a heavy burden on an individual level as well as on a societal level, and the costs of psychotic disorders are high. Schizophrenic psychoses have been ranked between fourth and sixth among the leading causes of disability. Schizophrenia is third in all causes of disability-adjusted life-years in the world among people aged 10-24 years (Gore *et al.* 2011). Schizophrenia associates with excess somatic and psychiatric comorbidity and mortality, and has extensive negative social and personal consequences.

The treatment of schizophrenia consists of several factors, but the mainstay treatment is antipsychotic medication, which may last for decades. Antipsychotic drugs relieve symptoms and prevent relapses, but have limited efficacy particularly on negative and cognitive symptoms, and they have various neurological and metabolic side-effects.

Long-term antipsychotic treatment brings up at least some of the challenges brought up by, for instance, long-term treatment of diabetes mellitus and cardiovascular diseases. For example, Hamid *et al*. (2014) report medicine-related problems being a major health threat in adult patients with diabetes mellitus and/or cardiovascular diseases in their review of contributory factors leading to medicine-related problems. In their review, factors such as non-adherence and polypharmacy came up, both of which are commonly seen when observing long-term use of antipsychotics, and these are also referred to within this study.

Another challenge concerning long-term treatment with antipsychotics is the *efficacy of treatment*. In the short run, the advantages of antipsychotics in the treatment of positive symptoms have been shown (Leuch *et al.* 2012, 2013). In the long term, it has even been suggested that antipsychotics are an iatrogenic cause of poor outcomes, even chronicity in schizophrenia (Whitaker 2004, 2010). Sohler *et al.* (2015) aimed to test that hypothesis in a systematic review. They stated that the data were inadequate to conclusively evaluate whether long-term antipsychotic medication treatment results in better outcomes on average, and concluded that new data may be needed to understand the benefits and risks of long-term treatment with antipsychotics in schizophrenia (Sohler *et al.* 2015).

This study focuses on the use and non-use of antipsychotic medication in schizophrenia and the effects of antipsychotic medication several years, even decades, after the onset of illness. The main purpose was to find new information on the long-term use of antipsychotics and on the effects of discontinuation of

antipsychotics treatment in terms of clinical and functional outcome and brain morphometry.

2 Schizophrenia

2.1 Definition of schizophrenia

Eugen Bleuler (1911) was the first to use the term schizophrenia, in 1911. The basis of his definition of schizophrenia came from Emil Kraepelin's (1919) definition of dementia praecox, of which the main characteristics were hallucinations, delusions, stereotypes, thought disorder, negativism, and blunted affect. The term schizophrenia was chosen to express the presence of schisms between thought, emotion, and behavior in patients with the disorder. The symptoms included associational disturbances of thought, especially looseness, affective disturbances, autism, and ambivalence. Secondary symptoms were hallucinations and delusions. One major difference compared with Kraepelin's concept of dementia praecox was that schizophrenia does not need to have a deteriorating course.

During many decades, there have been suggestions about whether the term schizophrenia should be removed because of its connotation with hopeless chronic brain disease (e.g. van Os 2016). The criticism against it has partly arisen from comparison with other psychotic disorders, which tend to be ignored and are not referred to as brain disorders, even though these disorders form the majority of all psychotic disorders (van Os 2016).

2.2 Diagnosis of schizophrenia

The diagnoses of the subjects within this study are validated based on the Diagnostic and Statistical Manual of Mental Disorders, Third edition, Revised version (DSM-III-R, APA 1987) (I, III), which has been updated to DSM-IV in 1994 and to DSM-5 in 2013, or using information obtained from the Care Register for Health Care (Terveyden ja Hyvinvoinnin Laitos 2012) (formerly known as the Finnish Hospital Discharge Register) (II), in which diagnoses are based on the International Classification of Diseases, Revision 10 (ICD-10; WHO 1992). DSM-III-R and ICD-10 diagnostic criteria for schizophrenia are shown in Table 1.

Table 1. Diagnostic criteria of schizophrenia according DSM-III-R and ICD-10

DSM-III-R[1]		ICD-10[2]	
Diagnostic criteria	Description	Diagnostic criteria	Description
Criterion A (at least two symptoms)	1. Bizarre delusions (e.g. being controlled, thought broadcasting, thought insertion/withdrawal) 2. Somatic, grandiose, religious, nihilistic or other delusions without persecutory or jealous content 3. Delusions with persecutory or jealous content if accompanied with hallucinations of any type 4. Auditory hallucinations (commenting voices or voices conversing) 5. Auditory hallucinations on several occasions with content of more than one or two words, having no apparent relation to depression or elation 6. Incoherence, marked loosening of associations, markedly illogical thinking, or marked poverty of content of speech if associated with blunted, flat or inappropriate affect/delusions or hallucinations/catatonic or other grossly disorganized behavior.	Either at least one symptom in this description	a) Thought echo, thought insertion/withdrawal, thought broadcasting b) Delusions of control, influence or passivity, clearly referred to body or limb movements or specific thoughts, actions, or sensations; delusional perception c) Hallucinatory voices commenting or voices conversing or voices coming from some part of the body d) Persistent bizarre delusions
Criterion B	Deterioration from a previous level of functioning in such areas as work, social relations and self-care.	Or at least two of the symptoms in this description	a) Persistent hallucinations in any modality b) Neologisms, thought disorder, incoherence or irrelevant speech c) Catatonic behavior (e.g. excitement, posturing or waxy flexibility, negativism, mutism and stupor) d) "Negative" symptoms (e.g. marked apathy, paucity of speech, and blunting or incongruity of emotional responses)

DSM-III-R[1]		ICD-10[2]	
Diagnostic criteria	Description	Diagnostic criteria	Description
Criterion C	Continuous signs of the disturbance persist for at least 6 months, including active phases of criterion A symptoms for at least one week, with or without prodromal or residual symptoms.	Duration criteria	Symptoms should be present for most of the time during an episode of psychotic illness lasting for at least one month (or at some time during most of the days).
Criterion D	The full depressive or manic syndrome, if present, developed after any psychotic symptoms or was brief in duration relative to the duration of the psychotic symptoms in A		If the patient also meets criteria for manic episode or depressive episode, the criteria listed above must have been met before the disturbance of mood developed.
Criterion E	Onset of the prodromal or active phase of the illness before age of 45.		
Criterion F (Exclusion criteria)	Organic mental disorder or mental retardation	Exclusion criteria	The disorder is not attributable to organic brain disease, or to alcohol- or drug-related intoxication, dependence or withdrawal.

[1] Diagnostic and Statistical Manual of Mental Disorders, Third edition, Revised version.

[2] International Classification of Diseases, Revision 10.

2.3 Treatment of schizophrenia

Subjects with a schizophrenia diagnosis form a very heterogeneous group, pointing out that the treatment should be planned individually in co-operation with the person suffering from schizophrenia. The course of illness can vary from a single psychotic episode to continuous symptoms (Wiersma *et al.* 1998), which means that treatment can last from months to a life-long period.

According to the *current evidence-based Finnish guidelines* for the treatment of schizophrenia (2015), treatment should be individually planned and should integrate different forms of treatment, including psychosocial treatment and treatment with antipsychotic medication (www.kaypahoito.fi). The main aim is to remove or relieve symptoms, to prevent relapses, and to improve both psychosocial functioning and quality of life.

2.4 Schizophrenia and outcome

Since Kraepelin's definition of dementia praecox in 1909, perceptions concerning the outcome of schizophrenia have changed. The term outcome includes both of the terms recovery and remission. Recovery is used when normal levels of social and vocational functioning are achieved and the subject is also in remission from psychiatric symptoms (Liberman *et al.* 2002, Robinson *et al.* 2004). For remission, the standardized criteria of Andreasen *et al*. (2005) have been widely used in schizophrenia research. In these criteria, remission is defined by the severity of core symptoms in schizophrenia being mostly mild, and the duration criterion being at least six months.

Recent meta-analysis by Jääskeläinen *et al*. (2013) showed a recovery rate of 13.5% in subjects with schizophrenia, comprising recovery both clinically and socially. Depending on the population in question and its characteristics, the remission criteria are fulfilled by 22-66% of subjects with schizophrenia (Emsley *et al*. 2011, Haro *et al*. 2011, ten Velden Hegelstad *et al*. 2013). Altogether, approximately 40% of subjects with schizophrenia have been reported to have a good outcome (Hegarty *et al*. 1994, Menezes *et al*. 2006).

2.5 Schizophrenia and brain morphometry

In schizophrenia, morphological changes in the brain structures have been widely reported. In the meta-analysis by Honea *et al*. (2005), the most consistent findings were deficits in the left superior temporal gyrus and in the left medial temporal lobe. Longitudinally, there is evidence of volume change in the gray matter of the anterior cingulate, frontal and temporal lobes, hippocampus/amygdala, thalamus, and insula (Shepherd *et al*. 2012, Torres *et al*. 2013), and of changes in both gray and white matter (Olabi *et al*. 2008).

3 Antipsychotic medication

Antipsychotic medication forms a cornerstone in the treatment of schizophrenia. The effect of antipsychotics on positive symptoms and relapse prevention has been shown (Tandon *et al*. 2008, Leucht *et al*. 2012, Bruijnzeel *et al*. 2014), but antipsychotics also have a lot of harmful side-effects (Tandon *et al*. 2008, Young *et al*. 2014), which have to be carefully considered at an individual level when planning treatment. The effectiveness of antipsychotics in the long term is not fully known (Sohler *et al.* 2014).

3.1 Background information on antipsychotics

Below is a brief description of the history of antipsychotics, the proposed mechanism behind their antipsychotic actions, and the harmful adverse effects that have been recognized over time.

3.1.1 History

Chlorpromazine was introduced in 1952 and it heralded a pharmacological revolution in psychiatry (Pichot 1996, Shen 1999). It is the first of the so-called *typical antipsychotics*. After evidence of efficacy of chlorpromazine was established (Lehmann and Hanrahan 1954), numerous other antipsychotic agents, all sharing chlorpromazine's dopamine$_2$ (D_2) receptor-blocking activity, were synthesized and tested. The last typical antipsychotic agent approved by the U.S. Food and Drug Administration was molindone in 1975.

After multicenter trials of antipsychotic medications found that the medications were substantially and significantly better than the placebo in alleviation of acute psychotic symptoms and relapse prevention (Cole *et al*. 1964), antipsychotic medication became the standard somatic treatment for schizophrenia. Over time, the adverse effects of antipsychotic medication began to be recognized as more difficult, which led to a search for better tolerated agents, *atypical antipsychotics*. Simply described, an atypical antipsychotic is one that produces minimal extrapyramidal symptoms (EPS) at clinically effective doses (Meltzer 2000). The classification into typical and atypical antipsychotics has been challenged, because the groups are derived from several different classes of compounds (Bonham and Abbot 2008).

The very first of the atypical antipsychotics, *clozapine*, was first synthesized in 1958. Studies with it began in the late 1960s, and showed decreases in symptoms of psychosis without causing movement disorder side-effects. Clozapine was partially withdrawn due to concerns over agranulosytosis in the 1970s (first reported in Finland), but was later reintroduced and has a position as the "golden standard" therapy for treatment resistance schizophrenia (Hippius 1999).

Clozapine was to be followed by other so-called atypical compounds in the 1990s, of which risperidone was approved in 1994, olanzapine in 1996, sertindole in 1997, and quetiapine in 1997 (Shen 1999). Several others have been introduced since then, and the classification of one of the latest atypical antipsychotic agents, named aripipratsole, has been suggested to be a third-generation antipsychotic (Mailman and Murthy 2010).

3.1.2 Mechanisms

After the discovery of antipsychotic medications, clinicians observed a Parkinson-like syndrome of tremor, akinesia, and rigidity among patients taking antipsychotics (Haase and Janssen 1965). Because it was known that Parkinson's disease is a disease of insufficient dopamine neurotransmission, and the observations of antipsychotic drug-induced parkinsonism suggested that antipsychotics interfered with dopamine pathways in the brain, the *dopamine hypothesis* of psychosis and antipsychotic drug action was born (Van Rossum 1967, Meltzer and Stahl 1976).

Although the dopamine hypothesis has since been questioned (Moncrieff 2009), it is known that all clinically effective antipsychotic agents have a property to block dopamine D_2 receptors, and the mechanism of action of antipsychotics is based on a hypothesis that schizophrenia involves a dysregulation of neurotransmission in brain dopaminergic circuits with excess dopaminergic activity in the mesolimbic pathway and reduced dopaminergic signaling in the mesocortical pathway (Kane *et al* 1991, Miyamoto *et al*. 2012). D_2 receptors are thought to mediate the positive symptoms of psychosis in the mesolimbic dopamine system and, by blocking them, the positive symptoms can be relieved (Seeman 1992, Miyamoto *et al*. 2012). In contrast, the hypoactivity of mesocortical dopaminergic projections to the prefrontal cortex is thought to produce negative and cognitive symptoms (Hensler *et al*. 2013).

After the dopamine hypothesis, other hypotheses such as the *glutamate hypothesis*, including the N-methyl-D-aspartate (NMDA) receptor hypofunction hypothesis, have been suggested, which has led to the development of newer types of antipsychotic agents affecting the NMDA receptors (Javitt *et al*. 2012, Citrome 2014). Although not yet firmly established, clinical trials in subjects with schizophrenia suggest that enhancing NMDA receptor function by increasing the availability of co-agonists with glycine, d-serine, or sarcosine has some efficacy (Tsai and Lin 2010, Javitt *et al*. 2012). Agents affecting metabotropic receptors of glutamate have also been studied but, for example, after the promising initial efficacy study with a selective agonist for mGluR2/3 (Schoepp 2006), further studies have failed to replicate the results (Patil *et al*. 2007, Kinon 2011).

Studies concerning agents affecting ionotrophic glutamate receptors other than NMDA have shown no effect, except for topiramate as an augmentation for those with insufficient response to clozapine: Goff *et al*. (2008) studied the effect of ampakine (Ampa receptor) with no advantages for cognition or other symptoms; Muscatello *et al*. (2011) studied topiramate (Kainate receptor) augmentation with a result of cognitive dulling, although they pointed out that topiramate may have some effect on those who have had an incomplete clinical response to clozapine. The results of a review by Sommer *et al.* (2012) were also in line with that. The basis of the glutamate hypothesis comes from glutamate's role as a regulator of dopamine activity either directly (excitatory) or indirectly (inhibitory) via the gamma-aminobutyric acid interneuron (Citrome 2011). In addition, the positive effects of lamotrigine as augmentation therapy are hypothesized to come from the inhibition of glutamate release (Sommer *et al*. 2005).

3.1.3 Harmful effects

As mentioned above, awareness of the adverse effects of typical antipsychotics grew over time and led to the development of better tolerated agents (Meltzer 2000). Nowadays, atypical antipsychotics have been in use for a reasonably long time and their adverse effects, such as weight gain, hyperprolactinemia, metabolic syndrome, dyslipidemia, and cardiovascular effects, have been recognized and frequently observed (Young *et al.* 2015). The risks of these adverse effects typically increase over time (Caroff *et al.* 2011).

The possible effects of antipsychotics *on suicidal ideation, mortality, and cognition* have also been studied in schizophrenia (Rissanen *et al*. 2012, Husa *et*

al. 2014, Torniainen *et al.* 2015). No association between antipsychotics and suicidal ideation was found in schizophrenia (Rissanen *et al.* 2012), and moderate antipsychotics exposure was associated with the lowest mortality, while the highest mortality was associated with non-medication (Torniainen *et al.* 2015). When studying the use of antipsychotics and cognition in schizophrenia, Husa *et al.* (2014) concluded that the use of high doses of antipsychotics may be associated with a decrease in verbal learning and memory in schizophrenia, years after illness onset. Faber *et al.* (2012) suggested a negative role for second-generation antipsychotics, specifically in the domain of speed of processing.

When observing *the long-term effects of antipsychotics*, Whitaker (2004, 2010) has even concluded that antipsychotics are an iatrogenic cause of chronicity of schizophrenia. Based on that, Sohler *et al.* (2015) conducted a systematic review to test the hypothesis that long-term treatment with antipsychotics is less beneficial than treatment without antipsychotics for patients with schizophrenia. Their study did not support the conclusion that long-term treatment with antipsychotics is harmful. Because of the lack of available data, they were not able to test the research question properly (Sohler *et al.* 2015).

