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Ina Rissanen

NERVOUS SYSTEM MEDICATIONS AND SUICIDAL IDEATION AND BEHAVIOUR

THE NORTHERN FINLAND BIRTH COHORT 1966

UNIVERSITY OF OULU GRADUATE SCHOOL;
UNIVERSITY OF OULU,
FACULTY OF MEDICINE;
MEDICAL RESEARCH CENTER OULU;
OULU UNIVERSITY HOSPITAL

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The Northern Finland Birth Cohort 1966

Academic dissertation to be presented with the assent of the Doctoral Training Committee of Health and Biosciences of the University of Oulu for public defence in Auditorium K101 of the Faculty of Medicine (Aapistie 7 A), on 22 May 2015, at 12 noon

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Abstract

The aim of this thesis was to explore the associations between the use of nervous system medications and suicidal ideation and behaviour in various different diagnostic groups in a large population-based cohort.

Information on prescribed antipsychotic, antidepressant, benzodiazepine and antiepileptic medications within the Northern Finland Birth Cohort 1966 was collected from the register of the Social Insurance Institution of Finland and from a postal questionnaire sent to all cohort members in 1997. The presence of suicidal ideation and depression and anxiety symptoms was assessed via the Hopkins Symptom Checklist-25 questionnaire in 1997. Data on suicides were collected from the cause-of-death statistics and on suicide attempts from the Finnish Care Register for Health Care in a 15-year follow up.

The use of antipsychotic, antidepressant, or benzodiazepine medication was associated with increased suicidal ideation, suicide attempts, and suicides. Antiepileptic medication was not associated with increased suicidality. The polypharmacy of nervous system medications was associated with increased suicidality. All nervous system medications were associated with increased severity of depression and anxiety symptoms. When depression and anxiety symptoms were taken into account, most of the associations between medication and suicidal ideation were statistically non-significant.

Regarding specific groups, among those who did not have psychosis, high doses of antipsychotic medication correlated particularly with increased suicidal ideation even when other symptoms of depression and anxiety were taken into account. Among those with insomnia, the use of antidepressant medication associated with increased suicidal ideation also when other symptoms were taken into account.

Although nervous system medication is associated with increased suicidal ideation, the association with other symptoms is also strong, and therefore it could not be stated that medication associates specifically with suicidal ideation. However, certain groups, i.e., non-psychotic subjects with high doses of antipsychotic medication, or subjects with insomnia and using antidepressant medication, should be closely monitored as they could be more vulnerable to suicidal ideation.

Keywords: antidepressants, antiepileptics, antipsychotics, benzodiazepines, cohort studies, suicidal ideation, suicide, suicide attempt

Rissanen, Ina, Hermostoon vaikuttavat lääkkeet ja itsetuhoinen ajattelu ja käyttäytyminen. Pohjois-Suomen vuoden 1966 syntymäkohortti

Oulun yliopiston tutkijakoulu; Oulun yliopisto, Lääketieteellinen tiedekunta; Medical Research Center Oulu; Oulun yliopistollinen sairaala

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Tiivistelmä

Tämän väitöstutkimuksen tarkoituksena oli tutkia hermostoon vaikuttavien lääkkeiden, lähinnä psykoosilääkkeiden, masennuslääkkeiden, bentsodiatsepiinien sekä epilepsialääkkeiden, yhteyttä itsetuhoisiin ajatuksiin, itsemurhayrityksiin ja itsemurhiin. Aihetta tutkittiin eri diagnoosiluokissa suuressa väestöaineistossa, Pohjois-Suomen vuoden 1966 syntymäkohortissa.

Tieto tutkimushenkilöiden lääkkeenkäytöstä vuodelta 1997 kerättiin Kelan lääkeostorekisteristä sekä postikyselyn avulla. Itsetuhoisten ajatusten ja muiden masennus- ja ahdistusoireiden vakavuutta mitattiin Hopkins Symptom Checklist-25 -kyselyn avulla vuonna 1997. Tieto itsemurhista kerättiin 15 vuoden seurannassa kuolinsyyrekisteristä ja tieto itsemurhayrityksistä hoitoilmoitusrekisteristä.

Psykoosilääkkeiden, masennuslääkkeiden ja bentsodiatsepiinien käyttö oli yhteydessä lisääntyneisiin itsetuhoisiin ajatuksiin, itsemurhayrityksiin ja itsemurhiin. Epilepsialääkkeet eivät liittyneet itsetuhoisuuteen. Usean hermostoon vaikuttavan lääkkeen yhtäaikainen käyttö oli yhteydessä lisääntyneeseen itsetuhoisuuteen. Kaikki hermostoon vaikuttavat lääkkeet liittyivät lisääntyneisiin masennus- ja ahdistusoireisiin. Kun lääkityksen yhteys masennus- ja ahdistusoireisiin otettiin huomioon, lääkkeet eivät olleet erityisesti yhteydessä itsetuhoisiin ajatuksiin.

Diagnostisten ryhmien välillä ei ollut eroa hermostoon vaikuttavien lääkkeiden ja itsemurhayritysten tai itsemurhien välisessä yhteydessä. Henkilöillä, joilla ei ole psykoosia, suuremmat psykoosilääkeannokset olivat yhteydessä itsetuhoisten ajatusten vakavuuteen kun muiden masennus- ja ahdistusoireiden vakavuus otettiin huomioon. Unettomuudesta kärsivillä henkilöillä masennuslääkkeen käyttö liittyi lisääntyneisiin itsetuhoisiin ajatuksiin kun muut oireet huomioitiin.

Hermostoon vaikuttavat lääkkeet ovat yhteydessä lisääntyneisiin itsetuhoisiin ajatuksiin, mutta ne ovat myös vahvasti yhteydessä muihin masennus- ja ahdistusoireisiin. Tietyt henkilöt voivat kuitenkin olla erityisen herkkiä nimenomaan itsetuhoisille ajatuksille, ja heitä tulisi seurata erityisen tiiviisti. Tällaisia ovat henkilöt, joilla ei ole psykoosia, mutta jotka käyttävät suuria psykoosilääkeannoksia, sekä vakavasta unettomuudesta kärsivät henkilöt, jotka käyttävät masennuslääkettä.

Asiasanat: bentsodiatsepiinit, epilepsialääkkeet, itsemurha, itsemurhayritys, itsetuhoiset ajatukset, kohorttitutkimus, masennuslääkkeet, psykoosilääkkeet

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I am grateful to the co-authors of the original publications for their valuable contribution: Professor Hannu Koponen, Professor Matti Joukamaa, Antti Alaräisänen, M.D., Ph.D., and Hanna Ansakorpi, M.D., Ph.D. Without your expertise the original publications have not been made. The statisticians Riikka Marttila, M.Sc., and Tanja Nordstöm, M.Sc., have helped me to manage with my data and given their excellent advice. I owe my thanks also to Jani Moisala, Niina Keränen, Pirkko Kaan, and other staff at the Department of Psychiatry for their help. With the right people, even the most challenging tasks can be accomplished with ease.

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It always seems impossible until it's done.

Oulu, April 2015 Ina Rissanen

Abbreviations

APA	American Psychiatric Association
ATC	Anatomical Therapeutic Chemical -coding
CI	confidence interval
CRHC	Care Register for Health Care
DDD	defined daily dose
DSM	Diagnostic and Statistical Manual of Mental Disorders
EEG	electroencephalography
e.g.	exempli gratia
EMA	European Medicines Agency
EPA	European Psychiatic Association
et al.	et alii
FDA	Food and Drug Administration
GABA	gamma-aminobutyric acid
i.a.	inter alia
ICD	International classification of diseases
i.e.	id est
IQR	interquartile range
MAOIs	monoamine oxidase inhibitors
MDD	major depressive disorder
NFBC 1966	Northern Finland Birth Cohort 1966
SCL	Hopkins Symptom Checklist -25
SD	standard deviation
SNRIs	serotonin norepinephrine reuptake inhibitors
SSRIs	selective serotonin reuptake inhibitors
THL	The Finnish National Institute for Health and Welfare
TCAs	tricyclic antidepressants
WHO	World Health Organization

List of original publications

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

I 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 Clin Exp 27: 476-485.

II Rissanen I, Jääskeläinen E, Isohanni M, Koponen H, Joukamaa M, Alaräisänen A & Miettunen J (2014) Use of antidepressant medication and suicidal ideation - the Northern Finland Birth Cohort 1966. Hum. Psychopharmacol Clin Exp 29: 559-567.

III Rissanen I, Jääskeläinen E, Isohanni M, Koponen H, Ansakorpi H & Miettunen J (2015) Use of antiepileptic or benzodiazepine medication and suicidal ideation - the Northern Finland Birth Cohort 1966. Epilepsy Behav: doi:10.1016/j.yebeh.2015.03.001.

Some unpublished data are also presented in this thesis.

Contents

1 Suicidality

1.1 Definitions of suicidality

Suicidality is an umbrella concept that includes all suicide-related terms, including suicidal ideation, suicide attempts, and suicides. The terminology of suicidal ideation and behaviour is complex, and is presently under international debate (WHO 2014).

Suicide is usually defined as "self-inflicted death with evidence (either explicit or implicit) that the person intended to die" (O'Carroll *et al.* 1996). The definition of suicide requires three components that are essential to distinguish suicide from other causes of death: 1) death as a result of some sort of injury, poisoning, or suffocation where 2) the injury was self-inflicted, and 3) the injury was intentionally inflicted (O'Carroll *et al.* 1996). The term *completed suicide* may be used as a synonym for the term suicide. Succinctly stated, suicide is the act of deliberately killing oneself (WHO 2014).

Suicide attempt can be defined as "self-injurious behaviour with a nonfatal outcome accompanied by evidence (either explicit or implicit) that the person intended at some level to die" (O'Carroll *et al.* 1996). In this definition, there needs to be at least some level of intention to die in order to distinguish a suicide attempt from *instrumental suicide-related behaviour* in which there is potentially self-injurious behaviour with evidence that the person did *not* intend to die. In the instrumental suicide-related behaviour, the person wishes to use the *appearance* of intending to kill himself/herself in order to attain some other end (e.g. to seek help or to receive attention). A *suicide attempt* may or may not result in injuries (O'Carroll *et al.* 1996).

The term *suicide attempt* is used by the World Health Organization (WHO) to mean any non-fatal suicidal behaviour and refers to intentional self-inflicted poisoning, injury or self-harm which may or may not have a fatal intent or outcome (WHO 2014). This means that non-fatal self-harm without suicidal intent is included under the term *suicide attempt* by WHO. The terms *self-harm* or *self-mutilation* can also be used to encompass all self-injurious behaviours regardless of suicidal intent (Kapur *et al.* 2013). The term *parasuicide* is closely related to these terms, defined as suicide attempt or suicidal gesture and self-harm where there is no result in death.

Suicidal ideation is usually defined as "thoughts of serving as the agent of one's own death" (APA 2010). The other definition "any self-reported thoughts of engaging in suicide-related behaviour" (O'Carroll *et al.* 1996) suggests that the person can have suicidal thoughts without having an intention to die, i.e., suicidal ideation contains also thoughts of instrumental suicide-related behaviour. Seriousness of suicidal ideation may vary depending on the specificity of suicide plans and the degree of suicidal intent. Suicidal ideation is usually considered as a separate phenomenon from *suicidal behaviour* which includes suicide attempts, suicides, and plans for suicide. However, e.g. the WHO includes suicidal ideation in the term suicidal behaviour (WHO 2014).

The term *suicidality* is used in this thesis to encompass both suicidal ideation and suicidal behaviour, i.e. suicide attempts and suicides. The terminology and estimated prevalence of suicidality is presented in Table 1.

Table 1. The WHO terminology and prevalence of suicidality.

Term	Definition	Prevalence
Suicide	The act of deliberately killing oneself.	1.4%[1]
Suicide attempt	Any non-fatal suicidal behaviour, *i.e.* intentional self-inflicted poisoning, injury or self-harm which may or may not have a fatal intent or outcome.	1.3-3.9%[2]
Suicidal ideation	Thinking about suicide.	7.8-13.5%[2]

[1] Proportion of total world mortality covered by suicide mortality (WHO 2014).

[2] Lifetime prevalence in the general population (Bernal *et al.* 2007, Kessler *et al.* 1999, Nock *et al.* 2008).

1.2 Measurement of suicidality

The practices in measuring suicides differ between countries. The WHO has estimated that of its 172 member states, only 60 have good-quality registration data that can be used directly to estimate suicide rates. In other states, the suicide rate estimates are based on modelling methods. Suicide registration is a complicated procedure that includes medical and legal concerns, as well as involving several public authorities, varying between countries. Suicides are often misclassified: as accidents, deaths of undetermined intent, homicides, or deaths due to unknown cause (WHO 2014).

In Finland, Statistics Finland produces the Finnish Cause of Death register that is based on data from death certificates and includes information i.a. on the cause and manner, and date and place of death. Finnish law requires police to

conduct an investigation into the cause of death and request a medicolegal autopsy when person's death is suspected to be a suicide. The decision on the cause and manner of the death, and the death certificate, is made in a medicolegal autopsy. This system can be considered reliable (WHO 2014).

The data on suicide attempts can be collected by two primary methods: either from self-reports or interviews of suicidal behaviour in surveys, or from medical records or registers about treatment for a suicide attempt. There are no internationally accepted methods for standardised collection of information on suicide attempts from medical records. The WHO does not collect data on suicide attempts.

The measurement of suicidal ideation is usually based on self-reporting or interviews. Different psychiatric scales include questions on suicidal ideation, e.g. Scale for Suicidal Ideation (SSI), Columbia Suicide Severity Rating Scale (C-SSRS), Hamilton Depression Scale (HAM-D), Beck Depression Inventory (BDI), and Hopkins Symptom Checklist (SCL) (Batterham *et al.* 2014, Veijola *et al.* 2003, Vuorilehto *et al.* 2014). Even though there are many measures developed for assessing the severity of suicidal ideation, there is no standard measure recommended for use in population-based studies (Batterham *et al.* 2014). In a previous Finnish study comparing SSI, HAM-D and BDI in people with depression, the method of assessment and cut-off used influenced the prevalence of suicidal ideation and none of the scales were optimal (Vuorilehto *et al.* 2014). The simple question whether a subject has seriously considered suicide might be a good indicator of increased suicidal ideation as well as the standardised scales (Vuorilehto *et al.* 2014).

There are several potential confounding factors that affect self-reported rates of suicidal ideation and behaviour. One confounder is the willingness of the subjects to report information on prior suicidal ideation or behaviour varying by age, gender, religion, ethnicity and other factors. In many countries, there is a stigma along with negative attitudes against suicidal ideation and behaviour, and in some countries, such as in those following Sharia law, it is illegal to attempt or commit a suicide (WHO 2014).

1.3 Worldwide epidemiology of suicidality

It is estimated that over 800,000 people die by suicide each year (WHO 2014). This means that every 40 seconds, a person dies by suicide somewhere in the world. The WHO has estimated that in 2012 suicide mortality accounted for 1.4%

of total world mortality, and the estimated annual suicide rate in the world as a whole was 11.4 per 100,000 inhabitants (15.0 for males and 8.0 for females) (WHO 2014). The Mental Health Action Plan 2013-2020 was established by WHO in May 2013. It encompasses a suicide prevention strategy with the goal of reducing the suicide rates in each country by 10% by the year 2020 (WHO 2014).

Suicide rates differ by gender and age. Globally, the suicide accounts 8.5% of all deaths among young adults aged 15-29 years old, and 4.1% of all deaths among adults aged 30-49 years old (WHO 2014). Globally, the most common methods for suicide are ingestion of pesticides, hanging, and use of firearms. Greater restriction to the access to these means of suicide would be a beneficial contribution to the prevention of suicides (WHO 2014).

Suicide attempts are more common than suicides. For every suicide, there are more than 20 suicide attempts (WHO 2014). Previous suicide attempt is the single most important risk factor of suicide. The prevalence of lifetime suicide attempts in the general population is 1.3-3.9% (Bernal *et al.* 2007, Kessler *et al.* 1999, Nock *et al.* 2008).

Suicidal ideation is also regarded as a strong risk factor of suicide attempt or suicide. The risk of suicide attempt among those who report suicidal ideation is about 26-29% (Kessler *et al.* 1999, Nock *et al.* 2008). The risk factors of suicide attempt among people with suicidal ideation include e.g. unemployment, somatic disorders, and negative relationships in social environment (Fairweather *et al.* 2006). Among people with suicidal ideation, the severity of depression and anxiety symptoms does not differ between those who make a suicide attempt and those who not (Fairweather *et al.* 2006). The lifetime prevalence of suicidal ideation in the general population is 7.8-13.5% (Bernal *et al.* 2007, Kessler *et al.* 1999, Nock *et al.* 2008).

Several risk factors act cumulatively increasing the risk of suicidality, and usually there is no single cause explaining the suicide, suicide attempt or suicidal ideation. However, the presence of several risk factors does not necessarily lead to suicidality if there are enough protective factors such as strong relationships or positive coping strategies. The individual-level risk factors of suicide named by WHO are previous suicide attempt, mental disorders, harmful use of alcohol, job or financial loss, hopelessness, chronic pain, family history of suicide, and genetic and biological factors (WHO 2014).

1.4 Epidemiology of suicidality in Finland

The latest national data on suicides for Finland was reported in 2009, showing annual suicide rates per 100,000 inhabitants to be 29.0 in males and 10.0 in females, resulting a total rate of 19.3 (WHO 2014). The suicide rates have decreased in Finland during the last decade, while in 1997 (at the time of data collection of the present study) the suicide rate was 25.7 per 100,000 inhabitants (data available in Finnish at: www.sotkanet.fi). In Finland the suicide rates of year 2009 were higher than in the whole Europe, where they were 12.0 per 100,000 inhabitants for both genders, 20.0 for males and 4.9 for females (WHO 2014). The most common methods of suicide in Finland include hanging, use of firearms, and self-poisoning in males, or self-poisoning and hanging in females (Park *et al.* 2014, Värnik *et al.* 2008).

The lifetime prevalence of suicide attempts in young Finnish adults was 6% (Suokas *et al.* 2011). The risk factors of a suicide after a suicide attempt in Finnish population were male gender, previous psychiatric treatment, previous suicide attempts, somatic disease and self-reported wish to die (Suokas *et al.* 2001).

The prevalence of suicidal ideation during the last year was 5.0% in 2012 according to the Health and Well-being for Residents -study (Kaikkonen *et al.* 2014). The prevalence was similar in males (5.1%) and females (5.0%). The prevalence was highest among 20-54 year old people (6.9%), compared to 55-74 year old people (2.4%) and people over 75 years old (2.0%). In Northern Finland, the prevalence was higher (5.7-6.1%) than the mean prevalence in Finland (Kaikkonen *et al.* 2014). Selected previous Finnish studies on suicidality are collected to Table 2. Only the largest studies were included, and one to three selected publications from each sample.

Table 2. Selected previous Finnish studies on suicidality.

Outcome	Study	Setting	Data source	Sample size	Follow-up	Main findings
Suicide	Heikkinen *et al*. 1995a	National Suicide Prevention Project[1]	Register, interview	1,022	Retrospective study	Among younger people died by suicide, separation, serious family arguments, financial trouble, job problems, unemployment and residence change were more common. Among older people died by suicide, somatic illness and retirement were more common.
Suicide	Heikkinen *et al*. 1995b	National Suicide Prevention Project[1]	Register, interview	1,067	Retrospective study	The high-risk factors of suicide were being single, unemployment, history of psychiatric admission, and alcohol abuse.
Suicide	Isometsä & Lönnqvist 1998	National Suicide Prevention Project[1]	Register, interview	1,397	Retrospective study	56% of people died by suicide died at their first attempt, a greater incidence among males (62%) than females (38%). 19% of males and 39% of females had made a non-fatal attempt during the previous 12-month period.
Suicide	Isometsä *et al.* 2014	MERTTU Project[2], bipolar disorder	Register	13,581 (52,747 discharges and 466 suicides)	Up to 1 year	Risk factors of suicide were intra-episodic suicide attempt and male gender. The risk was highest after discharge with depressive episode.
Suicide	Kiviniemi *et al.* 2010	Schizophrenia (onset 1995-2001)	Register	7,591	5 years	Suicide was the most common unnatural cause of death (standardised mortality ratio 14.0 in total, 12.0 in males and 23.4 in females). There was variation in suicide mortality between hospital districts.

Outcome	Study	Setting	Data source	Sample size	Follow-up	Main findings
Suicide	Lahti *et al.* 2011	All youth suicides in Finland 1969-2008	Register	901	Retrospective study	Male - female ratio was 3.6:1. The rates of male suicides increased to 1990 and then decreased. Among females, the rate was inconsistent until 1990 and then increased.
Suicide	Näyhä 2009	Suicides in Lapland during 1961-2005	Register	2,427	Retrospective study	Suicide prevalence in males is 51 per 100,000 person years, in females 13 per 100,000. In Lapland more males died by suicide than males in average in Finland.
Suicide	Partonen *et al.* 2004	All suicides in Finland during 1979-1999	Register	27,469	Retrospective study	The seasonal effect of suicides is strong. The risk of suicide is greatest in spring.
Suicide	Pesonen *et al.* 2004	Suicides in province of Kuopio 1988-1997	Register, medico-legal autopsy reports	777	Retrospective study	The male - female ratio was 3.6:1. Males died by suicide at a younger age than females. The number of suicides was highest in the age group of 34-44 years old.
Suicide	Pirkola *et al.* 2007	Comparing time periods 1985-1991 (1) and 1995-2001[3] (2)	Register	9,719 (1), 8,761 (2)	Retrospective study	In both periods, one-fifth of all people died by suicide had been psychiatrically hospitalised within the preceding 12-month period. The risk of suicides decreased significantly between the two time periods among several diagnostic categories indicating that downsizing of psychiatric hospitals has been a success.

Outcome	Study	Setting	Data source	Sample size	Follow-up	Main findings
Suicide	Pirkola *et al.* 2009	Finnish adult mental-health service units 2004-2005, suicides between 2000-2004	Register, Survey	428 municipalities	Retrospective study	Multifaceted, outpatient-based, and 24-h emergency mental-health services associated with lower suicide rates at municipal level.
Suicide	Suokas *et al.* 2001	Follow-up after suicide attempt[4]	Register	1,018	14 years	6.7% had died by suicide during follow-up (9.2% of males, 4.5% of females). The risk factors were male gender, previous psychiatric treatment, previous suicide attempts, somatic disease and self-reported wish to die.
Suicide	Suominen *et al.* 2009	All depressive individuals hospitalised after suicide attempt in Finland 1996-2003	Register	1,820	Mean 4.2 years	During follow-up, 6% died by suicide and 31% made a suicide attempt. Males died more by suicide than females. Subjects with psychotic symptoms had 3-fold risk of suicide. The risk of suicide was highest immediately after first admission.
Suicide and suicide attempt	Sourander *et al.* 2009	Finnish 1981 Birth Cohort Study[5]	Register, questionnaire	5,302	16 years	1% had died by suicide or made a serious suicide attempt. Childhood risk factors of adolescence/early adulthood suicidality were different between males and females. Among males, the pathway of suicidality starts in early childhood.

Outcome	Study	Setting	Data source	Sample size	Follow-up	Main findings
Suicide attempt	Haukka *et al.* 2008a	All hospitalised suicide attempts in Finland 1996-2003	Register	18,199	Mean 3.6 years	Risk of repeating suicide attempt was 30%, and risk of suicide 10%. Risk was highest immediately after discharge.
Suicide attempt	Holma *et al.* 2014	JoBS[6], bipolar disorder (1); VDS[7], depression (2)	Interview	176 (1); 249 (2)	18 months	During follow-up 19.9% of people with BD[8] and 9.5% of people with MDD[9] made a suicide attempt. Before the baseline, 51% of people with BD and 33% of people with MDD had made a suicide attempt.
Suicide attempt	Sokero *et al.* 2005	VDS[7], depression	Interview	198	18 months	8% of people with MDD[9] made a suicide attempt. The risk was greater during a major depressive episode or partial remission compared to full remission. Predictors of increased risk were previous suicide attempts, lacking a partner, and time spent in major depressive episodes.
Suicide attempt	Suokas *et al.* 2010	Health 2000[10], psychoses	Register, interview	264	Retrospective study	34.5% of people (34.1% of females, 34.5% of males) with psychotic disorder had history of suicide attempt. Risk was highest among substance-induced psychotic disorders. Suicide attempts were associated with younger age, comorbid substance use disorders, depressive symptoms, and physical violence against other people.
Suicide attempt	Suokas *et al.* 2011	MEAF[11], general population	Questionnaire, interview	546	Retrospective study	Lifetime prevalence of suicide attempts was 5.6% in males, 6.9% in females, and 6.2% in total. Mental disorders and poor educational and occupational functioning associated with increased risk.