3.2 Treatment guidelines for schizophrenia

The treatment of schizophrenia should be individually planned. It usually consists of several factors, including, for example, medication, specific psychological therapies, psychoeducation, and co-operation with the family. Gaebel *et al*. (2005) have made a wide comparison between national schizophrenia guidelines from different countries. They included altogether 24 guidelines from 18 countries. The recommendations had similarities. For example, clozapine was recommended in all guidelines for treatment-resistant schizophrenia; at least one to two years' duration of antipsychotic treatment after first-episode psychosis was mostly recommended; and pharmacological treatment with antidepressants was recommended as first-line treatment for depressive symptoms. Differences were found in the fields of management of side-effects, dosage recommendations (most recommended dosages were between 300 mg to 900 mg in chlorpromazine equivalents for typical antipsychotics for acute care), and antipsychotic polypharmacy.

To get an overview of some guidelines in treatment of schizophrenia, I have, in the following chapter, referred to the guidelines of the American Psychiatric Association (APA), the guidelines of the National Institute for Health and Care

Excellence (NICE), and current evidence-based Finnish guidelines. According to the APA guidelines, treatment planning has three goals: 1) to reduce or eliminate symptoms, 2) to maximize quality of life and adaptive functioning, and 3) to promote and maintain recovery from the debilitating effects of illness to the maximum extent possible. These goals are quite consistent with the goals mentioned in the current evidence-based Finnish guidelines for treatment of schizophrenia (www.kaypahoito.fi).

3.2.1 Antipsychotic treatment recommendations

Treatment of schizophrenia can be thought of according to the phase of illness. Within the guidelines referred to here, the recommendations concern the acute phase of illness, the stabilization phase of illness, the maintenance phase, and a possible relapse. Table 2 summarizes the recommendations for antipsychotic treatment in the different phases, excluding the stabilization phase, because in this phase changes in antipsychotic treatment are not recommended.

Table 2. Antipsychotic treatment recommendations by Finnish, NICE, and APA guidelines

Phase of illness	Finnish Guidelines[1] (2015)	NICE[2] Guidelines (2014)	APA[3] Guidelines (2010)
Dose[4] (mg)			
Acute	100 - 300	Slow titration upward within dose range.	160-1000[5]. The dose titration as quickly as tolerated to the target therapeutic dose.
Maintenance	150 - 400	-	Continuation of antipsychotic treatment with doses mentioned above for six months after adequate response. Then dose reduction strategy (included).
Relapsed	300 - 600	Same as acute phase	First episode patients often require a lower dose than patients with chronic schizophrenia.

[1] The current evidence-based Finnish guidelines (www.kaypahoito.fi).

[2] National Institute for Health and Care Excellence.

[3] American Psychiatric Association.

[4]Dose is expressed as Chlorpromazine equivalents if clearly mentioned in the guidelines.

[5]Chlorpromazine equivalents are only given for typical antipsychotics

3.2.2 Long-term use, withdrawal, and dose reduction

Long-term use or maintenance treatment with antipsychotics is recommended in schizophrenia (Baandrup *et al*. 2015, Sampson *et al*. 2013). Nevertheless, studies point out the commonness of medication withdrawal. For example, Tiihonen *et al*. (2011) reported in their study that only 45.7% of subjects with schizophrenia continued their initial treatment with antipsychotics for 30 days or longer after discharge from the first hospitalization. In the multinational incident cohorts of the World Health Organization (WHO), an average of 25.5% of patients with schizophrenic psychosis had been without antipsychotic medication for the last two years of the 15-year follow-up period (Hopper *et al*. 2007).

Knowing the commonness of *medication withdrawal* makes it rational to study its risks and benefits. It has been suggested that not all schizophrenia subjects need continuous antipsychotic medication for a prolonged period (Harrow and Jobe 2013). Wunderink *et al*. (2013) stated in their study that an early dose reduction or a discontinuation of antipsychotics in remitted first-episode psychosis shows superior long-term functioning after 7 years compared with maintenance treatment; these patients were at higher relapse risk during the first 2 years but not after the 7-year follow-up. In addition, Harrow and Jobe (2007) and Harrow *et al* (2012, 2014) reported in their 20-year longitudinal naturalistic study that non-medicated subjects with schizophrenia had favorable outcomes compared to medicated ones.

There are also *contrary findings* questioning the discontinuation of antipsychotic medication (Zipursky *et al*. 2014), although these findings concern mainly the recurrence of symptoms in the early stage of illness. An earlier review by Gilbert *et al*. (1995) studied the withdrawal of antipsychotics mainly within multi-episode schizophrenia subjects. They stated that the relapse proportion was 53% among those who were withdrawn from antipsychotic medication and 16% among those who continued antipsychotic treatment.

The current evidence-based Finnish guidelines (www.kaypahoito.fi) for the treatment of schizophrenia suggest that antipsychotic medication should be continued from two to five years after the remission of first episode psychosis. The National Institute for Health and Care Excellence (NICE) warns of a high risk of relapse if medication is stopped within one to two years after the acute period, and recommends monitoring for signs and symptoms of relapse for at least two years if antipsychotic medication is withdrawn. The recommendation of the American Psychiatric Association (APA) is continuation of antipsychotic

treatment for at least six months after first episode psychosis, although antipsychotic treatment is also strongly recommended in the stable phase of illness. Indefinite use of antipsychotic medication is recommended for subjects with schizophrenia who have had multiple prior episodes or two episodes within five years.

Some treatment models have intended to *individualize or minimize* the use of antipsychotics and reduce their harm. For example, in Finland, the need-adopted model (Bola *et al.* 2006) was aimed at individualized use of antipsychotics. However, exact mediation data and responses are not given. The therapeutic community model, popular from 1970 to the 1990s, aimed at minimization of antipsychotic medication; in the Soteria Project in the USA (Bola *et al.* 2003), half of schizophrenia patients survived well without antipsychotic medication; and in Finland, maximal use of psychosocial interventions reduced the dose of antipsychotics in the acute psychosis ward from 370 mg/day as chlorpromazine equivalents to 160 mg/day (Isohanni 1983). Clinically significant side-effects were reduced from 70% to 20% but remission rates were similar.

3.2.3 Polypharmacy

Treatment guidelines recommend monotherapy with antipsychotics, but antipsychotic polypharmacy (APP) is common and it has been used for decades in the treatment of schizophrenia (Gallego *et al.* 2012, Suokas *et al.* 2013). Evidence of the effectiveness of APP is lacking, and it is associated with greater prevalence of adverse effects and increased health costs (Lochmaan van Bennekom *et al.* 2013). No association between APP and increased mortality was found by Tiihonen *et al.* (2012). There is, however, some evidence of the effectiveness of APP in certain circumstances compared to monotherapy with antipsychotics (Correll *et al.* 2009, Fleischacker *et al.* 2014, Iasevoli *et al.* 2014).

3.3 Antipsychotic medication and outcome in schizophrenia

Antipsychotics are a core treatment in schizophrenia and their effect on positive symptoms has been persuasively shown (Tandon *et al*. 2008, Bruijnzeel *et al*. 2014), but after the first years of illness onset, the effects of antipsychotic medication compared to a placebo are not known (Leucht *et al*. 2012). Furthermore, it has been suggested that antipsychotics lose their effectiveness over time (Leucht *et al*. 2012), which is a common phenomenon in the treatment

of many somatic disorders like cancer, asthma, or infections. Whitaker (2004, 2010) has even concluded that long-term use of antipsychotics is an iatrogenic cause of chronicity of schizophrenia and may lead to deterioration of patients' health and well-being, which was not supported by the systematic review by Sohler *et al.* (2015). Studies concerning long-term treatment with antipsychotics and outcome are rare. New data may be needed to establish sufficient evidence to understand the benefits and risks of long-term treatment with antipsychotics (Sohler *et al.* 2015). The criticism against the long-term effectiveness of antipsychotics arises partly from the recovery studies, and Jääskeläinen *et al.* (2013) stated that the proportion of recoveries has not increased during last few decades despite the intervention of antipsychotics and their development.

3.4 Antipsychotic medication and brain morphometry in schizophrenia

It has been suggested that antipsychotics may have an effect on brain morphometry, and that antipsychotic treatments act regionally rather than globally on the brain (Torres *et al*. 2013, Navari and Dazzan 2009, Moncrieff and Leo 2020, Leung *et al*. 2011, Haijma *et al*. 2013, Fusar-Poli *et al*. 2013). Haijma *et al*. (2013) state that the main part of brain volume reduction in schizophrenia is present before treatment is initiated. Leung *et al*. (2011) reported major deficits in the frontal, superior temporal, insular, and parahippocampal regions of neuroleptic-treated compared with neuroleptic-naïve first-episode schizophrenia patients in their cross-sectional meta-analysis. In a cross-sectional meta-analysis by Haijma *et al*. (2013), decreased volumes in intracranial, total brain and total gray matter volumes were found in antipsychotic-naive subjects, although the decrease was somewhat less pronounced than that observed in medicated subjects. Longitudinally, Fusar-Poli *et al*. (2013) stated in their systematic review that antipsychotics may reduce the gray matter volume and increase lateral ventricles.

In all cases, the differences in brain morphometry found between the use of typical and atypical antipsychotics have been inconclusive (Shepherd *et al*. 2012). Some previous reviews (Lieberman *et al.* 2005, Navari and Dazzan 2009, Vita *et al*. 2012) have suggested that typical antipsychotics may have a greater effect on brain morphometry than atypical antipsychotics. In the study by Scherk and Falkai (2006), switching from typical to atypical antipsychotics had the effect of decreasing the pathologically increased basal ganglia volume to the same level as

in healthy controls. In their longitudinal study, Ho *et al*. (2011) reported brain morphometrical changes in different regions, depending on the type of antipsychotic in use (typical, atypical, clozapine).

4 Aims of the study

The purpose of this study was to analyze the associations of the use and non-use of antipsychotic medication with outcome and brain morphometry, and long-term use of antipsychotic medication in schizophrenia. The specific aims were:

I To determine the prevalence of non-medication in schizophrenia in the Northern Finland Birth Cohort 1966 (NFBC 1966) and to find predictors of successful withdrawal of antipsychotic medication

II To study the long-term use of antipsychotics and its association with outcome

III To clarify the possible association between antipsychotic use and brain morphometry

5 Material and methods

5.1 The Northern Finland Birth Cohort 1966

This study is based on the Northern Finland Birth Cohort 1966 (NFBC 1966), which is an unselected, general population birth cohort identified during mid-pregnancy. It is based on 12,058 children born in the provinces of Lapland and Oulu (Rantakallio *et al*. 1969). The formations of the study samples (I-III) are shown in Figure 1.

5.2 Psychiatric follow-up studies in the NFBC 1966

5.2.1 Psychiatric follow-up study at age 34 years

The original studies I and III are based on the 34-year follow-up conducted in 1999-2001. The Care Register for Health Care, previously known as the Finnish Hospital Discharge Register (FHDR), was used to detect cohort members with a psychotic episode by the end of the year 1997. During the follow-up assessment, subjects went through structural magnetic resonance imaging (MRI) of the brain (GE Signa 1.5T scanner), measures of cognitive functioning, psychiatric interviews, and questions relating to, for example, use of antipsychotic medication, social background, and substance use. Altogether, 90 subjects with a psychotic disorder (61 with schizophrenia) participated and provided written informed consent (Haapea *et al.* 2007, Haapea *et al.* 2011).

5.2.2 Psychiatric follow-up study at age 43 years

The original study II is based on the 43-year follow-up conducted in 2008-2010. In addition to those invited to participate in the 34-year follow-up, those who were later detected to have developed a psychosis were invited to participate, based on the following information: those who had developed a psychosis by 2008 according to the Care Register for Health Care (between 1998-2008); who had indications of a psychosis in the register data of the Social Insurance Institution of Finland (i.e. sick leave (data until 1999) or disability pension (until 2000) due to psychosis, or the right to reimbursement for psychoactive medication (until 2005)); or who reported having a psychosis or current high-dose

antipsychotic use (over 300mg chlorpromazine equivalents) at 31 years of age in the questionnaire. The procedure was extended from the 34-year follow-up with functional MRI and additional measures of cognitive functioning. Altogether, 99 subjects with a psychotic disorder (54 with schizophrenia) participated and provided written informed consent. Fifty-four subjects with a psychotic disorder (40 with schizophrenia) participated both at ages 34 and 43 years (Haapea *et al.* 2013).

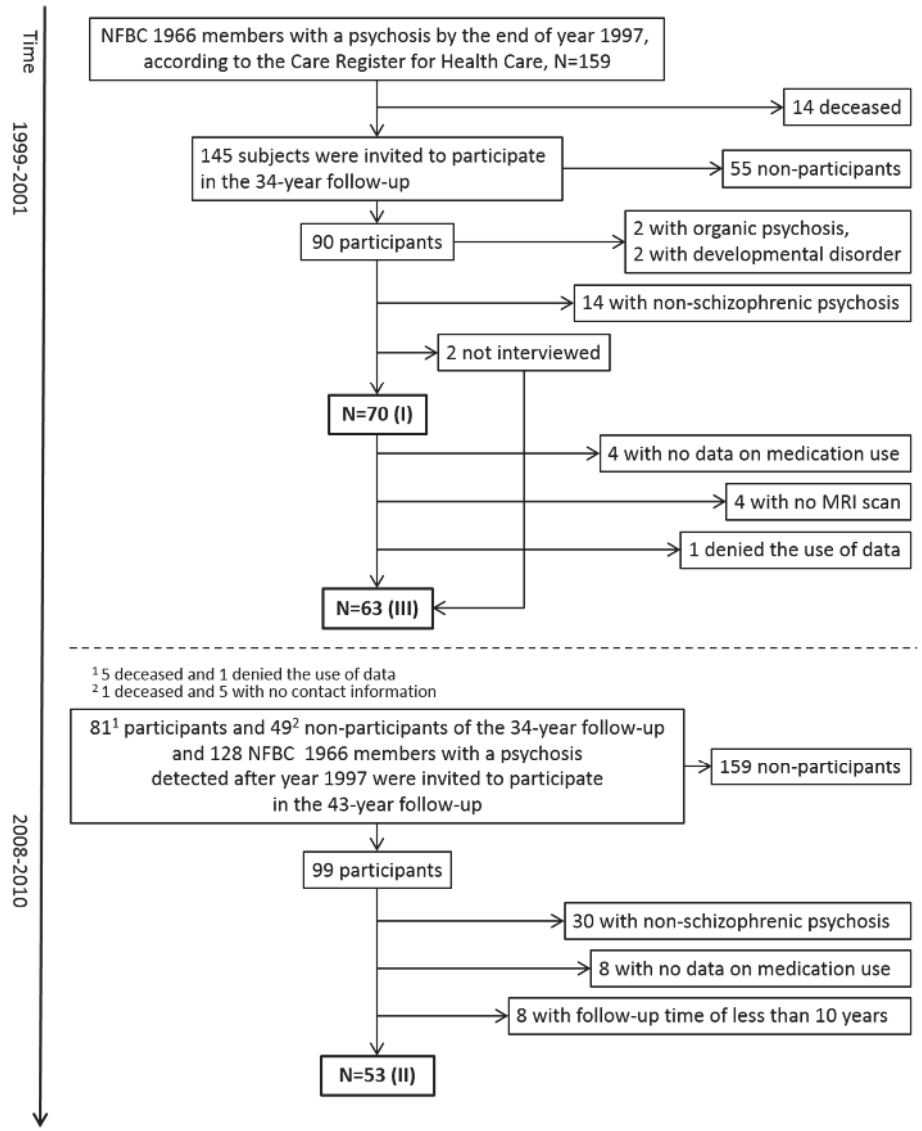

Fig. 1. Formation of the study samples in original publications I, II, and III.

5.3 Data on antipsychotic medication

5.3.1 Questionnaire (I, III) and register data (I, II, III)

The use of antipsychotic medication was examined in a follow-up interview at 34 years of age by asking about subjects' antipsychotic medication history during the previous three months (I). Based on that information, the subjects were divided into non-medicated and medicated groups in the original study I. The subjects were also asked about the use of antipsychotic medication during the previous year (III). This information was used together with the information derived from the medical records when dividing the subjects into non-medicated and medicated groups in the original study III. The register of the Finnish Social Insurance Institution on psychoactive medications consumed during 1997 was used to check which medication subjects bought during the year 1997. This information was used to support other medication data (I-III).

5.3.2 Medical records (II, III)

The data on the subjects' *life-time antipsychotic medication* use was collected using all the available medical records (hospital and out-patient care case notes). The medical records were obtained based on the information on subjects' treatment facilities, which was received from the Care Register. If a subject had no information in the Care Register, the medical records were requested from the outpatient facilities of the subject's area of residence. Subjects in this study had given their permission to collect medical records and signed the written informed consent. Permission to collect the data was given by the Ministry of Social Affairs and Health. All medical records were reviewed to record the antipsychotic agent, dose, and time period during which the medication had been used.

5.3.3 Chlorpromazine equivalents

Chlorpromazine equivalents were used to make the different antipsychotics comparable with each other. Chlorpromazine equivalents are a standardized quantitative method for comparing dosages of different antipsychotics (Andreasen *et al.* 2010). All the antipsychotics used by the subjects within this study, used chlorpromazine equivalents, and sources for chlorpromazine equivalents are seen in Table 3.

Table 3. Chlorpromazine equivalents of the antipsychotics used by the subjects within this study (modified from Supplementary Appendix in original study III)

Antipsychotic agent	ATC	Finnish trade name	Administration[1]	Equivalent[2]	Reference
Aripiprazole	N05AX12	Abilify	PO / inj.	7.5	Kroken *et al.* 2009
Asenapine	N05AH05	Asenapiini	PO	5	www.scottwilliamwoods.com
Chlorpromazine	N05AA01	Klorproman, Largactil	PO	100	Kroken *et al.* 2009
Chlorpromazine	N05AA01	Klorproman	Inj.	100	Kroken *et al.* 2009
Chlorprothixene	N05AF03	Truxal, Cloxan	PO	50	Kroken *et al.* 2009
Clozapine	N05AH02	Leponex, Froidir	PO	100	Kroken *et al.* 2009
Flupentixol	N05AF01	Fluanxol	PO	2	Kroken *et al.* 2009
Fluphenazine	N05AB02	Siqualone	Inj.	1.07	Bazire 2003
Fluphenazine	N05AB02	Pacinol	PO	2	Bazire 2003
Haloperidol	N05AD01	Haloperin, Serenase	PO	3	Kroken *et al.* 2009
Haloperidol	N05AD01	Haloperin	Inj.	2	Kroken *et al.* 2009
Levomepromazine	N05AA02	Levozin, Nozinan	PO	100	Kroken *et al.* 2009
Melperone	N05AD03	Melpax	PO	100	Janssen *et al.* 2004
Molindone	N05AE02	Moban	PO	10	Ahuja 1999
Olanzapine	N05AH03	Zyprexa	PO	5	Kroken *et al.* 2009
Periciazine	N05AC01	Neulactil, Neuperil	PO	24	Bazire 2003
Perphenazine	N05AB03	Peratsin, Pertriptyl	PO	8	Kroken *et al.* 2009
Perphenazine	N05AB03	Peratsin	Inj.	1.9	Kroken *et al.* 2009
Pimozide	N05AG02	Orap	PO	2	Bazire 2003
Pipotiazine	N05AC04	Piportyl	Inj.	1.43	Semple and Smyth
Promazine	N05AA03	Sparine	PO	100	Bazire 2003
Quetiapine	N05AH04	Ketipinor, Seroquel	PO	75	Kroken *et al.* 2009
Remoxipride	N05AL04	Roxiam	PO	75	Bazire 2003
Risperidone	N05AX08	Risperdal	PO	1.5	Kroken *et al.* 2009

Antipsychotic agent	ATC	Finnish trade name	Administration[1]	Equivalent[2]	Reference
Risperidone	N05AX08	Risperdal Consta	Inj.	1	Kroken *et al.* 2009
Sertindole	N05AE03	Serdolect	PO	5.33	Kroken *et al.* 2009
Sulpiride	N05AL01	Suprium	PO	200	Bazire 2003
Thioproperazine	N05AB08	Majeptil	PO	10	Ahuja 1999
Thioridazine	N05AC02	Orsanil, Tioridil	PO	100	Kroken *et al.* 2009
Ziprasidone	N05AE04	Zeldox	PO	60	Kroken *et al.* 2009
Zuclopenthixol	N05AF05	Cisordinol	PO	25	Kroken *et al.* 2009
Zuclopenthixol	N05AF05	Cisordinol	Inj.	14	Kroken *et al.* 2009
Zuclopenthixol	N05AF05	Cisordinol Acutard	Inj.	14	Kroken *et al.* 2009

ATC = code in the Anatomical Therapeutic Chemical classification system (www.whocc.no)

[1] PO = per oral, inj. = injection

[2] Dose (mg) equal to 100 mg of chlorpromazine.

5.3.4 Medication variables

Long-term cumulative antipsychotic use. The data on medication was used to calculate the long-term cumulative antipsychotic use during the whole follow-up period, expressed as dose-years of a daily dose of 100 mg chlorpromazine (II, III). The concept of dose-years has been developed to measure lifetime exposure to medication. The quantitative measure of lifetime exposure to antipsychotics using dose-years has been found to be reliable (Miller *et al.* 1995, Andreasen *et al.* 2010).

Proportion of time with medication since onset of treatment. The subjects were divided into three groups based on the regularity of daily antipsychotic use (less than 50%, from 50 to 95%, and over 95% of the time). The cut-offs were selected based on the distribution of the data. Due to the interest in studying the proportion of antipsychotic use in different phases of illness, the above-mentioned division was done for the periods of the first two years, two to five years, and five to ten years after onset of illness, as well as for the whole follow-up period (II).

Average dose when medicated. The average daily dose in chlorpromazine equivalents when using antipsychotics was categorized as low (<300 mg) or high

(≥300 mg) (Taylor *et al.* 2009). The cut-off dose of 300 mg has been used in previous studies (Sohler *et al.* 2003, Sim *et al.* 2009) (II).

Drug-free periods. Drug-free periods, meaning periods when a subject was not using antipsychotics, lasting for at least 30 days during the follow-up time (yes/no) (II).

Antipsychotic polypharmacy. Subjects were divided into three classes based on the proportion of time on APP, when using antipsychotic medication: less than 5%, 5 to 40%, and over 40%. The cut-offs were selected based on the distribution of the data (II).

Continuous time without antipsychotics was calculated using the exact dates obtained from the medical records (III).

The information on *type of antipsychotics* used during the lifetime (mostly typical vs. atypical) and currently (typical, atypical, or both) was obtained from medical records (III).

5.4 Data on outcome

Service utilization. The cumulative number of hospital treatment days and episodes due to any psychiatric disorder until the 34-year (I, III) or 43-year (II) follow-ups were evaluated using the Care Register. Treatments received before and at the time of the interviews were evaluated separately for non-medicated and medicated subjects (I, III). It was ascertained whether subjects had been treated in hospital during the previous five years and two years before the interview, whether they were in hospital or outpatient care at the time of the interview, and whether they were hospitalized due to a psychosis during the follow-up after the interview (I). Information on current hospital and outpatient treatments (I) was obtained in the interview. The proportions of time spent in a psychiatric hospital due to a psychosis after the interview up to the end of 2008 and 2013 were calculated. The Care Register was used as a source of information on hospitalizations.

Symptomatology and remission. Symptoms were measured at the follow-up interviews using the Positive and Negative Syndrome Scale (PANSS) (Kay *et al*. 1987), which measures the number and extent of psychopathological symptoms, especially psychotic ones, during the preceding week. Each PANSS item measures the severity of the symptoms on a scale of 1 to 7, with higher scores reflecting more severe symptoms. The total score (I-III), sums of positive and negative symptoms (I), and the subscales of positive, negative, disorganization,

excitement, and emotional (III) symptoms (van der Gaag *et al*. 2006) were used in the analyses.

Non-medicated and medicated subjects were divided into remission groups based on the criteria of Andreasen *et al*. (2005), with the exception that, as the symptoms had been assessed only once (for the previous week), the duration of remission criterion of six months was not applied (I-III). The symptom criteria for remission are: maximum scores of 3 (i.e. mild symptoms) in the PANSS items measuring the positive symptoms: delusions (P1), conceptual disorganization (P2), hallucinatory behavior (P3); negative symptoms: blunted affect (N1), passive/apathetic social withdrawal (N4), lack of spontaneity and flow of conversation (N6); and general symptoms: mannerisms and posturing (G5), unusual thought content (G9).

Functioning and clinical outcome. The Social and Occupational Functioning Assessment Scale (SOFAS) (Spitzer *et al.* 2000) measures patients' social and occupational functioning on a scale of 0-100, with higher scores reflecting better functioning. The Clinical Global Impression (CGI) (Guy 1976) describes the severity of illness on a scale from 1 to 7, where 1 = healthy and 7 = very ill. These scores were used as continuous variables (I, III) and as categorized into two groups (II) in the analyses. In Study II, in SOFAS, 0–60 points meant impairments and over 60 points relatively good functioning; and in CGI, 4–7 points meant at least moderately ill (poor clinical outcome) and 1–3 points at most mildly ill (good clinical outcome).

5.5 Data on brain morphometry (III)

A GE Signa system (General Electric, Milwaukee, WI) operating at 1.5T was used to get *structural MRI data* from participants. T1-weighted SPGR images of the whole brain were collected with a slice thickness of 1.5mm and in plane voxel size 0.94x0.94mm, TR=35ms, TE=5ms, Flip Angle =35^{o}. The images were quality controlled by radiological screening. The same MRI methods have been used in other NFBC 1966 brain-imaging studies (Ridler *et al*. 2006, Tanskanen *et al*. 2010).

FSL-VBM (http://www.fmrib.ox.ac.uk/fsl/fslvbm/index.html) was used for *gray matter volume maps constructions*. This is a voxel-based morphometry style analysis (Ashburner and Friston 2000, Good *et al.* 2001) carried out with FSL tools (Smith *et al.* 2004). BET (Smith 2002) was used first for brain-extraction. After that, FAST4 was used for tissue-type segmentation (Zhang *et al.* 2001). This

resulted in gray-matter partial volume images, which were then aligned to the MNI152 standard space with the affine registration tool FLIRT (Jenkinson and Smith 2001, Jenkinson *et al.* 2002). After that, FNIRT (Andersson *et al.* 2007) was used for nonlinear registration. This uses a b-spline representation of the registration warp field (Rueckert *et al.* 1999). After that, images were averaged for the creation of a study-specific template, to which the native gray matter images were then non-linearly re-registered. The registered partial volume images were then modulated (to correct for local expansion or contraction) by dividing by the Jacobian of the warp field. An isotropic Gaussian kernel was used to smoothen the modulated segmented images with a full-width-half-maximum of 4mm to minimize slight mis-registration errors, resulting in smoothed voxel-wise maps of gray-matter volume. When all that was done, voxel-wise GLM was applied using permutation-based non-parametric testing, correcting for multiple comparisons across space.

5.6 Covariates

Sex. Males versus females (I-III).

Onset age (I-III). In this birth cohort design, onset age corresponds with duration of illness. Onset age was ascertained from the medical records, utilizing additional information from health registers, and defined as the age when the first evident psychotic symptoms appeared.

Previous alcohol use disorder (I, III). The information on life-time alcohol use disorder was gathered from the case records and from the diagnostic interview in the 34-year follow-up study.

Parental psychosis (I, II). Information on parents' psychosis diagnosis during 1972–2012 was obtained from the Care Register (I, II). In addition, all the participants went through a Family Interview for Genetic Studies (FIGS) during the 34-year follow-up study (I). In FIGS, subjects and their mothers, or if the mother was not willing or able to participate, father or sibling, were asked whether any first-degree relatives have experienced psychotic symptoms.

Duration of follow-up (I, II). Duration of follow-up was calculated from the 34-year follow-up study up to the end of 2008 (I), and from the onset of illness to the 43-year follow-up study (II).

Level of education (I, II). Level of education was categorized as basic (9 years or less), secondary (10-12 years) or tertiary (over 12 years) using information from Statistics Finland (I). Non-vocational education (comprehensive

school, 9 years; or general upper secondary school, 12 years with matriculation examination) and vocational education (lower level: none, course or school (up to 3 years) in a vocational institution, currently a student; or higher level: polytechnic or university) were combined as follows: low = comprehensive school with lower level of vocational education; middle = comprehensive school with higher level of vocational education, or upper-secondary school with lower level of vocational education; and high = upper-secondary school with higher level of vocational education (II). Information was taken from the questionnaires in the 34-year (for the summary part of this thesis) and 43-year (II) follow-up assessments.

Marital status (I, II). Married or cohabiting versus others at the time of follow-up assessment. Information was taken from the questionnaires in the 34-year (I) or 43-year (II) follow-up assessments.

Employment status (I). Employed, unemployed, or on a disability pension at the time of the follow-up. Information was taken from the questionnaire in the 34-year follow-up assessment.

Psychiatric comorbidities. Substance use disorder or any other non-psychotic disorder (depressive, bipolar, anxiety, eating, or other disorder) until the end of follow-up. Information was taken from the Care Register for Health Care and from the register data of the Social Insurance Institution of Finland (II).

Somatic comorbidities included pulmonary diseases, cardiovascular diseases, endocrinological diseases, and others. Information was taken from the questionnaire in the 43-year follow-up assessment.

5.7 Statistical analyses

The illness-related background variables were compared between groups using an independent samples t-test, Chi-square test, Mann-Whitney's U test, Kruskal-Wallis H test, or the one-way analysis of variance (I-III). The Chi-square test or Mann-Whitney's U test were used to study the effect of medication variables on outcome variables (II). A Benjamini-Hochberg procedure was used to correct for multiple comparisons (II). If the association remained significant, a logistic regression analysis was used to control for selected confounding factors, such as for psychiatric hospital days and length of follow-up, which were used as proxy variables for the severity of illness. Long-term dose years were used to control for total antipsychotic exposure. The logarithmic transformations of the hospital treatment days and the dose years were used (II). Analysis of covariance was used

to study the effect of 1) antipsychotic medication use on TGM, and 2) type of current and lifetime antipsychotics on TGM (III). P-values less than 0.05 were considered to be statistically significant. Cohen's d (Cohen 1992) was used to describe the magnitude of differences in TGM between medicated and non-medicated subjects (III). Linear regression analysis was used to study the association between dose-years and TGM, and time without antipsychotics and TGM (III). Standardized beta coefficients were used and can be interpreted as: small (≥0.10), moderate (≥0.30), and large (≥0.50) effect, whereas in Cohen's d 0.2 indicates small, 0.5 moderate, and 0.8 large effect (Cohen 1992). IBM SPSS Statistics 18.0 (I), 21.0 (III), and 22.0 (II) were used to perform the analyses.

6 Ethical considerations and personal involvement

6.1 Ethical considerations

Approval for data gathering for the entire NFBC 1966 was obtained from the Ministry of Social Welfare and Health Affairs in 1993. The Ethical Committee of the Northern Ostrobothnia Hospital district has approved the study and keeps its study design under review. The research plans for the 34-year follow-up of the NFBC 1966 were accepted by the Ethical Committee of Oulu University, Faculty of Medicine, on March 30th 1998; and for the 43-year follow on February 18th 2008 by the Ethical Committee of the Northern Ostrobothnia Hospital district. Data protection has been scrutinized by the Privacy Protection Agency. Informed consent to the use of data has been obtained from each cohort member, and written informed consent has been obtained from each participant during the baseline and follow-up studies. Participants have been assigned an ID number and their identities will not be revealed. All the members of the cohort have the right to decline the use of the data concerning themselves at any time.

6.2 Personal involvement

I have planned my doctoral thesis in collaboration with my supervisors Professor (emeritus) Matti Isohanni, Professor Jouko Miettunen, and Professor Hannu Koponen. I have been part of the NFBC 1966 research group since 2007, and I have participated in collecting the neuroimaging and epidemiological data in the follow-up study in 2008-2011. Partly outside of this thesis, I have been a co-writer as an expert in antipsychotics in four other publications from the NFBC 1966 (Guo *et al.* 2015, Husa *et al.* 2014, Nykänen *et al.* 2016, Veijola *et al.* 2014).