Outcome	Study	Setting	Data source	Sample size	Follow-up	Main findings
Suicide attempt	Valtonen *et al.* 2006	JoBS[6], bipolar disorder	Interview	160	18 months	During the follow-up, 20% made a suicide attempt. Risk factors were previous suicide attempts, hopelessness, depressive phase of episode, and younger age at intake.
Suicide attempt and suicidal ideation	Hintikka *et al.* 1998	General population	(telephone) interview	4,868	Retrospective study	2.4% of females and 2.3% of males had suicidal ideation, and 0.9% of females and 1.1% of males had made a suicide attempt during previous 12 months. 85% of suicidal individuals had contacted primary care services during previous 12 months.
Suicide attempt and suicidal ideation	Sokero *et al.* 2003	VDS[7], depression	Interview	269	Retrospective study	During the current depressive episode, 58% (69% males, 54% females) had experienced suicidal ideation and 15% (13% males, 16% females) had made a suicide attempt. Of those who had made a suicide attempt, 95% had suicidal ideation. Risk factors of suicidal ideation and suicide attempt overlapped.
Suicide attempt and suicidal ideation	Valtonen *et al.* 2005	JoBS[6], bipolar disorder	Interview	191	Retrospective study	During current episode, 61% (65% of females, 56% of males) had suicidal ideation and 20% (27% of females, 13% of males) made a suicide attempt. Only 20% reported no suicidality during their lifetime.
Suicide attempt and suicidal ideation	Vuorilehto *et al.* 2006	VDS[7], depression	Interview	137	Retrospective study	37% of the subjects had considered suicide and 17% had made a suicide attempt within lifetime. Suicidal ideation had commonly remained unrecognised in treatment. Predictors for suicidality were psychiatric treatment history, comorbid personality disorders, and the severity of depression.

Outcome	Study	Setting	Data source	Sample size	Follow-up	Main findings
Suicidal ideation	Hintikka *et al.* 2009	General population	Postal questionnaire (BDI[12])	1,339	3 years	Annual incidence of Suicidal ideation was 4.3%. Males had higher prevalence of suicidal ideation than females. The severity of depression and onset of daily smoking predicted development of suicidal ideation on follow-up.

[1] All people died by suicide in Finland between April 1987 and March 1988 were investigated using the psychological autopsy.

[2] All people identified from the Finnish Hospital Discharge Register with diagnosis of bipolar disorder during 1987-2003.

[3] All suicides 1985-1991 and 1995-2001 in Finland representing service provision before and after structural changes.

[4] All unselected deliberate self-poisoning patients treated at emergency unit during 1983.

[5] Sample of all Finnish children born in 1981.

[6] Jorvi Bipolar Study, all people identified in a psychiatric hospital with a diagnosis of bipolar disorder 2002-2003.

[7] Vantaa Depression Study, all people identified in a psychiatric hospital with a diagnosis of major depressive disorder 1997-1998.

[8] BD = Bipolar disorder

[9] MDD = Major depressive disorder

[10] All people with psychotic or bipolar disorder from two sub-studies were screened and interviewed.

[11] Sub-study of Health 2000. At the time of questionnaire participants were 20-34 years old.

[12] BDI = Beck Depression Inventory

1.5 Psychiatric risk factors of suicidality

The studies conducting a psychological autopsy for individuals who have died by suicide have shown that mental disorders are present in about 90% of suicides (Arsenault-Lapierre *et al.* 2004, Cavanagh *et al.* 2003, Lönnqvist *et al.* 1995). Mood disorders, especially depression, cover biggest portion of mental disorders in people died by suicide. However, it should be noted that mental disorders, such as depression and substance use disorders, are relatively common in the general population, and most people with mental disorders are not suicidal. The comorbidity of mental disorders is notable among people died by suicide (Cavanagh *et al.* 2003). In a Finnish study, the total number of psychiatric disorders increased the risk of suicide attempt (Suokas *et al.* 2011).

In a large meta-analysis of suicide mortality looking at 44 different mental disorders, the suicide rates were significantly increased in all mental disorders except for mental retardation, and possibly dementia and agoraphobia (Harris & Barraclough 1994). Bipolar disorder (8%), substance use disorders (7%), schizophrenia (5%), and mood disorders (others than bipolar disorder) (4%) have been especially associated with increased risk of suicidality (WHO 2014). Regardless of psychiatric diagnosis, impulsivity and aggression are considered as common characteristics of individuals with an increased risk of suicidal behaviour (Pandey 2013).

1.5.1 Psychosis

Psychosis is a common name for psychiatric syndromes in which the individuals "has lost contact with reality", meaning that they have serious distortions of reality testing. The main symptoms of psychosis are delusions and hallucinations. Psychotic disorders include schizophrenia, schizophreniform disorder, schizoaffective disorder, brief psychotic disorder, delusional disorder, substance-induced psychotic disorders, and psychotic disorder due to a medical condition. Psychotic symptoms may also occur as associated features in affective disorders, including severe depression and bipolar disorder, especially mania. These disorders are called affective psychoses (WHO 1992).

Studies on suicides among people with psychosis have mainly involved people with schizophrenia, for whom the lifetime risk of suicide has been estimated in a meta-analysis to be 4.9% (Palmer *et al.* 2005). Suicide attempts are

more common than suicides in all forms of psychosis, where the lifetime rate of suicide attempts is 30-41% (Harkavy-Friedman *et al.* 1999, Radomsky *et al.* 1999, Suokas *et al.* 2010, Suokas *et al.* 2011). Suicidality risk is especially high in affective psychoses and substance-induced psychoses (Suokas *et al.* 2010).

1.5.2 Mood disorders

Depression is a state of low mood that can be a normal reaction in everyday life. When the low mood becomes pervasive and persistent it can be considered as mental illness, i.e. depressive disorder. In typical depressive disorder, the individual has depressed mood, loss of interest and enjoyment, and reduced energy leading to increased fatigability and diminished activity (WHO 1992). Depression can be divided into mild, moderate, or severe depression.

Suicidal ideation and behaviour are common among people with depressive disorder. In a Finnish study of people with major depressive disorder, 58% of the subjects had experienced suicidal ideation, and 15% of the subjects had made a suicide attempt during the current depressive episode (Sokero *et al.* 2003). In another Finnish study, the prevalence of suicide attempt in young adults with depression was about 12% (Suokas *et al.* 2011). The lifetime risk of suicide among people with depressive disorders has been estimated to be about 2-6% (Bostwick & Pankratz 2000, Inskip *et al.* 1998, Nordentoft *et al.* 2011). A meta-analysis has estimated the risk of suicide to be about 13-fold in mood disorders compared to general population (Yoshimasu *et al.* 2008).

Severity of depressive symptoms is a risk factor of suicide attempt in major depressive disorder (Sokero *et al.* 2005), and decline in hopelessness and anxiety symptoms is a significant predictor for the decline of suicidal ideation (Sokero *et al.* 2006). In major depressive disorder with psychotic features, the prevalence of suicide attempt was 43% (Suokas *et al.* 2010). Other risk factors of suicidal behaviour among people with depression include male gender, family history of psychiatric disorder, previous suicide attempts, hopelessness, and comorbid disorders, including anxiety (Hawton *et al.* 2013).

Bipolar disorder falls into the same category of *mood disorders* with depressive disorders. When in depression the individual is feeling constant low mood, in bipolar disorder the individual experiences periods of both low mood and markedly elevated mood, *mania* or *hypomania* (WHO 1992).

The prevalence of suicide attempt in bipolar disorder in Finnish studies was around 32% (Suokas *et al.* 2010, Suokas *et al.* 2011). Also high rates of suicidal

ideation (61%) have been reported among people with new episode bipolar disorder in Finland (Valtonen *et al.* 2005).

1.5.3 Anxiety

Like depression, anxiety as an emotion is also a normal reaction under threatening circumstances. However, when the anxious mood, with excessive and prolonged fear and worry, becomes exaggerated and causes disability and distress, it can be considered as psychiatric disorder. In Finland, the current International Classification of Diseases (ICD) -10 by WHO divides anxiety disorders into phobic anxiety disorders (including e.g. social phobias), other anxiety disorders (including e.g. panic disorder and generalised anxiety disorder), obsessive-compulsive disorder, and reactions to severe stress (including e.g. acute stress reaction and post-traumatic stress disorder) (WHO 1992).

The anxiety disorders are associated with 2.9-fold increased risk of suicidal ideation (Kanwar *et al.* 2013). The increased suicidal ideation has been found in each separate anxiety disorder except for obsessive-compulsive disorder (Kanwar *et al.* 2013). The prevalence of suicide attempts in young adults with anxiety disorders was about 15% in a Finnish study (Suokas *et al.* 2011). The increased suicidal ideation and behaviour in anxiety disorders has previously been suggested to be result from comorbid depression. However, the anxiety disorders have associated with increased suicidal ideation and behaviour even after adjusting for depression in previous studies (Norton *et al.* 2008, Sareen *et al.* 2005). Comorbid anxiety disorder and depression associates with increased suicidal ideation and behaviour compared to having either anxiety disorder or depression alone (Norton *et al.* 2008, Sareen *et al.* 2005).

1.5.4 Insomnia

Insomnia is a sleeping disturbance in which a person has either difficulty initiating sleep or a difficulty maintaining sleep, the person wakes up too early, or has poor quality of sleep. These night-time difficulties can cause several impairments during the daytime, e.g. decreased attention, difficulties with concentration or memory, daytime sleepiness, mood disturbances, or physical symptoms. Insomnia is a common symptom of a psychiatric disorder, e.g. anxiety or depression, but it can also be caused by psychiatric or other medications, substance use, physical disorders, or physical pain (WHO 1992).

Insomnia has been associated with increased suicidal ideation (Lee *et al.* 2010). In a large meta-analysis the risk of suicidal ideation in insomnia in general population was 2.8-fold in studies presenting unadjusted results and 1.9-fold in studies adjusting for confounding factors (Pigeon *et al.* 2012). The risk of suicidal ideation in all sleeping disturbances (including insomnia) in psychiatric disorders was 2.7-fold in another meta-analysis (Malik *et al.* 2014). The association between suicidal behaviour and sleeping disturbances is strong in some specific psychiatric conditions, e.g. in depression (Malik *et al.* 2014).

1.6 Somatic risk factors of suicidality

1.6.1 Somatic disorders

Increased risk of suicidal ideation and behaviour has been associated with several different somatic disorders. The presence of a somatic disorder associated with 1.3-fold increased risk of suicidal ideation and 1.6-fold increased risk of suicide attempt, even when the depressive symptoms, major depressive disorder, alcohol abuse, and demographic factors were controlled for (Druss & Pincus 2000). The presence of somatic disorder was a risk factor of suicidal ideation and behaviour even in the absence of mental disorders in a large 14-country sample of nearly 38,000 subjects (Scott *et al.* 2010).

Of somatic disorders, renal haemodialysis, head and neck neoplasms, human immunodeficiency virus infection and acquired immune deficiency syndrome, systemic lupus erythematosus, renal transplantation, spinal cord injury, multiple sclerosis, peptic ulcer, and malignant neoplasms significantly increased suicide risk in a meta-analysis of 63 somatic disorders (Harris & Barraclough 1994). Somatic disorders that associated significantly with increased suicidal ideation, when adjusted for mental disorders, were epilepsy, heart attack or stroke, heart disease, high blood pressure, respiratory diseases other than allergy, ulcer, arthritis, headache, back and neck pain, and other chronic pain (Scott *et al.* 2010). Additionally, suicidal ideation was increased in thyroid disorders, syncope and seizures, liver disorders, and alcoholism, even when adjusted for major depressive disorder, in an Australian population-based study including only male subjects (Sanna *et al.* 2014). Pain conditions were associated with increased suicidal ideation and suicide plans, even when adjusted for demographic, somatic and psychiatric risk factors (Braden & Sullivan 2008).

There is a high rate of comorbid depression in many somatic disorders, and somatic disorder and depression together represent a high cumulative risk of suicidal ideation and behaviour (Druss & Pincus 2000). Also having more than one somatic disorder is associated with an increased risk of suicidality compared to having only one disorder (Druss & Pincus 2000, Scott *et al.* 2010).

1.6.2 Epilepsy

Epilepsy is a neurological disorder characterised by predisposition to recurrent unprovoked seizures due to abnormal neuronal activity in the brain. The term *epilepsy* contains many different epilepsy syndromes that can be classified according to the type of seizure, the presence or absence of neurological abnormalities, and electroencephalographic (EEG) findings. The broad categorization is to divide epilepsies into two classes: generalised or partial epilepsies (WHO 1992).

Out of many somatic disorders, epilepsy associates most strongly with the increased risk of suicidality (Scott *et al.* 2010). The increased risk of suicidal ideation and behaviour has been related to epilepsy in several studies (Bell *et al.* 2009, Christensen *et al.* 2007, Jones *et al.* 2003). Also in Finland, a 2.5-fold increased suicide mortality among people with epilepsy, defined as reimbursement for antiepileptic medication, has been found (Nevalainen *et al.* 2013).

The lifetime prevalence of suicidal ideation in people with epilepsy is 25% (Tellez-Zenteno *et al.* 2007). People with epilepsy also have a high comorbidity of psychiatric disorders (Gaitatzis *et al.* 2004). High rate of suicidal ideation and behaviour among people with epilepsy associates with comorbid psychiatric disorders, especially depression and anxiety disorders (Christensen *et al.* 2007, Jones *et al.* 2003).

1.7 Neurobiology of suicidality

The neurobiology of suicidality is still unknown. In suicidality, there might be pathophysiological abnormalities in the serotonergic system, neuroendocrine system, and other neurotransmitter systems in the brain. These abnormalities, e.g. in serotonergic mechanisms, may vary between different mental disorders. In addition to biological abnormalities, genetic and environmental factors also play a role in the complex phenomenon of suicidality (Pandey 2013). The genes that

code for proteins regulating the serotonergic neurotransmission are major candidate genes of suicidality (Tsai *et al.* 2011). However, the genetic trait of suicidality is likely to be complex and highly polygenic (Mullins *et al*. 2014). Also, structural changes in frontal, temporal, and parietal lobes of the brain and functional changes in prefrontal cortex have been associated with suicidality in neuroimaging studies (Desmyter *et al.* 2011).

The pathomechanism of suicidality has mainly been studied in mood disorders. Suicidality has been associated e.g. to increased number of binding sites of serotonin receptor subtype $5HT_{2A}$, abnormal cortisol and prolactin responses, and altered levels of noradrenaline and its receptors (Pandey 2013). Structural and functional changes in the frontal-striatal circuitry of the brain, i.e. the orbital frontal cortex, anterior cingulate cortex and striatum, have been found in depressive subjects with suicidality, suggesting this area to play an important role in neurobiology of suicidality in mood disorders (Zhang *et al.* 2014). Among subjects with personality disorder, higher levels of neurotransmitter gamma-aminobutyric acid (GABA) in cerebrospinal fluid have been associated with a history of suicide attempt (Lee *et al.* 2009).

1.8 Treatment and prevention of suicidality

Suicidal people usually have various mental disorders. Therefore, the key of suicide prevention is the sufficient treatment of the underlying psychiatric disorder(s). The European Psychiatric Association (EPA) guidelines for treatment and prevention of suicide and the American Psychiatric Association (APA) practice guidelines for the assessment and treatment of people with suicidal behaviours recommend both pharmacological and psychological treatments and social support for suicidal individuals (APA 2010, Wasserman *et al.* 2012).

For depressive people with suicidal symptoms, long-term antidepressant treatment is recommended by both EPA and APA (APA 2010, Wasserman *et al.* 2012). Non-tricyclic, non-monoamine oxidase inhibitor antidepressants are especially recommended. However there is still a high risk of suicidality during the first two weeks of antidepressant medication, as well as in medication non-respondent individuals. For people with comorbid anxiety and/or insomnia symptoms, a short-term supplementary medication with anxiolytics (such as benzodiazepines) or sleeping pills is recommended by EPA (Wasserman *et al.* 2012). In Finland the Current Care Guideline of depression does not recommend the use of anxiolytics (Depression: Current Care Guidelines, 2014).

In bipolar disorder, the monotherapy of antidepressant medication can worsen the disease and increase suicidality. Therefore, the use of mood-stabilisers is recommended for suicidal people with bipolar disorder. Both in the EPA and APA guidelines, lithium is seen as the drug of choice (APA 2010, Wasserman *et al.* 2012). Individuals non-respondent to lithium should be given another mood-stabiliser (e.g., divalproex, valproate or carbamazepine) in combination with lithium (Wasserman *et al.* 2012). In Finland, the use of atypical antipsychotics is also recommended for bipolar disorder, but their effects on suicidality are not mentioned (Bipolar Disorder: Current Care Guidelines, 2013).

For suicidal people with psychotic disorders, the antipsychotic medication is the mainstay of treatment. However, older antipsychotics may cause adverse effects, like akathisia, possibly worsening the mood. Therefore, especially the APA guideline recommends the use of atypical antipsychotics (APA 2010). In both EPA and APA guidelines the atypical antipsychotic clozapine is mentioned to be the most effective in reducing suicidality in psychotic disorders, and is therefore recommended (Wasserman *et al.* 2012). Also in Finland, clozapine is mentioned to potentially be more effective in treatment of psychotic symptoms, but its effects on suicidality are not mentioned (Schizophrenia: Current Care Guidelines, 2013).

In addition to pharmacological treatment, the cognitive behavioural therapy is considered as evidence-based method in treatment of suicidality. Other psychological treatments have also been studied, e.g. dialectical behavioural therapy, brief in-home interpersonal psychotherapy, family psychotherapy, developmental group therapy, and psychodynamic therapy, with promising results (Wasserman *et al.* 2012). These therapies can be used as an adjuvant treatment to pharmacological treatment.

Suicide is a major public health problem, and therefore the key of suicide prevention should be in national prevention strategies, with government's commitment to the issue (WHO 2014). The national strategies could include several smaller strategies such as surveillance, restriction of means, media guidelines, stigma reduction, raising public awareness, crisis intervention services, and training for health workers, educators and police officers.

2 Nervous system medications

All drugs are classified by WHO in Anatomical Therapeutic Chemical (ATC) classification system (WHO Collaborating Centre for Drug Statistics Methodology 2010). In this classification the active substances are divided into different groups according to the organ or system on which they act, and according their therapeutic, pharmacological and chemical properties.

Nervous system medications are coded by the WHO with code *N*. The group contains anesthetics (N01), analgesics (N02), antiepileptics (N03), anti-parkinson drugs (N04), psycholeptics (N05), psychoanaleptics (N06), and other nervous system drugs (N07) (WHO Collaborating Centre for Drug Statistics Methodology 2010). In this study, the groups antipsychotics (N05A and N06CA), antidepressants (N06A and N06CA), benzodiazepines (N05BA and N05CD), and antiepileptics (N03), were selected to represent nervous system medications. Based on the name of the ATC category, these four medication groups are referred in this study as *nervous system medications*, even though they primarily affect the central nervous system rather than the nervous system as a whole.

In addition to the ATC classification, the WHO also compiles the Defined Daily Dose (DDD) that is the assumed average maintenance dose per day for a pharmaceutical drug used for its main indication in adults. The DDD is a unit of measurement and does not reflect the recommended or prescribed daily dose. The DDDs for plain substances are normally based on monotherapy. The purpose of the ATC/DDD classification system is to serve as a tool for research in order to make a comparison of drug consumption. The classification of a substance in the ATC/DDD system is not a recommendation for use, nor does it imply any judgments about efficacy of drugs (WHO Collaborating Centre for Drug Statistics Methodology 2010).

The *indications* for drugs are regulated by licensing bodies that determine whether to approve a drug for a certain indication based on the studies on drug's safety and efficacy for that specific use. In European Union (and in Finland as part of the union) the licensing body is European Medicines Agency (EMA), and e.g. in United States that is Food and Drug Administration (FDA). The indications for a drug are based on studies conducted, and they are placed in the package insert and other sales material. The *off-label use* can be defined as the use of a drug for an unapproved indication, or in an unapproved age group, unapproved dose, or an unapproved form of administration.

A *black box warning* is a warning text that appears on the package insert of a prescription drug in United States if the drug carries a significant risk of serious or life-threatening adverse effects. The FDA can require a pharmaceutical company to place the warning on the outside of the package of a prescription drug, or in the package inserts, product brochures and other consumer information describing it.

2.1 Epidemiology of nervous system medication use in Finland

The most recently available statistics of drug consumption in Finland is from year 2013 (available in Finnish at: http://www.fimea.fi/laaketieto/kulutustiedot). The consumption of nervous system drugs (ATC code N) was 265.50 DDD per 1000 inhabitants per day. The antipsychotic consumption was 22.52, antidepressant consumption 70.35, benzodiazepine consumption 34.39, and antiepileptic consumption 19.90 DDD/1000/day. According to Finnish national registers, 9.1% of Finnish 18 to 64 years old people has received reimbursement for antidepressant medication in 2013 (available in Finnish at www.sotkanet.fi). No corresponding data were available from other nervous system medications.

2.2 Antipsychotic medication

2.2.1 Neurobiology of antipsychotic medication

Antipsychotics are usually divided into two classes: typical and atypical antipsychotics. The main difference between classes is their different actions on neurotransmission. The therapeutic action of typical antipsychotics is the blocking of dopamine-2 (D2) receptors. This action reduces the positive psychotic symptoms (i.e. delusions and hallucinations) but also causes hyperprolactinemia and extrapyramidal side effects, like akathisia. Atypical antipsychotics cause less extrapyramidal side effects than typical antipsychotics because of their different pharmacological actions in the brain, especially because of their antagonism of serotonin-2A (5HT2A) receptors. However, they may have some other side-effects, such as weight gain, hypertriglyceridemia, and excess metabolic syndrome. The actions of atypical antipsychotics on serotonin receptors may also have effects on negative symptoms of psychoses (i.e. apathy, anhedonia, cognitive blunting, dysphoria) (Stahl 2008).

Lithium is classified by the WHO as an antipsychotic though it usually can be considered as a mood stabiliser. Lithium is an ion whose actions in the brain are not fully known, and there might even be various mechanisms of action. Whatever the mechanism, lithium seems to be effective in stabilizing the mood: in the prevention and treatment of manic, and to a lesser extent, depressive episodes in bipolar disorder (Stahl 2008).

2.2.2 Indications for antipsychotic medication

The main indications for antipsychotic medication are schizophrenia, other psychoses and bipolar disorder. However, they are increasingly used off-label worldwide (Alexander *et al.* 2011, Monasterio & McKean 2011, Trifiro *et al.* 2005), e.g. 60% of the use of antipsychotic medication in United States between years 1998 and 2009 was off-label (Graziul *et al.* 2012). The common off-label uses of antipsychotic medication include depression, anxiety, insomnia, personality disorders, substance abuse, obsessive-compulsive disorder, post-traumatic stress disorder, Tourette's syndrome, autism, and conduct disorders in dementia and developmental disorders (Fountoulakis *et al.* 2004). Antipsychotic medication is recommended to use as monotherapy with lowest effective dose for long-term treatment of schizophrenia, and use of more than two antipsychotic medications should be avoided (Schizophrenia: Current Care Guidelines, 2013). The polypharmacy of antipsychotic medications is recommended only after unsuccessful attempts of multiple monotherapies. For acute psychosis, short-term polypharmacy can be indicated, and the doses can be higher than for long-term treatment. The main indication for lithium is bipolar disorder.

2.2.3 Antipsychotic medication and suicidality

The association between antipsychotic medication and suicidality is still partly unknown. Among people with schizophrenia, the antipsychotic medication associates with decreased rate of suicide attempts and suicide mortality (Barak *et al.* 2004, Haukka *et al.* 2008b). The higher doses of antipsychotic medication have been associated with decreased suicide mortality among people with schizophrenia (Torniainen *et al.* 2014). However, there are also studies showing no such decrease in suicidality, e.g., the rates of suicide attempts or suicides did not differ between active antipsychotics (risperidone, olanzapine or quetiapine fumarate) and placebo in the analysis of the FDA database of clinical trials in

people with psychosis (Khan *et al.* 2001). It has been suggested that there might be differences between anti-suicidal properties of antipsychotics, e.g., clozapine could be more effective in reducing suicidality than other antipsychotics (Hennen & Baldessarini 2005). However, there are also data suggesting that clozapine is not associated with decreased rate of suicides (Sernyak *et al.* 2001).

Considering the off-label use of antipsychotic medication and risk of suicidality, the data are limited. The risk of suicidality did not differ between quetiapine and placebo in a randomised, placebo-controlled study of quetiapine fumarate in subjects with major depressive disorder with low baseline suicidality risk (Weisler *et al.* 2014).

The suicide reducing properties of lithium has been extensively studied. The use of lithium in both unipolar and bipolar mood disorders associated with reduction in suicide rates compared to placebo in a meta-analysis (Cipriani *et al.* 2013). Furthermore, combining antipsychotic medication olanzapine to mood stabilizing medication (lithium or divalproex) might reduce suicidal ideation more than mood stabiliser as monotherapy (Houston *et al.* 2006).

2.3 Antidepressant medication

2.3.1 Neurobiology of antidepressant medication

Antidepressants are usually divided into following classes: serotonin selective reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and other antidepressants. The main therapeutic action of antidepressants is thought to be that they balance the levels of monoamine neurotransmitters (especially serotonin, and also norepinephrine and dopamine). The differences between antidepressant classes are in their actions on different monoamines, e.g. SSRIs are selective for serotonin, bupropion for noradrenaline and dopamine, and SNRIs and TCAs affect both serotonin and norepinephrine levels (Stahl 2008).