I recorded the medication data obtained from the interviews and calculated the chlorpromazine equivalents (I, II). I collected, recorded, and analyzed the medication data from the medical records (II, III). I evaluated personally all medical records between 2008 and 2012 to collect all the data (antipsychotic agent, dose, and time period in use) needed to get detailed information on subjects' antipsychotic use.

I planned the original studies I, II, and III under the supervision of my supervisors, did the statistical analyses with the co-author PhD statistician

Marianne Haapea, interpreted the results, and wrote the first and final drafts of the manuscripts. I am the corresponding author in all three original studies, and I organized the rewriting, correction, and resubmission of all manuscripts.

7 Results

7.1 Sample characteristics (I, II, III)

The characteristics and sizes of the study samples are shown in Table 4. The slight differences concerning characteristics come from the differences between study samples, which are described above. Duration of follow-up means different things in original studies I and II, meaning the actual follow-up after the 34-year follow-up study in the first one, and the time from illness onset to the 43-year follow-up study in the second one.

Table 4. Characteristics of the samples in original studies I, II, and III.

Background and clinical variables	Study I, n=70	Study II, n=53	Study III, n=63
Sex, n (%)			
Male	38 (54%)	30 (57%)	34 (54%)
Female	32 (46%)	23 (43%)	29 (46%)
Education[1,2], n (%)			
Low	39 (56%)	30 (58%)	35 (56%)
Middle	19 (27%)	11 (21%)	15 (24%)
High	12 (17%)	11 (21%)	11 (18%)
Marital status[2], n (%)			
Married or in cohabitation	23 (33%)	17 (32%)	22 (35%)
Unmarried, divorced, or widowed	47 (67%)	36 (68%)	39 (62%)
Diagnosis[3], n (%)			
Schizophrenia	58 (83%)	46 (87%)	53 (84%)
Schizophrenia spectrum disorder	12 (17%)	7 (13%)	10 (16%)
Onset age, mean (SD)	23.7 (4.0)	24.0 (4.9)	23.6 (4.1)
Duration of follow-up[4], mean (SD)	8.7 (0.6)	19.0 (4.8)	10.4 (3.7)

SD = standard deviation

[1] Vocational education from the questionnaire at 34 years (I, III) and at 43 years (II).

[2] Information from the questionnaire at 34 years (I, III) and at 43 years (II).

[3] Validated diagnosis at 34 years (I, III) and diagnosis based on all possible information (II).

[4] From the 34-year study until the end of 2008 (I), or from the onset of illness until the 43-year study (II), or until the 34-year study (III).

7.2 Clinical characteristics of subjects with and without antipsychotic medication at age 34 years (I)

The age at onset did not differ between medicated and non-medicated subjects; neither did the prevalence of previous alcohol use disorder. Non-medicated subjects were more often without treatment contact compared to medicated ones, when observing the treatment received in hospital or outpatient care at the time of the follow-up study. There were 16 (67%) non-medicated subjects compared to 3 (6%) medicated subjects receiving neither outpatient nor hospital care at the time of the interview. Non-medicated subjects spent less time in psychiatric hospital care preceding the follow-up, and they scored better in CGI, SOFAS, and PANSS (Table 5).

Table 5. Illness-related variables for the NFBC 1966 subjects with a schizophrenia spectrum disorder at age of 34 years (modified from Table 2 in original study I).

Illness-related variables	Medicated (n=46)	Non-medicated (n=24)	P
Age at onset (years), median (range)	23.5 (16-31)	25.5 (19-30)	0.37 [1]
Outpatient care, n (%)	40 (87%)	7 (29%)	<0.001 [2]
Hospital care, n (%)	3 (7%)	1 (4%)	>0.99 [2]
Alcohol use disorder, n (%)	9 (20%)	3 (12.5%)	0.53 [2]
Psychiatric hospitalization, median (range)			
Treatment times	7 (0-31)	2 (1-17)	0.003 [1]
Treatment days	277 (0-4627)	56 (11-1195)	0.011 [1]
CGI, mean (SD)	5.00 (1.19)	3.62 (1.66)	<0.001 [3]
SOFAS, mean (SD)	46.0 (13.6)	60.5 (14.5)	<0.001 [3]
PANSS, mean (SD)			
Total symptom score	56.9 (21.4)	43.3 (14.9)	0.007 [3]
Positive symptoms	13.4 (4.67)	11.5 (5.69)	0.15 [3]
Negative symptoms	17.9 (10.9)	10.0 (5.47)	0.001 [3]
Hospitalization, mean (SD)			
Previous 2 years	0.48 (0.51)	0.22 (0.42)	0.039 [3]
Previous 5 years	0.73 (0.45)	0.39 (0.50)	0.007 [3]

SD = standard deviation. CGI = Clinical Global Impression. SOFAS = Social and Occupational Functioning Scale. PANSS = Positive and Negative Syndrome Scale.

[1] Significance from the Mann-Whitney U test.

[2] Significance from the Fisher's exact test.

[3] Significance from the independent samples t-test.

Non-medicated subjects spent less time in psychiatric hospital due to psychosis during the follow-up compared to medicated subjects. The difference was not statistically significant among subjects in remission. In addition, the relapses were more frequent among medicated subjects, although the difference was not statistically significant (Table 6).

Table 6. Proportion of time spent in psychiatric treatment due to psychosis from the interview at 34 years until the end of 2008 and 2013 (modified from Table 3 in original study I).

Remission status		Psychiatric hospitalization (%)					
		Until 2008			Until 2013		
	N	n (%)[1]	Median[2] (IQ range)	P[3]	n (%)[1]	Median[2] (IQ range)	P[3]
Remission				0.79			0.32
Medicated	9	5 (55.6)	0.15 (0.0-4.8)		7 (77.8)	0.33 (0.03-4.4)	
Non-medicated	15	7 (46.7)	<0.01 (0.0-1.7)		7 (46.7)	<0.01 (0.0-2.0)	
No remission				0.073			0.024
Medicated	37	23 (62.2)	1.82 (0.0-5.0)		26 (70.3)	2.37 (0.0-7.4)	
Non-medicated	9	5 (55.6)	0.56 (0.0-1.0)		5 (55.6)	0.34 (0.0-0.7)	

IQ range = interquartile range.

[1] Number and proportion of subjects who attended a psychiatric hospital due to psychosis.

[2] Proportion (%) of the follow-up time after the interview spent in a psychiatric hospital due to psychosis.

[3] Significance from the Mann-Whitney's U test.

Table 7 shows the differences among non-medicated subjects between those who relapsed and those who did not. The only statistically significant difference was found between those who had and those who had not been in psychiatric hospital care during the five years preceding the 34-year follow-up. The difference was not found when the comparison was made concerning the two years preceding the follow-up.

Table 7. Illness-related variables for the NFBC 1966 subjects with a schizophrenia spectrum disorder at age of 34 years among the subjects in remission[1] who relapsed and who did not during the follow-up (modified from Supplement Table 2 in original study I).

Illness-related variables	Relapse[2]		P
	Yes (n=7)	No (n=8)	
Age at onset (years), median (IQ range)	25 (20-29)	26.5 (19-28)	0.68[3]
Outpatient care, n (%)	2 (29%)	1 (13%)	0.57[4]
Hospital care, n (%)	1 (14%)	0 (0%)	0.47[4]
Alcohol use disorder, n (%)	2 (29%)	1 (13%)	0.57[4]
Psychiatric hospitalization, median (range)			
Treatment times	3 (1-9)	2 (1-5)	0.063[3]
Treatment days	113 (32-565)	46 (11-123)	0.082[3]
CGI, mean (SD)	3.14 (1.57)	2.38 (1.30)	0.32[5]
SOFAS, mean (SD)	62 (10)	71 (16)	0.22[5]
PANSS, mean (SD)			
Total symptom score	36.4 (7.6)	33.1 (6.2)	0.37[5]
Positive symptoms	8.9 (3.3)	7.4 (0.7)	0.24[5]
Negative symptoms	9.1 (2.3)	7.3 (0.7)	0.079[5]
Hospitalization, n (%)			
Previous 2 years	2 (29%)	0 (0%)	0.20[4]
Previous 5 years	4 (57%)	0 (0%)	0.026[4]

SD = standard deviation. CGI = Clinical Global Impression. SOFAS = Social and Occupational Functioning Scale. PANSS = Positive and Negative Syndrome Scale.

[1] Remission criteria: maximum scores of 3 in PANSS items P1, P2, P3, N1, N4, N6, G5, and G9.

[2] Relapse: A hospitalization due to a psychosis during the follow-up.

[3] Significance from the Mann-Whitney U test.

[4] Significance from the Fisher's exact test.

[5] Significance from the independent samples t-test.

7.3 Long-term use of antipsychotic medication and outcome at the age of 43 years (II)

7.3.1 Descriptive results of long-term use

During the first two years of the follow-up, 22 (42%) subjects had used antipsychotics less than 50% of the time, between two to five years 17 (32%) subjects, between five to ten years 14 (26%) subjects, and during the whole follow-up 13 (25%) subjects. Male subjects had used antipsychotics on average

69% (median 86%) of the follow-up time and female subjects 77% (median 88%) of the follow-up time. In total, 44 (83%) subjects had drug-free periods lasting for at least 30 days during the whole follow-up. During the first two years of the follow-up, the number of persons having drug-free periods lasting for at least 30 days was 35 (66%), between two to five years 33 (62%), and between five to ten years 23 (43%).

The long-term cumulative antipsychotic use in dose-years during the whole follow-up varied from 0 to 252 (mean 53, median 32.2). The mean dose when using antipsychotics within the whole sample was 319 mg in chlorpromazine equivalents; in male subjects (n=30) it was 350 mg (median 290 mg; range 0–1060 mg); and in females (n=23) 281 mg (median 246 mg, range 49–847 mg). The proportion of antipsychotic use and the mean doses when using medication during the ten-year follow-up after onset of illness can be seen in Figure 2. The mean dose increased during the first ten years, from approximately 150 to 250 chlorpromazine equivalents, whereas the proportion of those using antipsychotics was lowest after six months (approximately 53%) and was relatively stable after five years (approximately 70%). At some point in the follow-up, clozapine was used by 14 (26%) subjects.

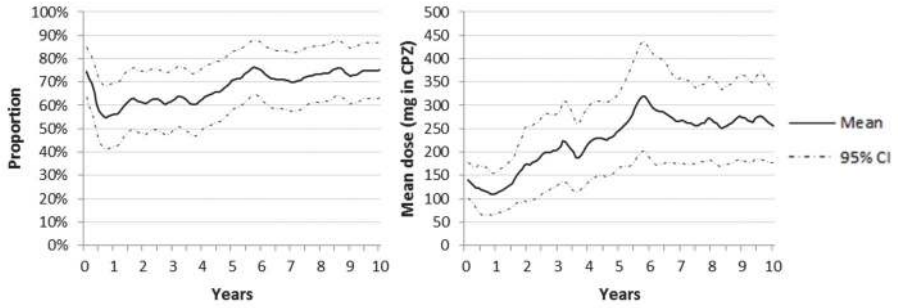

Fig. 2. Proportion (%) of antipsychotic use and mean antipsychotic dose (mgs in chlorpromazine equivalents) during a ten-year follow-up after onset of illness. Lines are smoothed using 5-month moving averages. (Figure 2 in original study II).

7.3.2 Long-term use and outcome

Proportion of medication use

Those who used antipsychotics less than 50% of the time had better clinical outcomes measured by CGI (P=0.022) at the follow-up compared to those who used antipsychotics more than 50% of the time (Table 8).

Average dose when medicated

Subjects who had used less than 300 mg of antipsychotic medication daily had better functioning based on SOFAS (P=0.013), were more often in remission (P=0.026), and had a better clinical outcome (P=0.050) compared to those who had used 300 mg or more (Table 8). The statistical significance remained in SOFAS after a Benjamini-Hochberg correction (P=0.039) and after being adjusted for the treatment days and the length of the follow-up (P=0.041 and P=0.038, respectively), but not after being adjusted for the total dose years (P=0.20). Figure 3 shows the proportion of those on antipsychotics and the average antipsychotic dose when medicated during the first ten years of the follow-up by functioning, remission, and clinical outcome. The average dose was stable among those with a relatively good level of functioning, those with remission, and those with a good clinical outcome. The average dose increased during the follow-up among those with poor outcomes.

Drug-free periods, polypharmacy, and cumulative use

Subjects who had no drug-free periods lasting for at least 30 days had better functioning based on SOFAS (P=0.048) (Table 8). APP and long-term cumulative antipsychotic use was associated with less likelihood of remission and with poorer functioning and clinical outcome (Table 8). Statistical significance remained when adjusted for the treatment days and the length of the follow-up. When adjusted for the total dose years, APP remained significantly associated with SOFAS and CGI, but not with remission (P=0.068).

Table 8. The long-term use of antipsychotic medication and its association with outcome at the age of 43 years (Table 2 in original study II).

Medication variables	Functioning (SOFAS)			Remission[1]			Clinical outcome (CGI)		
	Impairments (N=38)	Relatively good (N=15)	P	No (N=35)	Yes (N=15)	P	Poor (N=40)	Good (N=13)	P
Proportion of long-term antipsychotic use, n(%)			0.23[2]			0.096[2]			0.022[2]
< 50 %	7 (54%)	6 (46%)		6 (46%)	7 (54%)		6 (46%)	7 (54%)	
50-95 %	18 (82%)	4 (18%)		18 (82%)	4 (18%)		19 (86%)	3 (14%)	
> 95%	13 (72%)	5 (28%)		11 (73%)	4 (27%)		15 (83%)	3 (17%)	
Average dose[3], n(%)			0.013*,[2]			0.026[2]			0.050[2]
< 300 CPZ	18 (58%)	13 (42%)		18 (58%)	13 (42%)		20 (65%)	11 (35%)	
≥ 300 CPZ	20 (91%)	2 (9%)		17 (81%)	2 (11%)		20 (91%)	2 (9%)	
Drug-free periods[4], n(%)			0.048[2]			0.20[2]			0.66[2]
No	4 (44%)	5 (56%)		4 (50%)	4 (50%)		6 (67%)	3 (33%)	
Yes	34 (79%)	9 (21%)		31 (76%)	10 (24%)		34 (79%)	9 (21%)	
Antipsychotic polypharmacy[5], n(%)			0.002*,[2]			0.003*,[2]			0.002*,[2]
< 5 %	11 (48%)	12 (52%)		11 (48%)	12 (52%)		12 (52%)	11 (48%)	
5-40 %	13 (81%)	3 (19%)		12 (80%)	3 (20%)		14 (87%)	2 (13%)	
> 40 %	14 (100%)	0 (0%)		12 (100%)	0 (0%)		14 (100%)	0 (0%)	
Long-term dose-years, median (IQR)	41 (19-96)	19 (2-27)	0.004*,[6]	36 (19-85)	11 (1-30)	0.003*,[6]	41 (21-92)	9 (1-23)	0.001*,[6]

SOFAS = Social and Occupational Functioning Assessment Scale (0-100; under 60 points meaning impairment; 60 points or more meaning relatively good), CGI = Clinical Global Impression scale (1-7; 4-7 meaning clinically poor; 1-3 meaning clinically good).

* Significant after Benjamini-Hochberg correction.

[1] Remission criteria: maximum scores of 3 in PANSS items P1, P2, P3, N1, N4, N6, G5, and G9.

[2] Significance from Chi square test.

Medication variables	Functioning (SOFAS)			Remission[1]			Clinical outcome (CGI)		
	Impairments (N=38)	Relatively good (N=15)	P	No (N=35)	Yes (N=15)	P	Poor (N=40)	Good (N=13)	P

[3] Average daily dose in chlorpromazine equivalents (CPZ) when using antipsychotic medication.

[4] Any drug-free period lasting for at least 30 days.

[5] Proportion of antipsychotic polypharmacy when using antipsychotic medication.

[6] Significance from Mann-Whitney's U test.