2.3.2 Indications for antidepressant medication

The main indication for antidepressant medication is usually thought to be depression. However, antidepressant medication is commonly used also in other conditions, such as in anxiety disorders, eating disorders, insomnia, migraine

headache prevention, chronic or neuropathic pain and fibromyalgia, and premature ejaculation (Lunn *et al.* 2014, Montague *et al.* 2004, Pizarro *et al.* 2014, Strawn *et al.* 2015). Some of these conditions are on-label indications for certain antidepressants and some of them might be considered off-label use. Off-label use of antidepressant medication is common, e.g. 18% of antidepressant medications prescribed by French general practitioners were prescribed for non-psychiatric conditions (Mercier *et al.* 2014).

2.3.3 Antidepressant medication and suicidality

There has been a wide discussion about the association of antidepressant medication and suicidality in recent years. The FDA issued a public health advisory in 2004 that newer antidepressants may be associated with increased suicidality in all age groups. Later in the same year, the FDA extended this to a black box warning covering all antidepressants and all age groups. This warning was based on a meta-analysis on randomised controlled trials of antidepressants. In 2007, after re-analysing the trials data, the FDA changed the warning to cover only potential treatment of emergent suicidality in children and adolescents using antidepressant medication (Laughren 2006).

Additionally to the data of the FDA, also in several other meta-analyses from clinical trial datasets, the use of antidepressant medication has been associated with increased risk of suicidal ideation and behaviour among children and adolescents (Hammad *et al.* 2006, Stone *et al.* 2009). However, the increase in suicidality seems to be age-related such that antidepressant medication increases suicidality in young subjects but is protective in adults (Barbui *et al.* 2009, Laughren 2006, Olfson *et al.* 2006, Olfson & Marcus 2008, Stone *et al.* 2009).

The association of antidepressant medication and suicidality has also been widely studied in observational and ecological settings. The increased use of antidepressant medication has been associated with a lower number of suicides in several countries, suggesting that antidepressant medication might protect from suicide (Guaiana *et al.* 2011, Hall & Lucke 2006, Kelly *et al.* 2003, Ludwig *et al.* 2009, Olfson *et al.* 2003). The rate of psychotropic medication poisonings has also been seen to increase while the use of antidepressant medication decreased after the FDA's warning (Lu *et al.* 2014). The anti-suicidal effects of antidepressant medication have also been proposed in a Finnish study showing people with schizophrenia using antidepressant medication to have decreased suicide rates (Tiihonen *et al.* 2012).

There are studies suggesting differences in suicidality between different antidepressants (Rubino *et al.* 2007, Simon 2006, Tiihonen *et al.* 2006), but there are also studies suggesting that there are no differences (Fergusson *et al.* 2005, Grunebaum *et al.* 2011, Jick *et al.* 2004).

2.4 Benzodiazepine medication

2.4.1 Neurobiology of benzodiazepine medication

Benzodiazepines are a group of drugs which are divided into three different major categories by the WHO. Some benzodiazepine derivatives (e.g. diazepam) are classified as anxiolytics (ATC code N05BA), some (e.g. midazolam) are classified as hypnotics and sedatives (N05CD), and clonazepam is classified as an antiepileptic (N03AE). Benzodiazepines act by enhancing GABA actions in the brain. GABA-system is the main inhibitory system in the brain, and by increasing its actions, benzodiazepines are sedative, hypnotic (sleep-inducing), anxiolytic, anticonvulsant, and muscle relaxant drugs. Benzodiazepines have usually been also divided to short-, intermediate-, or long-acting ones (Stahl 2008).

2.4.2 Indications for benzodiazepine medication

Indications for benzodiazepine medication include treatment of anxiety symptoms and distress, phobias, insomnia, status epilepticus, severe alcohol withdrawal symptoms and delirium tremens, muscle spasms, and tension headache. They can be used also as premedication for surgical procedures and as adjunctive medication of antidepressant or antipsychotic medication in depression or in psychosis (Stahl 2008).

The main problem of the long-term use of benzodiazepine medication is the development of tolerance and dependence. Therefore the long-term use of benzodiazepine medication is not recommended by the guidance of National Supervisory Authority for Welfare and Health in Finland (available in Finnish at: www.valvira.fi/ohjaus_ja_valvonta/terveydenhuolto/laakehoito). The non-medical use or abuse of benzodiazepine medication and other sedative medications is quite common, e.g. in United States the lifetime prevalence of non-medical use of sedative medication is about 4%, and the lifetime prevalence of sedative medication abuse or dependence is about 1% (Huang *et al.* 2006).

2.4.3 Benzodiazepine medication and suicidality

There are contrary findings on how benzodiazepine medication associates with the risk of suicidality. The regular use of hypnotic medication, including benzodiazepine medication, has been associated with increased risk of suicide (Mallon *et al.* 2009), and the use of benzodiazepine medication with increased risk of suicide attempts (Neutel & Patten 1997). The use of sedative-hypnotic medication has been found to associate with an increased risk of suicidal ideation, plans, and suicide attempts, even when adjusted for demographic characteristics, physical and mental disorders, and sleep disturbances (Brower *et al.* 2011). However, in a meta-analysis studying the use of alprazolam (a benzodiazepine derivate) in the treatment of depression, alprazolam bore a similar risk of the emergence and worsening of suicidal ideation as a placebo, while alprazolam showed a higher rate of improvement than the placebo in the case of suicidal ideation (Jonas & Hearron 1996).

2.5 Antiepileptic medication

2.5.1 Neurobiology of antiepileptic medication

Overall, antiepileptics effect by modifying the bursting properties of neurons and by reducing synchronization in localised neuronal ensembles to prevent epileptic activity. Antiepileptics also inhibit the spread of abnormal firing to distant sites and by that mechanism prevent the expression of behavioural seizure activity. They have different mechanisms of action, e.g. modulation of voltage-gated ion channels (sodium and calcium channels), or enhancement of synaptic inhibition or inhibition of synaptic excitation (i.e. neurotransmitter-regulated channels) thus stabilizing the neurotransmission. A key mechanism of many antiepileptic actions is the potentiation of inhibitory neurotransmission mediated by GABA-A receptors. Glutamatergic receptors are also targeted by some antiepileptics. (Rogawski & Loscher 2004).

2.5.2 Indications for antiepileptic medication

The main indication for antiepileptic medication is to prevent epileptic seizures. Antiepileptic medication has also indications for bipolar disorder, neuropathic pain, migraine prophylaxis, or even generalised anxiety disorder (Spina & Perugi

2004). The complex mechanisms of actions of certain antiepileptics might explain their efficacy also in other conditions than epilepsy. However, there is lack of knowledge on e.g. the mood-stabilizing mechanisms of antiepileptic medication, and not all antiepileptics are effective in treating bipolar disorder (Bialer 2012). The mechanism of action in treatment of neuropathic pain might be due the inhibition of neuronal hyperactivity underlying both epilepsy and neuropathic pain.

The use of antiepileptic medication for non-epileptic conditions has increased. In a recent study, only 14% of prescriptions of newer antiepileptics and 45% of prescriptions of older antiepileptics were for epilepsy (Italiano *et al.* 2014). The most common non-epileptic indications for prescriptions were pain (71% of newer antiepileptic prescriptions) and mood disorders (39% of older antiepileptic prescriptions).

2.5.3 Antiepileptic medication and suicidality

The FDA presented a black box warning on antiepileptic medication in 2008 due to the increased risk of suicidality (US Food and Drug Administration). This warning was based on a meta-analysis that showed a 1.8-fold risk of suicidal ideation or behaviour in all 11 antiepileptics included in the study. The risk of suicidal behaviour was higher than the risk of suicidal ideation (odds ratio (OR) 2.92 vs. 1.45). Divided into subgroups by the indication for medication, the highest risk was revealed in the epilepsy indication subgroup (OR 3.53), compared to psychiatric indications (OR 1.51) or other indications (OR 1.87).

Since the FDA warning was issued, there has been a broad discussion of the suicidality risk of antiepileptic medication. In contrast to the FDA study, a study by Arana *et al.* (2010) suggested that the use of antiepileptic medication was not associated with an increased risk of suicidality in people with epilepsy, but was associated with an increased risk in people with depression, or in people without epilepsy, depression or bipolar disorder. However, in another study, there were no statistically significant differences in suicide-related behaviours between subjects using antiepileptic medication for new-onset epilepsy compared to subjects using antiepileptic medication for other indications among elderly people (VanCott *et al.* 2010). There are studies showing temporal trends of suicidal ideation and suicide attempt rates to be higher before the initiation of antiepileptic medication than afterwards, suggesting that the medication has a protective effect (Gibbons *et al.* 2009, Pugh *et al.* 2013).

2.6 Polypharmacy of nervous system medications

Polypharmacy is usually defined as the concurrent use of two or more medications by the same individual (NASMHPD 2001). However, the term *polypharmacy* is rather imprecise and it can be used in different meanings across the published literature. The National Association of State Mental Health Program Directors have made guidelines and recommendations for decreasing inappropriate use of multiple psychiatric medications in people with psychiatric disorders in United States (NASMHPD 2001). According to this report, *same-class polypharmacy* refers to the use of more than one medication from the same medication class, e.g. two SSRIs in use. When an individual is using two or more medications, with full therapeutic doses, from different medication classes for the same symptom cluster, it refers to *multi-class polypharmacy*. For instance, the use of both lithium and an atypical antipsychotic for treatment of mania can be defined as multi-class polypharmacy. *Adjunctive polypharmacy* is defined as the use of one medication to treat the side effects or secondary symptoms of another medication from different medication class, whereas *augmentation* can be defined as the use of one medication at a lower dose along with another medication from different class at its full therapeutic dose, for the same symptom cluster. Augmentation can also refer to the addition of a medication that would not be used alone for the same symptom cluster. Overall, the term *total polypharmacy* contains the total count of medications used by a person, or total drug load. It includes prescription medications, over-the-counter medications, and alternative medical therapies.

Psychiatric polypharmacy is rather common. Of all people with psychiatric disorders, 42% used more than one psychotropic medication, and the mean number of psychotropic drugs was 1.6 in a register-based study (De las Cuevas & Sanz 2004). Among psychiatric inpatients, the polypharmacy of psychotropic medications has increased, while the amount of subjects using monotherapy has declined from 48% to 20% from 1970s towards the 21st century (Rittmannsberger 2002). Similar trend have been found in United States among people visiting office-based psychiatrists (Mojtabai & Olfson 2010). In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial, the mean number of psychotropic drugs per person with schizophrenia at baseline was 2.0 drugs (Chakos *et al.* 2006). The polypharmacy of antipsychotic medication is common also in Finland, e.g. 46% of people with schizophrenia use two or more antipsychotics (Suokas *et al.* 2013).

The previous data are limited on safety and efficacy of the polypharmacy of nervous system medications. Polypharmacy might cause more adverse side effects than a certain monotherapy. There might also be harmful pharmacodynamic and pharmacokinetic interactions, cumulative neurotoxicity, medication errors, excessive dosing, and off-label use of medications when using polypharmacy of nervous system medications.

2.6.1 Polypharmacy of nervous system medications and suicidality

Polypharmacy increases the risk of medication-related adverse events and drug interactions (NASMHPD 2001). For example, the augmentation of benzodiazepine medication to antipsychotic medication in people with schizophrenia has been effective in treating psychotic symptoms (Dold *et al.* 2013), but has also increased the all-cause and suicide mortality (Tiihonen *et al.* 2012). The biological effects of the polypharmacy of nervous system medications on suicidality are unknown.

The number of previous suicide attempts has been associated with increased use of multiple nervous system medications among people with bipolar disorder (Gazalle *et al.* 2007). Those who had history of suicide attempt were more likely to use more than three psychotropic drugs compared to those who did not have previous suicidal attempts in a study of people with bipolar disorder (Goldberg *et al.* 2009). Of those people admitted to hospital after self-poisoning and using any prescribed drugs, 31% used multiple psychotropic drugs, and the use of polypharmacy of psychotropic drugs was associated with repeated self-poisoning (Prescott & Highley 1985). The concomitant use of antidepressant and benzodiazepine medication associated with increased risk of suicide attempt when compared to the risk with the use of either antidepressant or benzodiazepine medication as monotherapy (Neutel & Patten 1997).