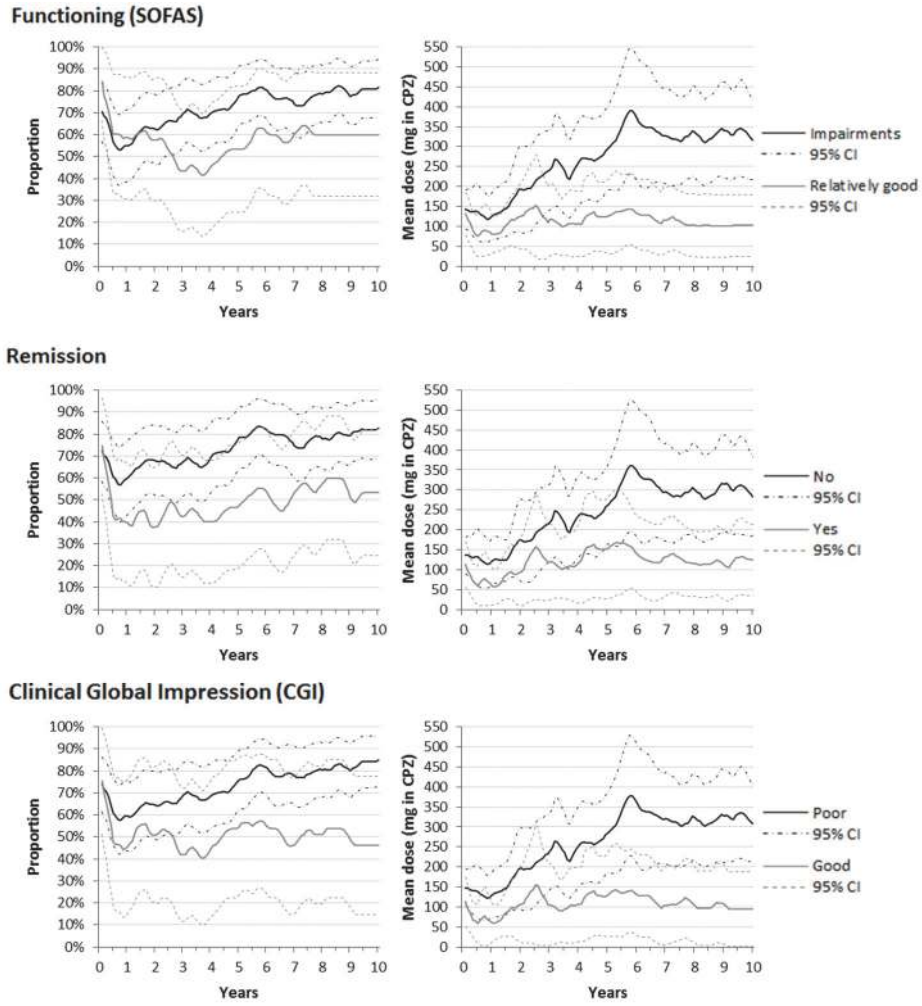

Fig. 3. Proportion (%) of antipsychotic use and mean antipsychotic dose (mgs in chlorpromazine equivalents) during a ten-year follow-up after onset of illness, divided by scores in SOFAS (Social and Occupational Functioning Assessment Scale; relatively good = 60 points or more; impairments = less than 60 points), remission status, and CGI (Clinical Global Impression scale; good = from 1 to 3; poor = from 4 to 7). Lines are smoothed using 5-month moving averages. (Figure 3 in original study II).

7.3.3 Psychiatric and somatic comorbidities

Depression had been diagnosed in 12 subjects, bipolar disorder in 4 subjects, anxiety disorder in 7 subjects, harmful alcohol use or dependence in 9 subjects, any substance use in 9 subjects, and eating disorder in 1 subject. Somatic comorbidities were reported by 10 subjects: 3 subjects reported having pulmonary diseases, 2 subjects reported having cardiovascular diseases, 3 subjects reported having endocrinological diseases, 1 subject reported having myasthenia gravis, and 1 subject reported having Crohn's disease (n=1).

7.4 Brain morphometry of subjects with and without medication at age 34 years (III)

Non-medicated subjects had, on trend level, greater TGM compared to medicated subjects (649 vs. 617 cm^3, d=-0.53, P=0.078; Table 9). Adjusted for gender, onset age, and psychiatric treatment days, there was no difference between these groups (637 vs. 618 cm^3, d=-0.34, P=0.24). No difference was found between medicated and non-medicated subjects in the voxel-based analyses. The current type of antipsychotic (typical (n=24), atypical (n=11), or both (n=10)) in use had no association with TGM (mean (SD): 620 (67), 611 (55), and 601 (54), respectively; P=0.72; Table 10), and neither did long-term type of antipsychotics (mostly typical (n=50) or atypical (n=12); 624 (63) vs. 628 (61), P=0.85). There were no differences in the voxel-based analyses between the types of antipsychotics in use. No association was found between cumulative dose of lifetime antipsychotic medication and TGM (Beta=-0.148; P=0.25; Table 11) or voxel-based gray-matter volumes.

Table 9. Total gray matter of the medicated and non-medicated subjects (Table 2 in original study III)

Adjustments	Estimated TGM means (SE)		Cohen's d	P[3]	P-values[3] of adjusting variables
	Medicated[1] n = 48	Non-medicated[2] n = 15			
Crude	617 (8.8)	649 (15.6)	-0.53	0.078	
Adjusted for					
Gender	617 (7.5)	638 (13.6)	-0.41	0.17	gender<0.001
Gender and remission	619 (8.4)	638 (13.8)	-0.33	0.26	gender<0.001, remission 0.68
Gender and onset age	617 (7.5)	638 (13.7)	-0.40	0.19	gender<0.001, onset age 0.74
Gender and psychiatric treatment days	616 (7.8)	642 (14.9)	-0.48	0.14	gender <0.001, treatment days 0.53

TGM = Total gray matter.

[1] Subjects who have used antipsychotic medication during the previous year

[2] Subjects who have not used antipsychotic medication during the previous year

[3] Significance from analysis of covariance: TGM as a dependent variable, medication as an explanatory variable, and gender, remission, onset age, or psychiatric treatment days as adjusting variables.

Table 10. Association between types of current antipsychotic medication and total gray matter.

Adjustments	Estimated TGM means (SE)			P[1]
	Only atypical n = 11	Only typical n=24	Both n = 10	
Crude	611 (17)	620 (14)	601 (17)	0.72
Adjusted for				
Gender	620 (16)	612 (11)	617 (18)	
Gender and onset age	620 (16)	612 (11)	617 (18)	

TGM = Total gray matter. SE = Standard error.

[1]Significance from analysis of covariance

Continuous time without antipsychotic medication preceding the MRI scan was associated statistically significantly with greater volume of TGM (Beta=0.278; P=0.028; Table 11) (Figure 4). Statistical significance did not persist when adjusted for gender, onset age, and remission (Beta=0.189; Table 11). In the voxel-based analyses, a longer continuous time without medication was associated with increased regional volume in the right precentral gyrus (P=0.024;

Talairach coordinates (x,y,z): 46,6,26; cluster size: 127) and right middle frontal gyrus (P=0.026; Talairach coordinates (x,y,z): 34,22,46; cluster size: 119) when adjusted for TGM, gender, and onset age (Figure 5). When also adjusted for remission, these associations did not persist.

Table 11. Associations between cumulative dose of lifetime antipsychotic medication and total gray matter, and length of continuous time without antipsychotic medication and total gray matter (Table 3 in original study III)

Medication-related variables	Coefficients from the linear regression models		P[1]	P-values[1] of adjusting variables
	B (SE)	Beta		
Dose-years				
Crude	-7.2 (6.2)	-0.148	0.247	
Adjusted for				
Gender	-6.3 (5.2)	-0.129	0.232	gender<0.001
Gender and onset age	-7.1 (6.4)	-0.145	0.269	gender<0.001, onset age 0.822
Gender and remission	-5.5 (6.2)	-0.111	0.386	gender<0.001, remission 0.803
Gender and psychiatric treatment days	-9.7 (6.6)	-0.198	0.148	gender<0.001, treatment days 0.405
Time without antipsychotic medication				
Crude	5.3 (2.3)	0.278	0.028	
Adjusted for				
Gender	3.6 (2.0)	0.193	0.075	gender<0.001
Gender and onset age	3.5 (2.1)	0.189	0.087	gender<0.001, onset age 0.824
Gender and remission	3.6 (2.3)	0.189	0.122	gender<0.001, remission 0.950
Gender and psychiatric treatment days	4.4 (2.2)	0.232	0.054	gender<0.001, treatment days 0.439

SE = Standard error.

[1] Significance from analysis of covariance.

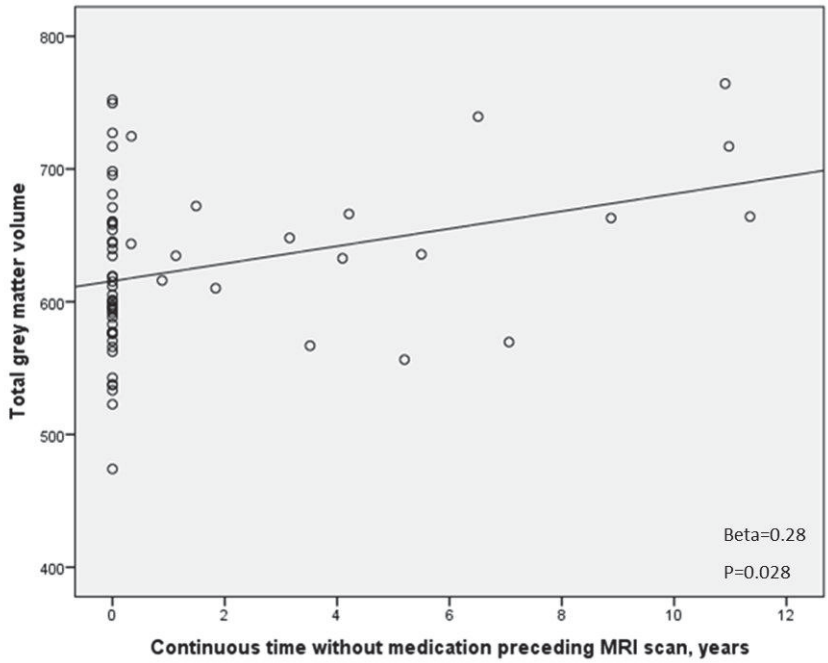

Fig. 4. Association between continuous time without antipsychotic medication and total gray matter volume (Figure 1 in original study III).

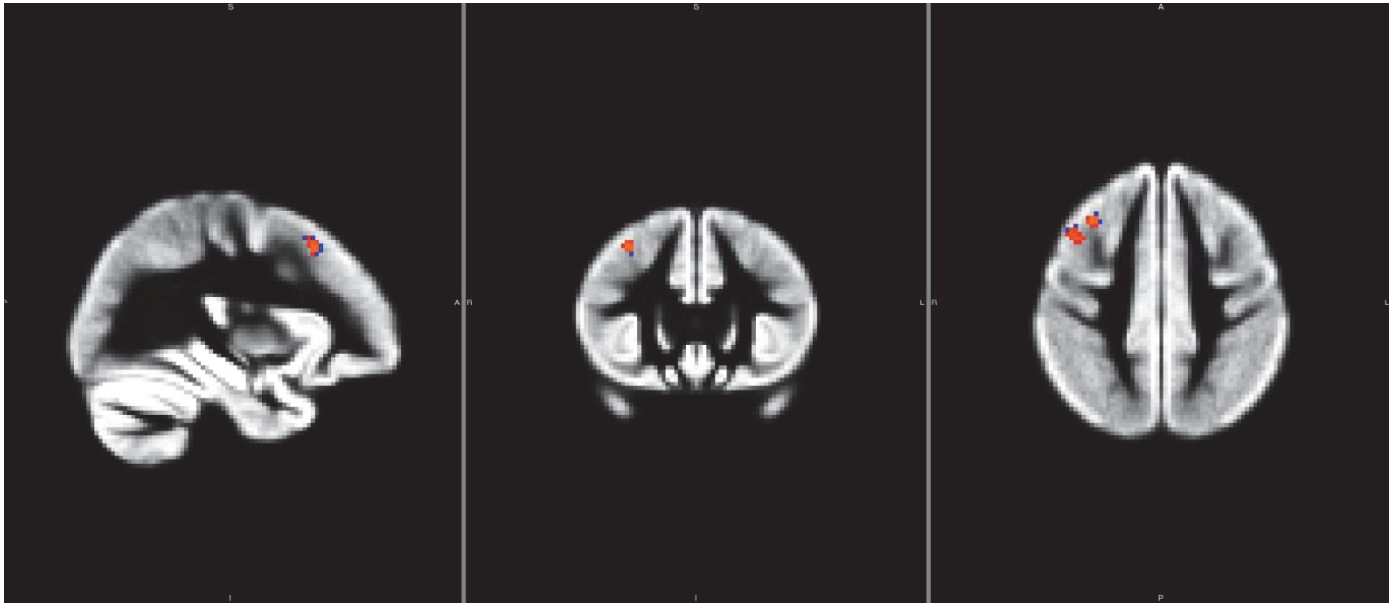

Fig. 5. Association between continuous time without antipsychotics and brain morphometry in voxel-based analyses when adjusted for total gray matter volume, gender, and onset age; longer continuous time without medication associated with increased regional volume in right precentral gyrus and right middle frontal gyrus (Figure 2 in original study III).

8 Discussion

8.1 Main findings

Subjects with schizophrenia spectrum disorder using no antipsychotic medication at the age of 34 years *differed* from medicated ones. They were more often males, less often pensioned, had better symptomatic outcome in terms of PANSS, CGI, and SOFAS scores, spent less time in psychiatric treatment, and had less severe schizophrenia spectrum diagnoses (I). A longer continuous time without antipsychotics preceding the MRI scan was associated statistically significantly with a greater volume of TGM, and in the voxel-based analyses a longer continuous time without medication was associated with increased regional volume in the right precentral gyrus and right middle frontal gyrus (III).

Following *non-medicated subjects in remission* in cases of relapse resulted in a finding that relapses were equally frequent between non-medicated and medicated subjects. Not being hospitalized during the five years before the follow-up differed between those who did not relapse and those who did among non-medicated subjects in remission (I).

The findings concerning *long-term use of antipsychotic medication* (mean 18.6 years since illness onset) showed steadier use over time. During the first two years of the follow-up, 22 (42%) subjects had used antipsychotics less than 50% of the time, between two to five years the number was 17 (32%), between five to ten years 14 (26%), and during the whole follow-up 13 (25%). In addition, drug-free periods became rarer during the follow-up (first two years 35 subjects, between two to five years of the follow-up 33, and after five years 23 subjects) (II). When studying the outcome and previous long-term medication, the main findings were that those subjects who had had a low antipsychotic dose and those with no drug-free periods had better outcomes (II).

8.2 Comparison with earlier studies

8.2.1 Non-medication in schizophrenia

At the age of 34, there were altogether 24 subjects without antipsychotics, accounting for 34.3% of the whole sample (I), of which 20 (28.6%) subjects had been without antipsychotics for at least a year. As a comparison, Hopper *et al*.

(2007) reported an average of 25.5% of patients with schizophrenic psychosis without antipsychotic medication for the last 2 years of the 15-year follow-up time in the multinational incident cohorts of the World Health Organization (WHO). Remission was achieved by 15 out of 24 (62.5%) non-medicated subjects (I). It is a high number and belongs to the upper end of remission rates when compared with previous studies, which suggests that remission criteria are fulfilled by 22-66% of subjects with schizophrenia (not only non-medicated subjects) (Emsley *et al*. 2011, Haro *et al*. 2011, ten Velden Hegelstad *et al*. 2013).

Non-medicated subjects compared to medicated ones

In this study, on average 10 years after illness onset, non-medicated and medicated subjects with schizophrenic psychoses differed by sex, employment status, clinical course, and brain morphometry.

Sociodemographic factors. Among non-medicated subjects, there were more men than women and fewer subjects on a disability pension. Onset age did not differ between the non-medicated and medicated groups, indicating approximately ten years' duration of illness. It should be noted that in this birth cohort study, onset age corresponds to duration of illness, which has often been used as a marker of severity of illness. Sex distribution differs from earlier studies (Usall *et al.* 2007, Ciudad *et al.* 2008, Suokas *et al.* 2013).

Outcome. Non-medicated subjects had been in psychiatric hospital care less than medicated subjects, they had less severe illness, higher social functioning, and fewer symptoms, compared to medicated subjects. These results are in line with previous findings concerning severity of illness and severity of psychotic symptoms (Kroken *et al.* 2009, Jönssön *et al.* 2011, Vares *et al.* 2011). All this could be thought to refer to a milder illness, which could in turn lead to non-medication. In another words, confounding by indication cannot be ruled out, while those with more severe illness could be thought to use medication. In this study, the reasons behind the non-medication were not known, but as Harrow and Jobe (2007) suggest, it is a "self-selected group" with better earlier prognostic and developmental potential, which in turn could support the point of view of milder disease.