2.7 Somatic medications and suicidality

There has been a debate whether some medications for somatic diseases might increase the risk of suicidality, e.g. the suicidality risks of smoking cessation medication, acne medication, weight loss medication, asthma medication, human immunodeficiency virus/acquired immunodeficiency syndrome medication, malaria prophylaxis medication, cholesterol lowering medication, non-steroidal anti-inflammatory drugs/paracetamol (Thomas *et al.* 2014), certain antibiotics

(Behera *et al.* 2014), and interferons (Dieperink *et al.* 2004) have been under discussion. However, in a study of spontaneous reports of suicidal adverse effects of all prescription drugs in United Kingdom between 1998 and 2011, the all top five drugs for reports of suicide attempts and suicides were psychiatric drugs (antidepressants or antipsychotics) (Thomas *et al.* 2014). Regarding depression as an adverse effect of medication, in the top five were smoking cessation medications (varenicline and bupropion), an antidepressant medication (paroxetine), an acne medication (isotretinoin), and a weight loss medication (rimonabant) (Thomas *et al.* 2014).

The increased risk of suicidality associated with somatic medications may be due the comorbid depressive symptoms related to somatic disorder that is treated for. In the present thesis, the association between the use of analgesic or cardiovascular system medications and suicidal ideation was studied to compare the use of nervous system medications and somatic medications.

3 Aims of the study

The purpose of this work was to study the associations between the use of nervous system medications, i.e. antipsychotic (original publication I), antidepressant (II), benzodiazepine (III) and antiepileptic medication (III), and suicidal ideation, suicide attempts and suicides. The specific aims were to study:

1. The associations between nervous system medications and suicidality.
2. The associations between nervous system medications and suicidality when the other symptoms of depression and anxiety were taken into account.
3. The association between polypharmacy of nervous system medications and suicidality.
4. The use of nervous system medications in different diagnostic groups and suicidality.
5. The association between dose and type of nervous system medications and suicidality.

4 Materials and methods

4.1 The Northern Finland Birth Cohort 1966

The Northern Finland Birth Cohort 1966 (NFBC 1966) is an unselected, population-based birth cohort containing data on 12,058 babies born alive in the Finnish provinces of Oulu and Lapland with an expected date of birth in 1966. Since mid-pregnancy, prospective data have been collected of the cohort members' health, socioeconomic conditions, family, and living. The current sample includes 10,799 (5,312 females; 5,487 males) subjects who were alive and lived in Finland 1982 and 1997, excluding those 84 who have denied permission for the use of their data. Permission to gather data was obtained from the Ministry of Social and Health Affairs, and the study was approved by the Ethical Committee of Northern Ostrobothnia Hospital District in Oulu, Finland.

The main sample of the present study were those 8,211 (76.0%) cohort members (females 4,279; males 3,932) who answered the question on suicidal ideation in a postal questionnaire (n=8,217) sent to all cohort members in 1997-1998, without those who left five or more items blank in the Hopkins Symptom Checklist -25 –questionnaire (n=6). Females were more responsive than males (80.1% vs. 70.4%) in answering the questionnaire.

4.2 Medication data

Information on the use of medications was received from two sources. Data were collected both from the register of the Social Insurance Institution of Finland (Kela) on physician-prescribed and reimbursed drugs purchased in 1997 (I), and from a postal questionnaire sent to all cohort members 1997-1998 (I, II, III), at the age of 31 years. The register data only included information on the name of the medication concerned, and not on the daily dose. The questionnaire data included questions about the use of prescribed medication including the name and the daily dose of used medications (Haapea *et al.* 2008, Haapea *et al.* 2010), and was the main source of medication data in this study.

According to the medication register data, the proportion of those using nervous system medication was greater in those who did not answer the postal questionnaire (n=2,588) than in those answering the questionnaire (8.0% vs. 4.4%, $p<0.001$). Of 183 subjects using antipsychotic medication according to registers,

94 (51.4%) answered the questionnaire. Similarly, of 311 subjects using antidepressant medication 210 (67.5%) answered the questionnaire; of 268 using benzodiazepine medication 156 (58.2%) answered; and of 92 using antiepileptic medication 55 (59.8%) answered.

All medication use in this study population was classified according to the Anatomical Therapeutic Chemical (ATC) classification system (WHO Collaborating Centre for Drug Statistics Methodology 2010) and of those we selected the groups N05A (antipsychotics), N06A (antidepressants), N03A (antiepileptics), N05BA (anxiolytics; benzodiazepine derivatives), N05CD (hypnotics and sedatives; benzodiazepine derivatives), and N05CF (hypnotics and sedatives; benzodiazepine derivatives) to these series. Pertriptyl (combination drug including amitriptyline and perphenazine, ATC code N06CA01) was included in both studies of antipsychotic (I) and antidepressant medications (II). The group N03AE (antiepileptics; benzodiazepine derivates) was also included both in groups of antiepileptics (III) and benzodiazepines (III). As additional analyses for nervous system medications, groups N02 (analgesics) and C (cardiovascular system medications) were also studied. The group of cardiovascular system medications contains e.g. antihypertensives, antiarrhythmics, and lipid modifying agents.

Attrition and validity of questionnaire data on medications has been described in detail by Haapea *et al.* (2008, 2010). The agreement between self-reported and medication register data was found to be moderate for psychoactive medication use, however, questionnaire data can be assumed accurate enough for study purposes (Haapea *et al.* 2010).

4.2.1 Type of medication (I, II, III)

The brief listing of hierarchical ATC classification of nervous system medications is presented in Appendix.

The antipsychotics were categorised as either atypical (in Finland, in 1997, this referred to clozapine, olanzapine and risperidone) or typical antipsychotics. The ATC category N05A includes also lithium, but none of the subjects used it, so it was not included in these series. If a subject was taking more than one antipsychotic, that with the highest dose in chlorpromazine equivalents was selected for examination when comparing the use of atypicals and typicals, and if the doses were exactly the same the subject was excluded (n=1) (Kroken *et al.* 2009). The sub-groups of antipsychotics in this sample were: N05AA

(Phenothiazines with aliphatic side-chain), N05AB (Phenothiazines with piperazine structure), N05AC (Phenothiazines with piperidine structure), N05AD (Butyrophenone derivatives), N05AF (Thioxanthene derivatives), N05AH (Diazepines, oxazepines, thiazepines and oxepines), N05AL (Benzamides), and N05AX (Other antipsychotics) (I).

Antidepressants were divided into the following groups: N06AA (non-selective monoamine reuptake inhibitors), N06AB (selective serotonin reuptake inhibitors), N06AG (monoamine oxidase A inhibitors), and N06AX (other antidepressants) (II).

In the WHO classification benzodiazepines, and benzodiazepine related drugs, are included in several different classes. The classes N03AE (antiepileptics; benzodiazepine derivates), N05BA (anxiolytics; benzodiazepine derivatives), N05CD (hypnotics and sedatives; benzodiazepine derivatives), and N05CF (hypnotics and sedatives; benzodiazepine related drugs) were analysed in this study (III).

Antiepileptics were divided into following groups by WHO classification: N03AA (barbiturates and derivatives), N03AB (hydantoin derivatives), N03AE (benzodiazepine derivatives), N03AF (carboxamide derivatives), and N03AG (fatty acid derivatives) (III).

4.2.2 Dose of medication (I, III, III)

Doses of antipsychotic, antidepressant, benzodiazepine, and antiepileptic medication were studied using the defined daily dose (DDD) –classification. DDD is the average maintenance dose estimated by the WHO based on global health statistics (WHO Collaborating Centre for Drug Statistics Methodology 2010). The daily dose the subject used was divided by the DDD to form the *DDD ratio*. A *DDD ratio* below 1 means that the dose used by the subject is lower than that average maintenance dose estimated by the WHO, and a value above 1 refers to a higher dose. The daily doses of benzodiazepine medication with a range of doses on prescription or used only when needed, were calculated by the maximum daily dose the subject could use (III).

Subjects using antipsychotic medication were classified into low or high dose categories by the median value of *DDD ratio* (I). Antidepressant doses were divided into three categories: high dose (*DDD ratio* > 1), medium dose (*DDD ratio* = 1), and low dose (*DDD ratio* <1) (II). Subjects using benzodiazepine

medication and antiepileptic medication were classified into low, medium, or high dose categories by tertiles of the *DDD ratio* (III).

Subjects receiving medication for whom no information on the daily dose was available (n=9 for antipsychotic, n=6 for antidepressant, n=3 for benzodiazepine, and n=4 for antiepileptic medication) were excluded from the dose analyses.

4.2.3 Polypharmacy of medications (I, II, III)

The subjects were divided into groups by whether they used only one type of nervous system medication (i.e. antipsychotic, antidepressant, benzodiazepine, or antiepileptic medication), two nervous system medications, or more than two medications. Subjects were also divided into two groups by whether they used only one or more than one drugs from the same medication class at the time (e.g. two antipsychotics). Also the concomitant use of certain nervous system medications (e.g. antipsychotic and antidepressant medication) was studied.

4.3 Suicidality data

4.3.1 Suicidal ideation and depression and anxiety symptoms (I, II, III)

Data on suicidal ideation were collected with the same postal questionnaire in 1997-1998 that assessed the use of medication (Haapea *et al.* 2010). The questionnaire included a 25-item version of the Hopkins Symptom Checklist (SCL) validated in Finnish (Veijola *et al.* 2003) with questions on symptoms related to depression and anxiety experienced in the previous week. One question was "How much have you suffered from suicidal thoughts during the last week?" The answers were scored on a scale from 1 ("not at all") to 4 ("very much"). The sensitivity of SCL questionnaire is moderate, and the specificity and negative predictive power is high for any psychiatric disorder (Veijola *et al.* 2003).

Not only the presentation of the crude suicidal ideation from the SCL, the score of suicidal ideation is also presented in relation to other symptoms in the SCL by dividing the score of suicidal ideation by the mean score of other answers in the questionnaire (for the *SCL ratio*). This relationship was based on previous studies' indication that suicidality correlates with the severity of both symptoms of depression and anxiety (Diefenbach *et al.* 2009, Norton *et al.* 2008, Suokas *et*

al. 2010). The total mean score (without suicidal ideation) in the SCL (*SCL total*) is also reported.

4.3.2 Suicides and suicide attempts (I)

Data on suicides (i.e. ICD-8-9 E950-E959; ICD-10 X60-X84, Y87.0) between 1998 and 2011 were collected from the cause-of-death statistics maintained by Statistics Finland, which are based on death certificates. Data on suicide attempts (i.e. ICD-8-9 E950-E959; ICD-10 X60-X84, Z72.8 and Z91.5) between 1997 and 2012 were collected from the nationwide Care Register for Health Care (CRHC) (formerly Finnish Hospital Discharge Register). The CRHC covers all mental and general hospitals, inpatient wards in local health centres, and private hospitals nationwide, and it also includes hospitalizations due to suicide attempts. Additionally, the information on suicide attempts was collected from speciality (years 1998-2012) and primary (years 2011-2012) health care outpatient registers, but both of these registers included only one additional suicide attempt.

Of those 83 subjects who attempted suicide between 1998 and 2012, 44 (53.0%) had answered the questionnaire in 1997, and of those 48 who died by suicide between 1998 and 2011, 23 (47.9%) had answered the questionnaire.

4.4 Diagnostic groups (I, II, III)

Information on psychiatric disorder diagnoses was collected from both nationwide registers and a 31-year follow-up questionnaire in 1997-1998 (I, II, III). All cohort members over 16 years of age appearing in the CRHC until 1997 for any psychiatric disorder (i.e. ICD-8 290–309; ICD-9 290–316; ICD-10 F00–F69 and F99) were identified. All case records until 1997 were scrutinised, and diagnoses were validated for the DSM-III-R criteria (Isohanni *et al.* 1997, Moilanen *et al.* 2003). The validation was done by six psychiatrists or psychiatry trainees, all cases were first examined by two evaluators independently and in problematic cases, the diagnoses were done in a consensus panel including experts in psychiatric diagnostics. The good reliability of psychiatric diagnoses between raters has been shown by Moilanen *et al.* (2003).

The validated psychiatric diagnoses were combined with register information until 1997 from the Social Insurance Institution of Finland about disability pensions, sick days, and reimbursement-eligible medication for psychiatric disorders. Self-reported diagnoses were collected from the postal questionnaire

sent to all subjects in 1997-1998, asking whether the subject had any of the following conditions diagnosed by a medical doctor: depression, psychosis, an alcohol-use disorder, some other substance-use disorder, or any other psychiatric disorder. All these data were combined to any non-organic mental disorder, excluding those who had organic mental disorder (i.e. ICD-8 290-294 and 309; ICD-9 290-294 and 310; ICD-10 F00-F09, F1x.0, and F1x.3-F1x.9).