8.2.2 Long-term use of antipsychotics

There is very little systematic information on long-term use of antipsychotic medication, although there are studies reporting the use of antipsychotics in the long term, such as works by Hopper *et al*. (2007) and Harrow and colleagues (2007, 2012, 2013, 2014). This study differs from earlier studies in the detailed daily information on the use of antipsychotics.

While long-term use of antipsychotic medication was investigated, this study described the proportion of antipsychotic use during the ten-year follow-up after the onset of illness. The proportion of antipsychotic use comes close to the terms *adherence* and *compliance*, which have been defined as 'the extent to which a person's behavior coincides with the medical advice he/she has received' (Kampman and Lehtinen 1999). In this study, the reasons behind the non-medication were not known. As known, compliance is not an all-or-nothing phenomenon, and therefore using the term partial compliance seems to be preferable (Llorca 2008). Llorca (2008) studied partial compliance in his review and stated that rates of partial compliance with antipsychotic treatment have been shown to increase over time with discharge from an in-patient facility. He presented that at least 50% of patients will be partially or non-compliant within 1 year, and 75% within 2 years of discharge. The follow-up of the current study (II) was longer, and within this sample it seemed that after the first years of illness, the proportion of antipsychotic use became higher, and after 5 years it remained at a higher level, which has not been shown in earlier studies. However, it might be that subjects with better adherence took part in this study, and this shows in these results.

When observing the long-term use of antipsychotics, the *use of APP* also comes up. In this study, a worse outcome was associated with APP and higher long-term cumulative antipsychotic use (II). Fleischacker and Uchida (2014) presented that APP could be used in some clinically difficult conditions and cases that may cause residual confounding. The results of this study concerning the association between APP and poorer outcomes could also be thought of in the way that APP has been used in such circumstances with subjects of this study. As further discussed in limitations, the association between higher long-term cumulative antipsychotic use and poorer outcome could also be thought of as being derived from more severe illness, as increasing the current dose of an administered antipsychotic drug is one strategy to treat patients with treatment-resistance (Dold & Leucht 2014). The results of higher long-term antipsychotic

use and poorer outcome can also be thought of from the pharmacogenetic point of view, as the responses to antipsychotics differ greatly from one individual to another, and many subjects do not respond well to antipsychotic treatment (Arranz *et al*. 2011, Xu *et al*. 2013).

8.2.3 Long-term use of antipsychotics versus withdrawal

While studies show a markedly high risk of relapse after medication discontinuation (Leucht 2012, Zipursky *et al*. 2013), this study (I) showed contrary findings, showing the stability of remission in non-medicated subjects to be as stable as in medicated subjects. This finding is in line with the study by Wunderink *et al*. (2013), in which they showed that patients in a discontinuation/dose reduction group were at higher relapse risk during the first two years, but not after the seven-year follow-up. In this study, the follow-up lasted over eight years. The results of this study together with the results of Wunderink *et al*. (2013) implicate different effects of antipsychotic discontinuation in the short term (first years) than in the longer term (several years).

While observing the *long-term use* of antipsychotics in this study, the good outcome was associated with a low dose, with continuous treatment with antipsychotics, and with a long-term proportion of use of less than half the time. These results seem to be in conflict with each other, and therefore need to be discussed a little further. The information on long-term use comes from daily information, and the proportion of use is an estimation of whether a subject has used medication each day or not. The association between good outcome and continuous antipsychotic treatment comes from the information on whether a subject had drug-free periods lasting at least 30 days or not. Shorter periods of non-medication lower the total proportion of use, but are not considered drug-free periods because of the short duration of non-medication. The other aspect is *the heterogeneity of schizophrenia*. The etiology of schizophrenia is thought to be multifactorial (Haller *et al.* 2014). The clinical course can vary from one psychotic episode to continuous symptoms (Wiersma *et al.* 1998), which shows in pharmacological treatment and makes causal interpretations in the research field difficult. *Heterogeneity and major interindividual variation of schizophrenia* also show in these results, suggesting that not all subjects with schizophrenia need permanent long-term antipsychotic medication, but then on the other hand, there

are subjects who benefit from it. The major problem is how to recognize those who manage without permanent antipsychotic medication.

Although the above-mentioned results seem to be in conflict with each other, they are in line with previous findings. Wunderink *et al*. (2013) reported better functional outcomes within the medication discontinuation group in their seven-year follow-up study. In their study, subjects in the discontinuation/dose reduction group were able to start medication if needed, but their use of an antipsychotic was lower in total compared to others. That is in line with the results of this study concerning better outcome among subjects who had used antipsychotics less than half of the time during the follow-up. The association between better outcomes and steady medication is in line with the study by Sampson *et al.* (2012) and De Hert et al. (2015), in which they reported that continuous antipsychotic therapy is more effective than intermittent antipsychotic drug treatment, and it 'remains the gold standard for good clinical practice'.

8.2.4 Antipsychotics and brain morphometry

There are several studies reporting the effect of antipsychotics on brain morphometry (Navari and Dazzan 2009, Moncrieff and Leo 2010, Leung *et al*. 2011, Fusar-Poli *et al*. 2013, Haijma *et al*. 2013, Torres *et al*. 2013). Fusar-Poli *et al*. (2013) reported, in their meta-analysis comprising longitudinal studies, that antipsychotics may reduce the gray matter volume and increase lateral ventricles. In this study, non-medicated subjects had, on a trend level, greater TGM compared to medicated subjects (III).

One focus in this study was to clarify whether the *time without antipsychotics* has an effect on brain morphometry, which has not previously been studied. Continuous time without antipsychotics was associated with increased TGM volume and with increased regional volume in the right precentral gyrus and right middle frontal gyrus in the voxel-based analyses.

Ho *et al.* (2011) reported the effect of all types (typical, non-clozapine atypical, and clozapine) of antipsychotics on brain morphometrical changes, while the earlier study by Lieberman *et al. (*2005) found significant reductions in gray matter volume within haloperidol-treated patients, but not within olanzapine-treated patients. In this study, we found no association between the type of antipsychotics and brain morphometry.

8.3 Comparison with treatment guidelines

Treatment guidelines for schizophrenia include recommendations concerning antipsychotics treatment in general (e.g. individually planned in co-operation with the patient and their family) and more specifically in different phases of illness. The subjects of this study have had a schizophrenia diagnosis for years, and that is why this comparison is made from the view of long-term treatment of schizophrenia.

8.3.1 Long-term use of antipsychotics, withdrawal, and dose

Treatment guidelines do not actually recommend discontinuation; they recommend continuation on antipsychotics at least for a certain time period, and after that period guided discontinuation is possible while monitoring for possible symptom recurrence. The duration of this time period in recommendations may vary from half a year to five years.

Long-term use of antipsychotics. Although there are guidelines for guided discontinuation of antipsychotics after first episode psychosis, maintenance treatment is also strongly recommended in the stable phase of illness. Results from the long-term use of antipsychotics in this study could be thought to be near the guideline recommendations, while a good outcome was observed among those who had had no drug-free periods (II).

Withdrawal. In this study, most of the non-medicated subjects in remission were first-episode patients, which makes comparison to the guidelines possible (I). Only five (33%) of the non-medicated subjects who were in remission had had two or more episodes of psychiatric treatment, while the remaining 10 (67%) fulfilled the criteria for the guided discontinuation of antipsychotic medication as laid down in the guidelines (I). The current evidence-based Finnish guidelines (www.kaypahoito.fi) for the treatment of schizophrenia suggest that when a patient who is on antipsychotic medication has had a symptom-free period lasting at least 2 to 5 years after the first episode of psychosis, the medication can be cautiously discontinued. On the basis of this study, 5 years without hospital treatment is better than 2 years, when comparing the successful withdrawal of antipsychotics in terms of relapses (I). However, caution should be used when interpreting this finding, as it is based on a small sample size and one study.

When the association between long-term antipsychotic use and outcome was studied, the results also showed that good outcome was associated with a

proportion of antipsychotic use of less than half the time (III). Within this sample, it is, however, impossible to say whether those subjects with a good outcome and a proportion of antipsychotic use of less than half the time fulfill the criteria of guided discontinuation as laid down in the guidelines.

Dose. In all phases of illness, the lowest dose needed is recommended in the guidelines, as well as monotherapy with antipsychotics. The results of this study could be thought to support that, while good outcome was associated with low dose, and poor outcome with high long-term cumulative use of antipsychotics and APP. However, it should be mentioned that direct causal interpretations in this kind of observational study may be impossible to make (Kundi 2006) and, for example, more severe illness could explain the association between higher dose and poorer outcome, as increasing the dose of antipsychotics is one strategy in treating treatment-resistance (Dold & Leucht 2014).

8.4 Clinical implications

This study focused on the use and non-use of antipsychotics mainly in the long term, and their effect on outcome and brain morphometry. The findings in this study support following the recommendations laid down in the guidelines; in addition, the discontinuation of antipsychotics is possible at least for some subjects with schizophrenia. A study by Thompson *et al.* (2015) suggests that current practice is different from that advised by the available guidelines. They conclude that the views of clinicians in England and Wales regarding prophylactic antipsychotic medication after remission from first episode psychosis are much less conservative than those in the current guidelines. The median answer was 6-12 months when the length of continuation on antipsychotics after remission was asked.

In addition, the results concerning time without antipsychotics and brain morphometry could be thought to support discontinuation, even though the clinical meaning behind this is still somewhat unclear. Andreasen *et al.* (2011) found association between frontal tissue loss and poorer performance in tests of verbal learning, attention, and working memory.

In all, *in clinical decision-making*, it is challenging to detect those who could be successfully withdrawn from antipsychotics. Treatment guidelines suggest a continuation of antipsychotics at least for a certain time period, which varies between the guidelines. Based on the results of this study, even though the sample

was rather small, the 5-year period of time without hospitalization could be used for that.

8.5 Methods: validity of medical data

The medication data in this study differs from previous long-term studies. In this study, *three sources* were used to gather a detailed and reliable estimation of subjects' antipsychotic use: 1. Interviews during the follow-ups were performed. In the interviews, subjects were asked about their antipsychotic use during the previous three months, during the previous year, and for as long as they could remember (I, III). 2. The Register of Finnish Social Insurance Institution on psychoactive medications consumed during 1997 was used (I-III). Unfortunately, we did not have register data on other years. 3. The most important and widest data were the medical records (II, III). All available medical records were gone through to find every antipsychotic agent, dose, and period of use during subjects' lifetimes. In the estimation, all the recordings concerning adherence were taken into account when formulating the subjects' daily data on lifetime antipsychotic use.

8.6 Strength and limitations

Detailed and extensive data on antipsychotics are a considerable strength of this study. All the available hospital and outpatient care medical records have been gone through, the subjects' antipsychotic medication history was asked about in the interview, and register data was also used.

A strength of this study is also the *epidemiologically sound, population-based* sample of mostly outpatients and some people without psychiatric treatment contact, which may reflect less severe illness than in many clinical settings and may make the results less prone to selection bias and more generalizable to the real-world schizophrenia population. The study population was in midlife, as most schizophrenia individuals are. In addition, *attrition* was analyzed carefully (Haapea *et al.* 2007). To decrease *the risk of residual confounding* in a naturalistic setting with a long follow-up, the most important confounders related to duration and severity of illness were available and taken into account. However, subjects with more severe illness or treatment-resistant schizophrenia may receive higher doses of antipsychotic medication, making higher doses a marker of a more serious illness course rather than a cause of decline. *Illness severity* is also one

potential confounding factor between antipsychotics and brain volume loss, as it is conceivable that the subjects with the most severe illness lose more brain volume over time and also use antipsychotics with high doses and for long periods. The severity of a lifetime illness is difficult to assess. In this birth cohort study, we used onset age, which corresponds to duration of illness, which in turn has often been used as a marker of severity of illness. Psychiatric treatment days and measures of remission status (remission criteria of Andreasen *et al*. (2005), with the exception that, as the symptoms had been assessed only once (for the previous week), the duration of remission criterion of six months was not applied) were also used to assess the severity of illness.

There are also *limitations* in the data on medication. A lack of information on the use of *other* medications, such as anxiolytics or mood stabilizers, is an unfortunate limitation. Although different approaches were used to get the best estimation of subjects' antipsychotic use and to evaluate *adherence*, it is always possible that the estimation of this data differs from reality. No blood tests were taken to control the drug concentrations. The limitations of the study also include the *small sample sizes* and that subjects were in different phases of the illness. The *causalities* between antipsychotic use, outcome, and brain morphometry were difficult to detect and interpret, because in this study there was only one follow-up assessment of outcomes, and only one MRI scan was performed.

9 Conclusions

9.1 Main conclusions

Schizophrenia is a heterogeneous condition, which also shows in antipsychotics treatment and its responses. The results of this study show that there are subjects with schizophrenia with and without antipsychotic medication who achieve good outcomes. Clinically, it is a challenge to detect these different drug response groups, including those managing with low doses, tolerating pauses, or even discontinuation. The main factor predicting the successful discontinuation of antipsychotics was previous treatment history: subjects who had not been hospitalized during the previous five years had a statistically lower risk of a relapse.

The observations on effects of antipsychotic discontinuation on brain morphometry led to a novel finding of positive correlation between time without antipsychotics and total gray matter. These results, together with the results of non-medication and good outcome in the long term, indicate that the possible effect of medication discontinuation on brain morphometry and functioning in schizophrenia requires further investigation.

9.2 Future research

Despite the fact that the course of schizophrenia, and simultaneously the recommended treatment with antipsychotics, can often be long, the long-term effect of antipsychotic treatment is not fully known (Sohler *et al.* 2015). Long-term studies are needed to clarify this and also the harmful effects of antipsychotics in the long term. Lowering the dose is one way to deal with adverse effects; studies concerning the effects of dose reduction and individual medication tapering in the long term are also needed. Personalized medication is recommended in the guidelines, and this has resulted, together with other personalized treatments, in improvements in clinical and functional outcomes (Kane *et al.* 2015).

Another hot topic in the field is antipsychotic withdrawal. Thompson *et al.* (2015) studied the views of clinicians on this topic, stating that the views of clinicians are less conservative than the current guidelines. It is a difficult topic, not only because of the lack of practical predictors for successful withdrawal of

antipsychotics, but also because of possible relapse if the withdrawal fails: the consequences of relapse can sometimes be devastating. Further studies of guided discontinuation/withdrawal of antipsychotics and investigations on predicators for successful withdrawal are needed.

Even though there are findings concerning the association between antipsychotics and brain morphometry, the clinical meaning of these findings and the mechanism behind them are somewhat unclear. Andreasen *et al.* (2011) found an association between frontal tissue loss and poorer performance in tests of verbal learning, attention, and working memory; and lowering of astrocyte and oligodendrocyte numbers in antipsychotic-exposed monkeys compared to non-exposed has been found (Konopaske *et al.* 2008). Understanding the effects of antipsychotics on brain morphometry requires further studies.

The finding concerning the association between continuous time without antipsychotics and greater volume of TGM raises the question of whether the possible effect of antipsychotic medication on brain morphometry is reversible. In this study, there was only one MRI scan used, and that kind of interpretation is not possible to make based on the results of this study. In the future, it would be interesting to include brain morphometrical studies in studies concerning antipsychotic withdrawal.

References

Ahuja N (1999) Antipsychotic drugs. In:. Vyas AJ & Ahuja N (eds) Textbook of Postgraduate Psychiatry. Jaypee Brothers Medical Publishers (P) Ltd.

American Psychiatric Association (APA) (1987) American Diagnostic and Statistical Manual of Mental Disorders. 3rd ed., revised. Washington, American Psychiatric Association.

Anatomical Therapeutic Chemical classification system (www.whocc.no). Cited 2016/03/09.

Andersson JLR, Jenkinson M & Smith S (2007a) Non-linear optimisation. FMRIB technical report TR07JA1. URI: www.fmrib.ox.ac.uk/analysis/techrep. Cited 2016/01/16.

Andersson JLR, Jenkinson M & Smith S (2007b) Non-linear registration, aka spatial normalisation FMRIB technical report TR07JA2. URI: www.fmrib.ox.ac.uk/analysis/techrep. Cited 2016/01/16.

Andreasen NC, Carpenter WT, Kane JM, Lasser RA, Marder SR & Weinberger DR (2005) Remission in schizophrenia: proposed criteria and rationale for consensus. Am J Psychiatry 162(3): 441–449.

Andreasen NC, Nopoulos P, Magnotta V, Pierson R, Ziebell S & Ho BC (2011). Progressive brain change in schizophrenia: a prospective longitudinal study of first-episode schizophrenia. Biol Psychiatry 70(7): 672-679.

Andreasen Nc, Pressler M, Nopoulos P, Miller D & Ho BC (2010) Antipsychotic dose equivalents and dose-years: a standardized method for comparing exposure to different drugs. Biol Psychiatry 67(3): 255-262.

APA (2010) Practice Guideline for the Treatment of Patients with Schizophrenia. American Psychiatric Association, Arlington (VA).

Baandrup L, Østrup Rasmussen J, Klokker L, Fitzgerald Austin S, Bjørnshave T, Fuglsang Bliksted V, Fink-Jensen A, Hedegaard Fohlmann A, Peter Hansen J, Kristine Nielsen M, Sandsten KE, Schultz V, Voss-Knude S & Nordentoft M (2015) Treatment of adult patients with schizophrenia and complex mental health needs - a national clinical guideline. Nord J Psychiatry 2:1–10 [Epub ahead of print].

Bazire S (2003) Psychotropic Drug Directory 2003/2004. Fivepin publishing: 179-180.

Bleuler E (1911) Dementia Praecox or the group of schizophrenias. Monograph series on schizophrenia No. 1. New York, Intern University Press.

Bola JR, Lehtinen K, Aaltonen J, Räkköläinen V, Syvälahti V & Lehtinen V (2006) Predicting medication-free treatment response in acute psychosis: cross-validation from the Finnish Need-Adapted project. Nerv Ment Dis 194(10): 732-739.

Bola JR & Mosher LR (2003) Treatment of acute psychosis without neuroleptics: two-year outcomes from the Soteria project. Nerv Ment Dis 191(4): 219-229.

Bruijnzeel D, Suryadevara U & Tandon R (2011) Antipsychotic treatment of schizophrenia: an update. Asian J Psychiatr 11: 3–7.

Caroff SN, Hurford I, Lybrand J & Campbell EC (2011) Movement disorders induced by antipsychotic drugs: implications of the CATIE schizophrenia trial. Neurol Clin 29(1): 127–148.

Citrome L (2011) Neurochemical models of schizophrenia: transcending dopamine. Curr Psychiatry 10(9): S10–S14.

Citrome L (2014) Unmet needs in the treatment of schizophrenia: new targets to help different symptom domains. J Clin Psychiatry 75, Suppl. 1: 21–26.

Cohen J (1992) A power primer. Psychol Bull 112(1): 155–159.

Cole JO, Goldberg SC & Klerman GL (1964) Phenothiazine in treatment of acute schizophrenia. Arch Gen Psychiat 10: 246–61.

Correll CU, Rummel-Kluge C, Corves C, Kane JM & Leucht S (2009) Antipsychotic combinations vs. monotherapy in schizophrenia: a meta-analysis of randomized controlled trials. Schizophr Bull 35(2): 443–457.

Davis KL, Kahn RS, Ko G & Davidson M (1991) Dopamine in schizophrenia: a review and reconceptualization. Am J Psychiat 148(11): 1474–1486.

De Hert M, Sermon J, Geerts P, Vansteelandt K, Peuskens J & Detraux J (2015) The use of continuous treatment versus placebo or intermittent treatment strategies in stabilized patients with schizophrenia: a systematic review and meta-analysis of randomized controlled trials with first- and second-generation antipsychotics. CNS Drugs 29(8): 637-658.

Emsley R, Chiliza B, Asmal L & Lehloenya K (2011) The concepts of remission and recovery in schizophrenia. Curr Opin Psychiatr 24(2): 114–121.

Faber G, Smid HG, Van Gool AR, Wiersma D & Van Den Bosch RJ (2012) The effects of guided discontinuation of antipsychotics on neurocognition in first onset psychosis. Eur Psychiatry 27(4): 275–280.

Fleischacker WW & Uchida H (2014) Critical review of antipsychotic polypharmacy in the treatment of schizophrenia. Int J Neuropsychopharmacol 17(7): 1083–1093.

Fusar-Poli P, Smieskova R, Kempton MJ, Ho BC, Andreasen NC & Borgwardt S (2013) Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies. Neurosci Biobehav Rev 37(8): 1680–1691.

Gaebel W, Weinmann S, Sartorius N, Rutz W & McIntyre J (2005) Schizophrenia practice guidelines: international survey and comparison. Br J Psychiatry 187: 248–255.

Gallego JA, Bonetti J, Zhang J, Kane JM & Correl CU (2012) Prevalence and correlates of antipsychotic polypharmacy: a systematic review and meta-regression of global and regional trends from the 1970s to 2009. Schizophr Res 138(1): 18–28.

Gilbert PL, Harris MJ, McAdams LA & Jeste DV (1995) Neuroleptic withdrawal in schizophrenic patients. A review of the literature. Arch Gen Psychiatry 52: 173–188.

Ciudad A, Haro JM, Alonso J, Bousoño M, Suárez D, Novick D & Gilaberte I (2008) The Schizophrenia Outpatient Health Outcomes (SOHO) study: 3-year results of antipsychotic treatment discontinuation and related clinical factors in Spain. Eur Psychiatry 23(1): 1–7.

Goff DC, Lamberti JS, Leon AC, Green MF, Miller AL, Patel J, Manschreck T, Freudenreich O & Johnson SA (2008) A placebo-controlled add-on trial of the Ampakine, CX516, for cognitive deficits in schizophrenia. Neuropsychopharmacology 33(3): 465–472.

Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ & Frackowiak RS (2001) Voxel-based morphometric study of ageing in 465 normal adult human brains. Neuroimage 14(1 Pt 1): 21–36.

Gore FM, Bloem PJ, Patton GC, Ferguson J, Joseph V, Coffey C, Sawyer SM & Mathers CD (2011) Global burden of disease in young people aged 10–24 years: a systematic review. Lancet 377(9783): 2093–2102.

Guo JY, Huhtaniska S, Miettunen J, Jääskeläinen E, Kiviniemi V, Nikkinen J, Moilanen J, Haapea M, Mäki P, Jones PB, Veijola J, Isohanni M & Murray GK (2015) Longitudinal regional brain volume loss in schizophrenia: Relationship to antipsychotic medication and change in social functioning. Schizophr Res 168(1-2): 297-304.

Guy W (1976) EDCEU Assessment Manual for Psychopharmacology – Revised (DHEW Pupl No ADM 76 338). Rockville, MD, U.S. Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, NIMH Psychopharmacology Research Branch, Division of Extramural Research Programs: 534–537.

Haapea M, Isohanni M, Jääskeläinen E, Veijola J & Miettunen J (2013) Using home recruitment to increase representativeness of schizophrenia research. Eur Psychiatry 28: Suppl. 1, meeting abstract 1725.

Haapea M, Miettunen J, Veijola J, Lauronen E, Tanskanen P & Isohanni M (2007) Non-participation may bias the results of a psychiatric survey: an analysis from the survey including magnetic resonance imaging within the Northern Finland 1966 Birth Cohort. Soc Psychiatry Psychiatr Epidemiol 42(5): 403–409.

Haapea M, Veijola J, Tanskanen P, Jääskeläinen E, Isohanni M & Miettunen J (2011) Use of inverse probability weighting to adjust for non-participation in estimating brain volumes in schizophrenia patients. Psychiatry Res 194(3): 326–332.

Haase HJ & Janssen PAJ (1965) The action of neuroleptic drugs: a psychiatric, neurologic and pharmacological investigation. Chicago: Year Book Medical Publishers.

Haijma SV, Van Haren N, Cahn W, Koolschijn PC, Hulshoff Pol HE & Kahn RS (2013) Brain volumes in schizophrenia: a meta-analysis in over 18 000 subjects. Schizophr Bull 39(5): 1129–1138.

Haller CS, Padmanabhan JL, Lizano P, Torous J & Keshavan M (2014) Recent advances in understanding schizophrenia. F1000Prime Rep 6:57.

Hamid A, Ghaleb M, Aljadhey H & Aslanpour Z (2014) A systematic review of qualitative research on the contributory factors leading to medicine-related problems from the perspectives of adult patients with cardiovascular diseases and diabetes mellitus. BMJ Open 4(9): e005992.

Haro JM, Novick D, Bertsch J, Karagianis J, Dossenbach M & Jones PB (2011) Cross-national clinical and functional remission rates: Worldwide Schizophrenia Outpatient Health Outcomes (W-SOHO) Study. Brit J Psychiat 199(3): 194–201.

Harrow M & Jobe TH (2007) Factors involved in outcome and recovery in schizophrenia patients not on antipsychotic medications: a 15-year multifollow-up study. J Nerv Ment Dis 195(5): 406–414.

Harrow M & Jobe TH (2013) Does long-term treatment of schizophrenia with antipsychotic medications facilitate recovery. Schizophr Bull 39(5): 362–365.

Harrow M, Jobe TH & Faull RN (2012) Do all schizophrenia patients need antipsychotic treatment continuously throughout their lifetime? A 20-year longitudinal study. Psychol Med 42(10): 2145–2155.

Harrow M, Jobe TH & Faull RN (2014) Does treatment of schizophrenia with antipsychotic medication eliminate or reduce psychosis? A 20-year multi-follow-up study. Psychol Med 44(14): 3007–3016.

Hegarty JD, Baldessarini RJ, Tohen M, Waternaux C & Oepen G (1994) One hundred years of schizophrenia: a meta-analysis of the outcome literature. Am J Psychiat 151(10): 1409–1416.

Hensler J, Artigas F, Bortolozzi A, Daws L, De Deurwaerdère, Milan L, Navailles S & Koek W (2013) Catecholamine/serotonin interactions: systems thinking for brain function and disease. Adv Pharmacol 68: 167–197.

Hippius H (1999) A historical perspective of clozapine. J Clin Psychiat 60, Suppl. 12: 22–23.

Ho BC, Andreasen NC, Ziebell S, Pierson R & Magnotta V (2011) Long-term antipsychotic treatment and brain volumes: a longitudinal study of first-episode schizophrenia. Arch Gen Psychiatry 68(2): 128–137.

Honea R, Crow TJ, Passingham D & Mackay CE (2005) Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. Am J Psychiat 162(12): 2233–2245.

Hopper K, Harrison G & Wanderling JA (2007) An overview of course and outcome in ISoS. In: Hopper K, Harrison G, Janca A & Sartorius N (eds) Recovery from schizophrenia. An international perspective. New York, Oxford University Press: Table 3.6.

Husa AP, Rannikko I, Moilanen J, Haapea M, Murray GK, Barnett J, Jones PB, Isohanni M, Koponen H, Miettunen J & Jääskeläinen E (2014) Lifetime use of antipsychotic medication and its relation to change of verbal learning and memory in midlife schizophrenia - an observational 9-year follow-up study. Schizophr Res 158(1–3): 134–141.

Iasevoli F, Buonaguro EF, Marconi M, Di Giovambattista E, Rapagnani MP, De Berardis D, Martinotti G, Mazza M, Balletta R, Serroni N, Di Giannantonio M, de Bartolomeis A & Valchera A (2014) Efficacy and clinical determinants of antipsychotic polypharmacy in psychotic patients experiencing an acute relapse and admitted to hospital stay: results from a cross-sectional and a subsequent longitudinal pilot-study. ISRN Pharmacol 2014: 762127.

Isohanni M (1983) The psychiatric ward as a therapeutic community. Acta Universitatis Ouluensis D 111 n:o 5.

Javitt DC, Zukin SR, Heresco-Levy U & Umbricht D (2012) Has an angel shown the way? Etiological and therapeutic implications of the PCP/NMDA model of schizophrenia. Schizophr Bull 38(5): 958–966.

Jenkinson M, Bannister PR, Brady JM & Smith SM (2002) Improved optimisation for the robust and accurate linear registration and motion correction of brain images. Neuroimage 17(2): 825–841.

Jenkinson M & Smith S (2001) A global optimisation method for robust affine registration of brain images. Med Image Anal 5(2): 143–156.

Jääskeläinen E, Juola P, Hirvonen N, McGrath J, Saha S, Isohanni M, Veijola J & Miettunen J (2013) A systematic review and meta-analysis of recovery in schizophrenia. Schizophr Bull 39(6): 1296–1306.

Jönsson EG, Saetre P, Vares M, Strålin P, Levander S & Lindström E (2011) Use of antipsychotics – an analysis of lifetime treatment in 66 patients with psychoses. Psychiatry Res 187(1–2): 80–88.

Kampman O & Lehtinen K (1999) Compliance in psychoses. Acta Psychiat Scand 100(3), 167–175.

Kane JM, Robinson DG, Schooler NR, Mueser KT, Penn DL, Rosenheck RA, Addington J, Brunette MF, Correll CU, Estroff SE, Marcy P, Robinson J, Meyer-Kalos PS, Gottlieb JD, Glynn SM, Lynde DW, Pipes R, Kurian BT, Miller AL, Azrin ST, Goldstein AB, Severe JB, Lin H, Sint KJ, John M & Heinssen RK (2015) Comprehensive Versus Usual Community Care for First-Episode Psychosis: 2-Year Outcomes From the NIMH RAISE Early Treatment Program. Am J Psychiatry appiajp201515050632.

Kay SR, Fiszbein A & Opler LA (1987) The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 13(2): 261–276.

Kinon BJ, Zhang L, Millen BA, Osuntokun OO, Williams JE, Kollack-Walker S, Jackson K, Kryzhanovskaya L, Jarkova N & HBBI Study Group (2011) A multicenter, inpatient, phase 2, double-blind, placebo-controlled dose-ranging study of LY2140023 monohydrate in patients with DSM-IV schizophrenia. J Clin Psychopharmacol 31(3): 349–355.

Konopaske GT, Dorph-Petersen K-A, Sweet RA, Pierri JN, Zhang W, Sampson AR & Lewis D (2008) Effect of chronic antipsychotic exposure on astrocyte and oligodendrocyte numbers in macaque monkeys. Biol Psychiatry 63(8): 759-765.

Kraepel E (1919) Dementia Paraecox and Paraphrenia. New York, Kreiger Publishing Co.

Kroken RA, Johnsen E, Ruud T, Wentzel-Larsen T & Jørgensen HA (2009) Treatment of schizophrenia with antipsychotics in Norwegian emergency wards, a cross-sectional national study. BMC Psychiatry 9: 24.

Kundi M (2006) Causality and the Interpretation of Epidemiologic Evidence. Environ Health Perspect 114: 969–974.

Large CH, Webster EL & Goff DC (2005) The potential role of lamotrigine in schizophrenia. Psychopharmacology 181(3): 415–436.

Lehmann HE & Hanrahan GE (1954) Chlorpromazine new inhibiting agent for psychomotor excitement and mania states. AMA Arch Neurol Psy 71(2): 227–237.

Leucht S, Cipriani A, Spineli L, Mavridis D, Örey D, Richter F, Samara M, Barbui C, Engel RR, Geddes JR, Kissling W, Stapf MP, Lässig B, Salanti G & Davis JM (2013) Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple treatments meta-analysis. Lancet 382(9896): 951–962.

Leucht S, Tardy M, Komossa K, Heres S, Kissling W & Davis JM (2012) Maintenance treatment with antipsychotic drugs for schizophrenia. Cochrane Database Syst Rev 5: CD008016.

Leucht S, Tardy M, Komossa K, Heres S, Kissling W, Salanti G & Davis JM (2012) Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. Lancet 379(9813): 2063–2071.

Leung M, Cheung C, Yu K, Yip B, Sham P, Li Q, Chua S & McAlonan G (2011) Gray matter in first-episode schizophrenia before and after antipsychotic drug treatment. Anatomical likelihood estimation meta-analyses with sample size weighting. Schizophr Bull 37(1): 199–211.

Liberman RP, Kopelowicz A, Ventura J & Gutkind D (2002) Operational criteria and factors related to recovery from schizophrenia. Int Rev Psychiatr 14(4): 256–272.