All subjects with a diagnosis of epilepsy or seizures (i.e. ICD-8 345 and 331.2; ICD-9 345; ICD-10 G40-G41) during the period 1966–1997 were identified from the CRHC, and from the records of the Social Insurance Institution of Finland about reimbursement-eligible medication for epilepsy (Löfgren *et al.* 2009) (III). Also self-reported data collected from cohort members or their parents were used, as prescribed by Löfgren *et al.* (2004). The patient files of all subjects predisposed to epilepsy were examined using systematic medical chart abstraction, and epilepsy was diagnosed if there had been at least two unprovoked seizures or one unprovoked seizure with EEG findings consistent with epilepsy, as defined by the International League Against Epilepsy (ILAE 1989, Löfgren *et al.* 2009). The final epilepsy diagnoses were done by specially trained medical doctor, who in problematic cases consulted experienced neurologist. Only those subjects who were diagnosed with epilepsy before the end of 1997 were included in the analyses.

4.5 Insomnia (II, III)

The impact of insomnia as judged from the SCL questionnaire was studied, to find groups of subjects who might be at higher risk of suicidal ideation when using antidepressant or benzodiazepine medication. One question in the SCL was "How much have you suffered from insomnia during the last week?" The answers were scored on a scale of 1 to 4. The severity of insomnia was classified into low score (1 or 2) and high score (3 or 4).

All used variables regarding medication, suicidality, depression and anxiety symptoms, insomnia, and psychiatric and epilepsy diagnoses are described in Figure 1.

4.6 Statistical methods

The mean values (and standard deviations, SDs) for the SCL variable suicidal ideation, mean SCL score with suicidal ideation excluded (*SCL total*), and relative

suicidal ideation (ratio of suicidal ideation and mean SCL score, *SCL ratio*) are presented. Also mean values (and SDs), and median values (and interquartile ranges, IQRs) for *DDD ratio* are presented. Differences in suicidal ideation between medication users and non-users were tested with Mann-Whitney U-test, and in continuous variables (*SCL total* and *SCL ratio*) with Student's *t*-test. The median values and IQRs were not presented for suicidal ideation because of the skewed distribution of values which resulted the median to be 1 and IQRs to be in most cases 1 to 1.

The correlation of dose of antipsychotic medication as *DDD ratio* and adjusted suicidal ideation (*SCL ratio*) is presented. Also, the correlation between insomnia and suicidal ideation in subjects using antidepressant medication is presented. For correlations the Spearman's correlation coefficients were used.

The associations between the number of nervous system medications and suicidal ideation, *SCL total* and *SCL ratio* were tested with trend of means test.

For studying the associations between use of nervous system medications and suicide attempts and suicides, Fisher's exact test was used. The Mantel-Haenzel Chi-Square test was performed to study the number of nervous system medications and risk of suicide attempts and suicides.

Binary logistic regression analyses were performed to ascertain the effects of any nervous system medication and any mental disorder on the likelihood of having suicidal ideation (suicidal ideation score 1 vs. 2-4) as sensitivity analyses for *SCL ratio*. Due to small sample size, when using the presence of any mental disorder as covariate, the ordinal regression analyses were not possible.

IBM SPSS versions 19-22 were used for statistical analyses. A p-value < 0.05 was considered as statistically significant.

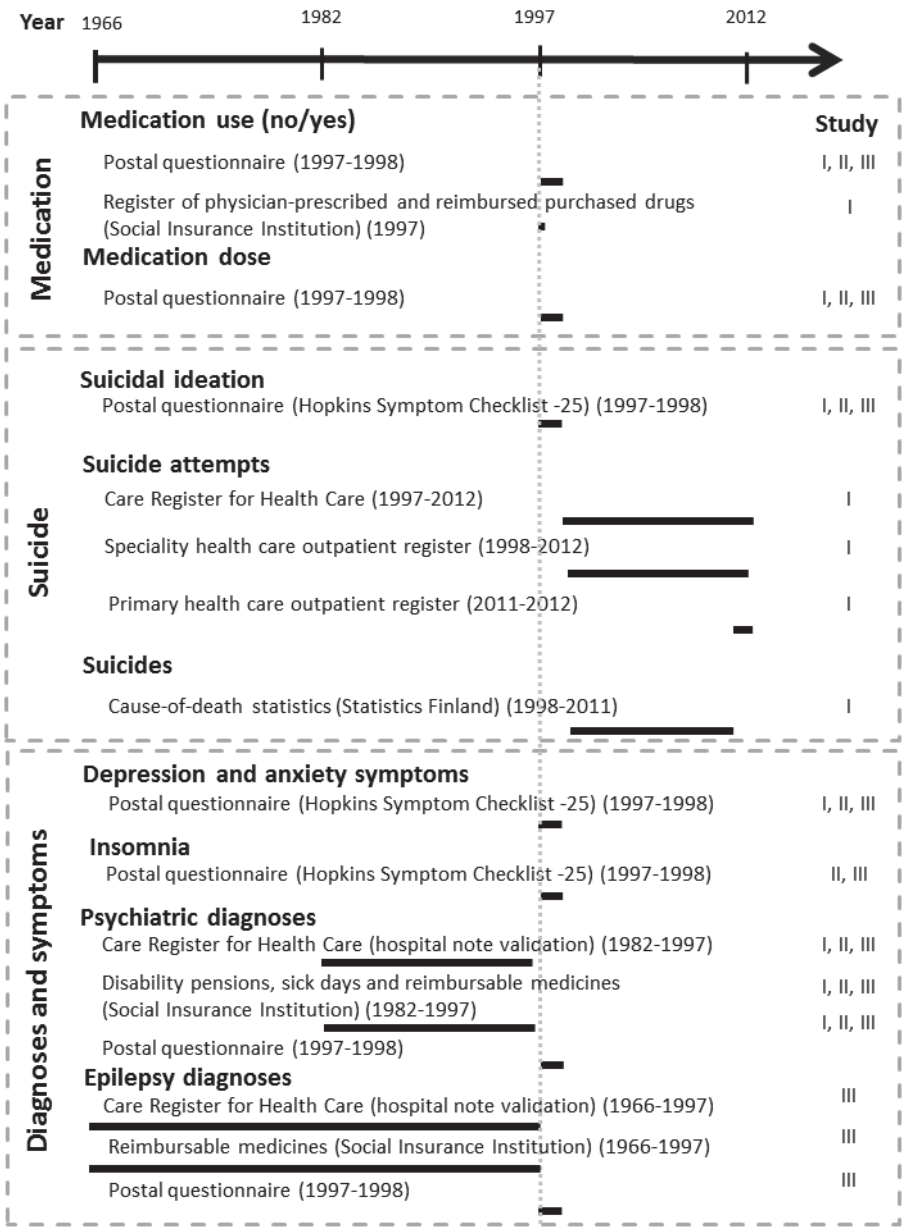

Fig. 1. Data sources of main variables.

5 Ethical considerations and personal involvement

The study design of the 31-year follow-up of the Northern Finland Birth Cohort 1966 (NFBC 1966) has been approved by the Ethical Committee of the Faculty of Medicine, University of Oulu on June 17th 1996. Permission to gather data was obtained from the Ministry of Social Affairs and Health, as well as data protection was scrutinised by the Privacy Protection Agency, in 1994. Informed consent was inquired from all the participants, and those subjects who declined use of their data, were excluded from the study. The topic of this doctoral thesis was approved by the Postgraduate Research Committee of the Faculty of Medicine at the University of Oulu on 15th of December 2009.

The author of this thesis has participated in the NFBC 1966 study since 2008 as a researcher. Due the longitudinal nature of the study, the author has not participated in the collection of the data used in this study. The author has participated in designing all the original studies, and analysing the data and reporting the results. Statistical analyses of all original studies have been made by the author in consultation with a professional statistician. The author has conducted all of the literature searches. The author has written the first and final versions of all original studies (I-III). The author has also been the corresponding author in all the original studies, and coordinated the revision and resubmission processes for all the studies.

6 Results

6.1 Characteristics of questionnaire sample

Of all 10,799 cohort members, 8,211 subjects (76.0%) answered the question on suicidal ideation in a postal questionnaire (those who left five or more items blank (n=6) in the SCL questionnaire were excluded from the sample). The characteristics of nervous system medication users in questionnaire data are presented in Table 3. In total there were 294 (3.6%) subjects using either antipsychotic, antidepressant, benzodiazepine, or antiepileptic medication. Of them 224 (76.2%) subjects used only one particular medication, 55 (18.7%) subjects used two different medications, 13 (4.4%) subjects used three medications, and 2 (0.7%) subjects used all four medications.

6.2 Nervous system medications and suicidal ideation

Subjects using any of the four nervous system medications studied (antipsychotic, antidepressant, benzodiazepine, or antiepileptic medication) had more suicidal ideation than control population (mean 1.26 vs. 1.04, Mann-Whitney U-test $p<0.001$) (Table 4). However, they had also more other symptoms of depression and anxiety, and when suicidal ideation was adjusted for other symptoms, they had lower mean score than control population (mean *SCL ratio* 0.74 vs. 0.80, $p<0.001$). Subjects using antipsychotic medication had greatest score of suicidal ideation (mean 1.43), followed by antidepressant medication (mean 1.37), and benzodiazepine medication (mean 1.29). Subjects using antiepileptic medication did not have statistically significantly more suicidal ideation than control population.

Table 3. Characteristics of nervous system medication users.

Variables	Nervous system medication	Antipsychotics	Antidepressants	Benzodiazepines	Antiepileptics
	n (%)	n (%)	n (%)	n (%)	n (%)
Characteristics of medication use					
Total (N=8,211)	294 (3.6%)	69 (0.8%)	111 (1.4%)	147 (1.8%)	54 (0.7%)
Males (n=3,932)	125 (3.2%)	35 (0.9%)	49 (1.2%)	62 (1.6%)	27 (0.7%)
Females (n=4,279)	169 (3.9%)	34 (0.8%)	62 (1.4%)	85 (2.0%)	27 (0.6%)
Characteristics within medication groups					
One medication	224 (79.2%)	55 (79.7%)	104 (93.7%)	131 (89.1%)	50 (92.6%)
Polypharmacy[1]	70 (23.8%)	31 (44.9%)	51 (45.9%)	60 (40.8%)	15 (27.8%)
Concomitant antipsychotic		14 (20.3%)	23 (20.7%)	21 (14.3%)	4 (7.4%)
Concomitant antidepressant		23 (33.3%)	7 (6.3%)	41 (27.9%)	4 (7.4%)
Concomitant benzodiazepine		21 (30.4%)	41 (36.9%)	16 (10.9%)	13 (24.1%)
Concomitant antiepileptic		4 (5.8%)	4 (3.6%)	13 (8.8%)	4 (7.4%)
DDD ratio[2] mean (SD[3])		0.72 (0.67)	1.07 (0.59)	1.11 (0.90)	0.67 (0.51)
DDD ratio median (IQR[3])		0.50 (0.20-1.00)	1.00 (0.71-1.00)	1.00 (0.50-1.28)	0.60 (0.39-0.80)

[1] Polypharmacy of different nervous system medications

[2] DDD ratio = used daily dose divided by defined daily dose (DDD)

[3] SD = standard deviation, IQR = interquartile range

Table 4. Use of nervous system medications and suicidal ideation.

Variables	Suicidal ideation mean (SD)	SCL total[1] mean (SD)	SCL ratio[2] mean (SD)
Total (N=8,211)	1.05 (0.26)	1.35 (0.32)	0.80 (0.16)
Any medication (n=294)	1.26 (0.60)[4]	1.72 (0.49)[4]	0.74 (0.23)[4]
Antipsychotics (n=69)	1.43 (0.76)[4]	1.84 (0.52)[4]	0.77 (0.25)
Antidepressants (n=111)	1.37 (0.69)[4]	1.81 (0.52)[4]	0.76 (0.26)
Benzodiazepines (n=147)	1.29 (0.60)[4]	1.80 (0.49)[4]	0.72 (0.22)[4]
Antiepileptics (n=54)	1.07 (0.33)	1.51 (0.40)[3]	0.73 (0.17)[3]

Differences between medication users and non-users were tested using the Mann-Whitney U –test for suicidal ideation and Student's t-test for other variables.

[1] SCL total = Symptom Checklist-25 (SCL) total score without suicidal ideation

[2] SCL ratio = suicidal ideation adjusted for SCL total score without suicidal ideation

[3] $p < 0.05$

[4] $p < 0.001$

6.2.1 Polypharmacy of nervous system medications and suicidal ideation

The polypharmacy of nervous system medications was a risk factor of suicidal ideation (Table 5). The mean values of suicidal ideation for subjects not using nervous system medication or using only one medication, two medications, or more than two medications were 1.04, 1.21, 1.36, and 1.67 respectively. There was a statistically significant trend of suicidal ideation means ($F=99.2$, $p<0.001$). Similar results were found in severity of depression and anxiety symptoms (trend of *SCL total* score means $F=117.9$, $p<0.001$). When adjusted with other symptoms, subjects using nervous system medication had lower score of *SCL ratio* than subjects not using any medication. There were no trend of difference in *SCL ratio* means between the groups based on number of medications used ($F=2.1$, $p=0.15$).