Lieberman JA, Tollefson GD, Charles C, Zipursky R, Sharma T, Kahn RS, Keefe RS, Green AI, Gur RE, McEvoy J, Perkins D, Hamer RM, Gu H & Tohen M (2005) Antipsychotic drug effects on brain morphology in first-episode psychosis. Arch Gen Psychiatry 62(4): 361-370.

Llorca P-M (2008) Partial compliance in schizophrenia and the impact on patient outcomes. Psychiatry Res 161(2): 235–247.

Lochmaan van Bennekom MW, Gijsman HJ & Zitman FG (2013) Antipsychotic polypharmacy in psychotic disorders: a critical review of neurobiology, efficacy, tolerability and cost effectiveness. J Psychopharmacol 27(4): 327–336.

Mailman RB & Murthy V (2010) Third generation antipsychotic drugs: partial agonism or receptor functional selectivity. Curr Pharm Des 16(5): 488–501.

Meltzer HY (2000) An atypical compound by any other name is still a... Psychopharmacology 148(1): 16–19.

Meltzer HY & Stahl SM (1976). The dopamine hypothesis of schizophrenia: a review. Schizophr Bull 2(1): 19–76.

Menezes NM, Arenovich T & Zibursky RB (2006) A systematic review of longitudinal outcome studies of first-episode psychosis. Psychol Med 36(10): 1349–1362.

Miller DD, Flaum M, Nopoulos P, Arndt S & Andreasen NC (1995) The concept of dose years: A reliable method for calculating lifetime psychotropic drug exposure. Schizophr Res 15:159.

Miyamoto S, Miyake N, Jarskog LF, Fleischhacker WW & Lieberman JA (2012) Pharmacological treatment of schizophrenia: a critical review of the pharmacology and clinical effects of current and future therapeutic agents. Mol Psychiatry 17(12): 1206–1227.

Moncrieff J & Leo J (2010) A systematic review of the effects of antipsychotic drugs on brain volume. Psychol Med 40(9): 1409–1422.

Muscatello MR, Bruno A, Pandolfo G, Micò U, Bellinghieri PM, Scimeca G, Cacciola M, Campolo D, Settineri S & Zoccali R (2011) Topiramate augmentation of clozapine in schizophrenia: a double-blind, placebo-controlled study. J Psychopharmacol 25(5): 667–674.

Navari S & Dazzan P (2009) Do antipsychotic drugs affect brain structure? A systematic and critical review of MRI findings. Psychol Med 39(11): 1763–77.

NICE (2014) Psychosis and schizophrenia in adults: prevention and management. National Institute for Health and Care Excellence, Clinical Guideline: nice.org.uk/guidance/cg178. Cited 2016/03/07.

Nykänen S, Puska V, Tolonen JP, Salo H, Isohanni M, Koponen H, Pirkola S, Penttilä M, Haapea M, Moilanen J, Miettunen J & Jääskeläinen E (2016) Use of psychiatric medications in schizophrenia and other psychoses in a general population sample. Psychiatry Res 235: 160-168.

Olabi B, Ellison-Wright I, McIntosh AM, Woods SJ, Bullmore E & Lawrie SM (2011) Are there progressive brain changes in schizophrenia? A meta-analysis of structural magnetic resonance imaging studies. Biol Psychiat 70(1): 88–96.

Patil ST, Zhang L, Martenyi F, Lowe SL, Jackson KA, Andreev BV, Avedisova AS, Bardenstein LM, Gurovich IY, Morozova MA, Mosolov SN, Neznanov NG, Reznik AM, Smulevich AB, Tochilov VA, Johnson BG, Monn JA & Schoepp DD (2007) Activation of mGlu2/3 receptors as a new approach to treat schizophrenia: a randomized phase 2 clinical trial. Nat Med 13(9): 1102–1107.

Pichot P (1996) The discovery of chlorpomazine and the place of psychopharmacology in the history of psychiatry. In: Healy D (ed): The Psychopharmacologists. New York, Chapman & Hall: 1–27.

Rantakallio P (1969) Groups at risk in low birth weight infants and perinatal mortality. Acta Paediatr Scand 193, Supll.: 1–71.

Ridler K, Veijola JM, Tanskanen P, Miettunen J, Chitnis X, Suckling J, Murray GK, Haapea M, Jones PB, Isohanni MK & Bullmore ET (2006). Frontocerebellar systems are associated with infant motor and adult executive functions in healthy but not in schizophrenia. Proc Natl Acad Sci U S A 103(42): 15651–15656.

Rissanen I, Jääskeläinen E, Isohanni M, Koponen H, Joukamaa M, Alaräisänen A & Miettunen J (2012) Use of antipsychotic medication and suicidality - the Northern Finland Birth Cohort 1966. Hum Psychopharmacol 27(5): 476–485.

Robinson DG, Woerner MG, McMeniman M, Mendelowitz A & Bilder RM. Symptomatic and functional recovery from a first episode of schizophrenia or schizoaffective disorder. Am J Psychiat 161(3): 473–479.

Rueckert D, Sonoda LI, Hayes C, Hill DLG, Leach MO & Hawkes DJ (1999) Non-rigid registration using free-form deformations: application to breast MR images. IEEE Trans Med Imaging 18(8): 712–721.

Salomon C, Hamilton B & Elsom S (2014) Experiencing antipsychotic discontinuation: results from a survey of Australian consumers. J Psychiatr Ment Health Nurs 21(10): 917–923.

Sampson S, Joshi K, Mansour M & Adams CE (2013) Intermittent drug techniques for schizophrenia. Schizophr Bull 39(5): 960–961.

Scherk H & Falkai P (2006) Effects of antipsychotics on brain structure. Curr Opin Psychiatry 19(2): 145–150.

Schizophrenia (online). Current Care Guidelines. Working group set up by the Finnish Medical Society Duodecim and the Finnish Psychiatric Association. Helsinki: The Finnish Medical Society Duodecim, 2014 (referred March 3, 2016). Available online at: www.kaypahoito.fi

Schoepp DD (2005) New directions in the treatment of schizophrenia: modulators of mGlu2 and/or mGlu3 receptors. Neuropsychopharmacology 31, Suppl. 1: S25–S26.

Seeman P (1992) Dopamine receptor sequences. Therapeutic levels of neuroleptics occupy D2 receptors, clozapine occupies D4. Neuropsychopharmacology 7(4): 261–284.

Semple D & Smyth R (2009) Oxford Handbook of Psychiatry. Oxford University Press, Second edition.

Shen W (1999) A History of antipsychotic drug development. Compr Psychiat 40(6): 407–414.

Shepherd AM, Laurens KR, Matheson SL, Carr VJ & Green MJ (2012) Systematic meta-review and quality assessment of the structural brain alterations in schizophrenia. Neurosci Biobehav Rev 36(4): 1342–1356.

Sim K, Chuan Su H, Fujii S, Yang SY, Chong MY, Si T, Ling He Y, Kee Chung E, Huak Chan Y, Shinfuku N, Hoon Tan C, Ungvari G & Baldessarini RJ (2009) Low doses of antipsychotic drugs for hospitalized schizophrenia patients in East Asia: 2004 vs. 2001. Int J Neuropsychopharmacol 12(1): 117-123.

Smith S (2002) Fast robust automated brain extraction. Hum Brain Mapp 17(3): 143–155.

Smith SM, Jenkinson M, Woolrich M, Beckmann CF, Behrens TEJ, Johansen-Berg H, Bannister PR, De Luca M, Drobnjack I, Flitney DE, Niazy RK, Saunders J, Vickers J, Zhang Y, De Stefano N, Brady JM & Matthews PM (2004) Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 23, Supll.: S208–S219.

Sohler N, Adams BG, Barnes DM, Cohen GH, Prins SJ & Schwartz S (2015) Weighing the evidence for harm from long-term treatment with antipsychotic medications: a systematic review. Am J Orthopsychiat (Epub ahead of print) http://dx.doi.org/10.1037/ort0000106.

Sohler N, Walkup J, McAlpine D, Boyer C & Olfson M (2003) Antipsychotic dosage at hospital discharge and outcomes among persons with schizophrenia. Psychiatr Serv 54(9): 1258-1263.

Sommer IE, Begemann MJ, Temmerman A & Leucht S (2012) Pharmacological augmentation strategies for schizophrenia patients with insufficient response to clozapine: a quantitative literature review. Schizophr Bull 38(5): 1003–1011.

Spitzer RL, Gibbon M & Endicott J (2000) Global Assessment Scale (GAS), Global Assessment of Functioning (GAF) scale, Social and Occupational Functional Assessment Scale (SOFAS). In: Rush AJ, Pincus HA, First MB, Blaker D, Endicott J, Keith SJ, Phillips KA, Ryan ND, Smith GR, Tsuang MT, Widiger TA & Zarin DA (eds) Handbook of Psychiatric Measures. Washington, American Psychiatric Association: 96–100.

Suokas JT, Suvisaari JM, Haukka J, Korhonen P & Tiihonen J (2013) Description of long-term polypharmacy among schizophrenia outpatients. Soc Psychiatry Psychiatr Epidemiol 48(4): 631–638.

Tandon R, Belmaker RH, Gattaz WF, Lopez-Ibor JJ Jr, Okasha A, Sinqh B, Stein DJ, Olie JP, Fleischhacker WW & Moeller HJ (2008) World Psychiatric Association Pharmacopsychiatry Section statement on comaparative effectiveness of antipsychotics in the treatment of schizophrenia. Schizophr Res 100(1–3): 20–38.

Tanskanen P, Ridler K, Murray G, Haapea M, Veijola J, Jääskeläinen E, Miettunen J, Jones PB, Bullmore ET & Isohanni MK (2010). Morphometric brain abnormalities in schizophrenia in a population-based sample: relationship to duration of illness. Schizophr Bull 36(4): 766–777.

Taylor D, Paton C, Kapur S (2009) The Maudsley Prescribing Guidelines. London, Informa Healthcare: 12.

Ten Velden Hegelstad W, Haahr U, Larsen TK, Auestad B, Barder H, Evensen J, Joa I, Johannessen JO, Langeveld J, Melle I, Opjordsmoen S, Rossberg JI, Rund BR, Simonsen E, Vaglum P, McGlashan T & Friis S (2013) Early detection, early symptom progression and symptomatic remission after ten years in a first episode of psychosis study. Schizophr Res 143(2–3): 337–343.

Terveyden ja Hyvinvoinnin Laitos (2012) HILMO - Sosiaalihuollon ja terveydenhuollon hoitoilmoitus 2013 - Määrittelyt ja ohjeistus.

Thompson A, Signh S & Birchwood M (2015) Views of early psychosis clinicians on discontinuation of antipsychotic medication following symptom remission in first episode psychosis. Early Interv Psychiatry. doi: 10.1111/eip.12244.

Tiihonen J, Haukka J, Taylor M, Haddad PM, Patel MX & Korhonen P (2011) A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. Am J Psychiatry 168(6): 603–609.

Tiihonen J, Suokas JT, Suvisaari JM, Haukka J & Korhonen P (2012) Polypharmacy with antipsychotics, antidepressants, or benzodiazepines and mortality in schizophrenia. Arch Gen Psychiatry 69: 476-83.

Torniainen M, Mittendorfer-Rutz E, Tanskanen A, Björkenstam C, Suvisaari J, Alexanderson K & Tiihonen J (2015) Antipsychotic treatment and mortality in schizophrenia. Schizophr Bull 41(3): 656–663.

Torres US, Portela-Oliveira E, Borgwardt S & Busatto GF (2013) Structural brain changes associated with antipsychotic treatment in schizophrenia as revealed by voxel-based morphometric MRI: an activation likelihood estimation meta-analysis. BMC Psychiatry 13: 342.

Tsai GE & Lin PY (2010) Strategies to enhance N-methyl-D-aspartate receptor-mediated neurotransmission in schizophrenia, a critical review and meta-analysis. Curr Pharm Des 16(5): 522–537.

Usall J, Suárez D, Haro JM & SOHO Study Group (2007) Gender differences in response to antipsychotic treatment in outpatients with schizophrenia. Psychiatry Res 153(3): 225–231.

van der Gaag M, Hoffman T, Remijsen M, Hijman R, de Haan L, van Meijel B, van Harten PN, Valmaggia L, de Hert M, Cuijpers A & Wiersma D (2006) The five-factor model of the Positive and Negative Syndrome Scale II: a ten-fold cross-validation of a revised model. Schizophr Res 85(1–3): 280–287.

van Os J (2016) "Schizophrenia" does not exist. *BMJ* 352:i375. doi:10.1136/bmj.i375.

Van Rossum J (1967) The significance of dopamine-receptor blockade for the action of neuroleptic drugs. In: Brill H, Cole J, Deniker P, Hippius H & Bradley PB, (eds) Neuropsychopharmacology, Proceedings 5th Collegium Internationale Neuropsychopharmacologicum. Amsterdam, Excerpta Medica: 321–329.

Vares M, Saetre P, Strålin P, Levander S, Lindström E & Jönsson EG (2011) Concomitant medication of psychoses in a lifetime perspective. Hum Psychopharmacol 26(4–5): 322–331.

Veijola J, Guo JY, Moilanen JS Jääskeläinen E, Miettunen J, Kyllönen M, Haapea M, Huhtaniska S, Alaräisänen A, Mäki P, Kiviniemi V, Nikkinen J, Starck T, Remes JJ, Tanskanen P, Tervonen O, Wink AM, Kehagia A, Suckling J, Kobayashi H, Barnett JH, Barnes A, Koponen HJ, Jones PB, Isohanni M & Murray GK (2014) Longitudinal changes in total brain volume in schizophrenia: relation to symptom severity, cognition and antipsychotic medication. PLoS One. 9:e101689.

Vita A, De Peri L, Deste G & Sacchetti E (2012) Progressive loss of cortical gray matter in schizophrenia: a meta-analysis and meta-regression of longitudinal MRI studies. Transl Psychiatry 2: e190.

Whitaker R (2010) Anatomy of an epidemic. New York, Broadway Paperbacks.

Whitaker R (2014) The case against antipsychotic drugs: a 50-year record doing more harm than good. Med Hypotheses 62(1): 5–13.

WHO (1992) International Classification of Diseases and Related Health Problems. 10th revision. World Health Organization, Geneva.

Wiersma D, Nienhuis NJ, Slooff CJ & Giel R (1998) Natural course of schizophrenic disorders: a 15-year followup of Dutch incidence cohort. Schizophr Bull 24(1): 75–85.

Woods (www.scottwilliamwoods.com) Cited 2016/01/20.

Wunderink L, Nieboer RM, Wiersma D, Sytema S & Nienhuis FJ (2013) Recovery in remitted first-episode psychosis at 7 years of follow-up of an early dose reduction/discontinuation or maintenance treatment strategy: long-term follow-up of a 2-year randomized clinical trial. JAMA Psychiatry 70(9): 913–920.

Young SL, Taylor M & Lawrie SM (2015) "First do no harm." A systematic review of the prevalence and management of antipsychotic adverse effects. J Psychophrmacol 29(4): 353–362.

Zhang Y, Brady M & Smith S (2001) Segmentation of brain MR images through a hidden Markov random field model and the expectation maximization algorithm. IEEE Trans Med Imaging 20(1): 45–57.

Zipursky RB, Menezes NM & Streiner DR (2014) Risk of symptom recurrence with medication discontinuation in first-episode psychosis: a systematic review. Schizophr Res 152(2–3): 408–414.

Original publications

I Moilanen J, Haapea M, Miettunen J, Jääskeläinen E, Veijola J, Isohanni M & Koponen H (2013) Characteristics of subjects with schizophrenia spectrum disorder with and without antipsychotic medication - A ten-year follow-up of the Northern Finland 1966 Birth Cohort Study. Eur Psychiatry 28(1): 53-58.

II Moilanen J, Haapea M, Jääskeläinen E, Veijola J, Isohanni M, Koponen H & Miettunen J Long-term antipsychotic use and its association with outcomes in schizophrenia - the Northern Finland Birth Cohort 1966. Eur Psychiatry, in press.

III Moilanen J, Huhtaniska S, Haapea M, Jääskeläinen E, Veijola J, Isohanni M, Koponen H & Miettunen J (2015) Brain morphometry of individuals with schizophrenia with and without antipsychotic medication - The Northern Finland Birth Cohort 1966 study. Eur Psychiatry. 30(5): 598-605.

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