Associations between suicidal ideation and use of two different nervous system medications are presented in Figure 2. The number of subjects in each group is presented in Table 3. Subjects using both antipsychotic and antidepressant medication had more suicidal ideation than subjects using either antipsychotic or antidepressant medication as monotherapy (mean 1.57 vs. 1.34, $p=0.0496$). The subjects using both antipsychotic and benzodiazepine medication had also more suicidal ideation than subjects using either of those as monotherapy (mean 1.81 vs. 1.22, $p<0.001$). However, when adjusted for other symptoms (*SCL ratio*) neither did concomitant use of antipsychotic and antidepressant

medications, or antipsychotic and benzodiazepine medications, differ from the use of either of medications as monotherapy. There were no difference in suicidal ideation or in *SCL ratio* among those using antipsychotic and antiepileptic medication, antidepressant and benzodiazepine medication, antidepressant and antiepileptic medication, or benzodiazepine and antiepileptic medication, compared to use of either of medications.

The subjects using more than one antipsychotic had more suicidal ideation than subjects using only one antipsychotic (mean 1.86 vs. 1.33, p=0.04), however, this association was no longer statistically significant when adjusted for other symptoms. There was no statistically significant difference in suicidal ideation between subjects using only one or several antidepressants. However, the SCL ratio was statistically significantly lower among subjects using more than one antidepressants as compared to those using only one drug (mean 0.62 vs. 0.77, p=0.002). There were no statistically significant differences in suicidal ideation in polypharmacy of benzodiazepine or antiepileptic medications.

Table 5. Number of nervous system medications and suicidal ideation.

Number of nervous system medications	Suicidal ideation mean (SD)	SCL total[1] mean (SD)	SCL ratio[2] mean (SD)
None (n=7917)	1.04 (0.24)	1.34 (0.30)	0.80 (0.16)
One (n=224)	1.21 (0.55)	1.66 (0.48)	0.74 (0.23)
Two (n=55)	1.36 (0.65)	1.82 (0.46)	0.75 (0.24)
More than two (n=15)	1.67 (0.82)	2.18 (0.51)	0.74 (0.22)

Associations between number of used nervous system medications and suicidal ideation, SCL total, and SCL ratio were tested with trend of means -test.

[1] SCL total = Symptom Checklist-25 (SCL) total score without suicidal ideation

[2] SCL ratio = suicidal ideation adjusted for SCL total score without suicidal ideation

Polypharmacy	Antipsychotics	Antidepressants	Benzodiazepines	Antiepileptics
Antipsychotics	1.86 (1.03)[1] / 0.88 (0.29)	1.57 (0.73)[1]	1.81 (0.93)[2]	1.50 (1.00)
Antidepressants	0.77 (0.23)	1.14 (0.38) / 0.62 (0.08)[1]	1.44 (0.67)	1.50 (1.00)
Benzodiazepines	0.79 (0.26)	0.72 (0.24)	1.38 (0.62) / 0.69 (0.23)	1.31 (0.63)
Antiepileptics	0.75 (0.28)	0.75 (0.28)	0.73 (0.21)	1.00 (0.00) / 0.82 (0.08)

The differences between subjects using certain polypharmacy and subjects using only either of the two medications in question were tested using the Mann-Whitney U –test for suicidal ideation and Student's t-test for SCL ratio.
[1] $p < 0.05$
[2] $p < 0.001$

Fig. 2. The means and SDs of suicidal ideation are presented with grey ground colour and the means and SDs of SCL ratio with white ground colour.

6.2.2 Use of nervous system medications and suicidal ideation in groups by diagnoses and symptoms

Mental disorders and nervous system medications

The subjects having any mental disorder and using antipsychotic, antidepressant or benzodiazepine medication had more suicidal ideation than those subjects not using those medications (Table 6). However, subjects using those medications also had a greater prevalence of other symptoms of depression and anxiety (*SCL total*) and when suicidal ideation was adjusted for these symptoms, there were no statistically significant differences. Subjects having any mental disorder and using antiepileptic medication did not differ from those not using medication.

Among subjects not having any known mental disorder, the use of antipsychotic medication associated with higher suicidal ideation (mean 1.17 vs. 1.03, p=0.048). However, this association disappeared after adjusting for other symptoms of depression and anxiety. Use of antidepressant, benzodiazepine, or antiepileptic medication was not associated with increased suicidal ideation. Subjects using antipsychotic or benzodiazepine medication had significantly more symptoms of depression and anxiety than non-users. After adjusting the suicidal ideation for other symptoms (*SCL ratio*), subjects using benzodiazepine or

antiepileptic medication had lower scores than subjects not using those medications.

Psychosis and antipsychotic medication (I)

Of 69 antipsychotic users, 41 (59.4%) had diagnosis of schizophrenia, 10 (14.5%) had other psychoses, and 18 (26.1%) did not have any diagnosed psychosis. The association of antipsychotic medication and suicidal ideation in different diagnostic groups is shown in Table 7. Among subjects with psychotic diagnoses, either schizophrenia or other psychosis, there were no statistically significant differences in suicidal ideation between subjects using or not using antipsychotic medication. Among subjects without any diagnosed psychosis, those using antipsychotic medication had significantly more suicidal ideation and other symptoms of depression and anxiety (*SCL total*) than those not using medication. However, when suicidal ideation was adjusted for other symptoms (*SCL ratio*), antipsychotic-users had a lower mean score than controls.

Depression and antidepressant medication (II)

Of 111 users of antidepressant medication, 99 (89.2%) had a diagnosis of any non-organic mental disorder. Depression was the diagnosis for 71 (64.0%) users of antidepressant medication, substance-use disorder was the only diagnosis for 14 (12.6%), whereas 11 (9.9%) users of antidepressant medication had substance-use disorder comorbid with depression. Psychosis was diagnosed in 19 (17.1%) users of antidepressant medication, 62 (55.9%) had other mental disorder (e.g. non-psychotic bipolar disorder, personality disorders, and subjects' self-reported other psychiatric disorder in the questionnaire), and 12 (10.8%) did not have any psychiatric diagnosis.

The associations between antidepressant medication and suicidal ideation in different diagnostic groups are shown in Table 8. There was no difference in crude or adjusted suicidal ideation between those using and those not using antidepressant medication among subjects with depression. The subjects not having diagnosed depression but using antidepressant medication had more suicidal ideation than those not using (mean 1.30 vs. 1.04, $p<0.001$). However, they had also more other symptoms of depression and anxiety, and after adjusting for the other symptoms the association disappeared.

Nervous system diagnoses and benzodiazepine medication (III)

Of 147 users of benzodiazepine medication, 90 (61.2%) had a diagnosis of any non-organic mental disorder, 21 (14.3%) had diagnosis of psychosis, 64 (43.5%) had diagnosis of depression, and 7 (4.8%) had diagnosis of epilepsy. The associations between the use of benzodiazepine medication and suicidal ideation are shown in Table 9. Both among subjects with psychosis and among subjects with depression the use of benzodiazepine medication associated with higher score of suicidal ideation. The use of benzodiazepine medication also associated with higher score of other symptoms of depression and anxiety (*SCL total*). When suicidal ideation was adjusted for other symptoms (*SCL ratio*), there were no associations. There were no association between use of benzodiazepine medication and suicidal ideation or symptoms of depression and anxiety among subjects with epilepsy.

Antidepressant or benzodiazepine medication and suicidal ideation by groups of insomnia (II, III)

Table 10 shows the associations between antidepressant and benzodiazepine medications and suicidal ideation among people with self-reported insomnia. The score of suicidal ideation was significantly higher among subjects with a high score of insomnia and using antidepressant medication than among those having a high score in insomnia but not using antidepressant medication (mean 1.63 vs. 1.22, $p=0.01$). This finding was significant even when adjusted for other symptoms (*SCL ratio* mean 0.78 vs. 0.68, $p=0.02$). Subjects with a low score of insomnia showed a significant difference in suicidal ideation between antidepressant medication users and non-users (mean 1.27 vs. 1.04, $p=0.001$), but with adjustment for other symptoms this association disappeared. The Spearman correlation coefficient between insomnia and suicidal ideation was 0.36 ($p<0.001$) for subjects using antidepressant medication, and 0.19 ($p<0.001$) for those not using antidepressant medication.

Among those who scored low for insomnia, the use of benzodiazepine medication was significantly associated with higher suicidal ideation (mean 1.26 vs. 1.04, $p<0.001$). However, when other symptoms were taken into account, the use of benzodiazepine medication was associated with lower score (*SCL ratio* mean 0.75 vs. 0.81, $p<0.001$). Among those who scored high for insomnia, there was no statistically significant difference in suicidal ideation between users of

benzodiazepine medication and non-users, but those using benzodiazepine medication had more other symptoms of depression and anxiety.

Epilepsy and antiepileptic medication (III)

Of 54 users of antiepileptic medication, 43 (79.6%) had a diagnosis of epilepsy, 13 (24.1%) had a diagnosis of any non-organic mental disorder, and 5 (9.3%) had neither of these. The associations between the use of antiepileptic medication and suicidal ideation are shown in Table 11. Among subjects diagnosed with epilepsy there were no statistically significant differences in suicidal ideation or symptoms of depression and anxiety between the those using antiepileptic medication and those not using them. Among subjects with no diagnosis of epilepsy there were no statistically significant difference in suicidal ideation, but the subjects using antiepileptic medication had statistically significantly more other symptoms of depression and anxiety than subjects not using antiepileptic medication (1.88 vs. 1.35, $p<0.001$).

Table 6. Association of nervous system medications and suicidal ideation in subjects having or not having a mental disorder.

Any non-organic mental disorder	Medication use	Suicidal ideation mean (SD)	SCL total score[1] mean (SD)	SCL ratio[2] mean (SD)
Yes (n=655)	All subjects (n=655)	1.26 (0.61)	1.69 (0.49)	0.75 (0.24)
	Antipsychotics (n=63)	1.46 (0.78)[3]	1.85 (0.52)[3]	0.78 (0.25)
	Antidepressants (n=99)	1.40 (0.71)[3]	1.86 (0.51)[4]	0.76 (0.27)
	Benzodiazepines (n=90)	1.43 (0.70)[4]	1.96 (0.48)[4]	0.72 (0.24)
	Antiepileptics (n=13)	1.31 (0.63)	1.89 (0.51)	0.70 (0.23)
No (n=7556)	All subjects (n=7556)	1.03 (0.19)	1.32 (0.28)	0.80 (0.15)
	Antipsychotics (n=6)	1.17 (0.41)[3]	1.68 (0.52)[3]	0.71 (0.15)
	Antidepressants (n=12)	1.08 (0.29)	1.41 (0.46)	0.79 (0.12)
	Benzodiazepines (n=57)	1.07 (0.26)	1.56 (0.40)[4]	0.72 (0.18)[4]
	Antiepileptics (n=41)	1.00 (0.00)	1.39 (0.27)	0.74 (0.14)[3]

Differences between medication users and non-users were tested using the Mann-Whitney U –test for suicidal ideation and Student's t-test for other variables.

[1] SCL total = Symptom Checklist-25 (SCL) total score without suicidal ideation

[2] SCL ratio = suicidal ideation adjusted for SCL total score without suicidal ideation

[3] $p < 0.05$

[4] $p < 0.001$

Table 7. Use of antipsychotic medication and suicidal ideation in diagnostic groups.

Diagnostic group	Antipsychotic use	Suicidal ideation mean (SD)	SCL total[1] mean (SD)	SCL ratio[2] mean (SD)
All subjects	no (n=8142)	1.05 (0.25)[4]	1.35 (0.32)[4]	0.80 (0.16)
	yes (n=69)	1.43 (0.76)[4]	1.84 (0.52)[4]	0.77 (0.25)
Schizophrenia	no (n=21)	1.14 (0.36)	1.67 (0.43)	0.70 (0.19)
	yes (n=41)	1.54 (0.87)	1.89 (0.58)	0.79 (0.24)
Other psychosis	no (n=23)	1.26 (0.69)	1.66 (0.67)	0.77 (0.20)
	yes (n=10)	1.30 (0.48)	1.73 (0.34)	0.78 (0.34)
No psychosis	no (n=8098)	1.05 (0.25)[4]	1.34 (0.31)[4]	0.80 (0.16)[3]
	yes (n=18)	1.28 (0.58)[4]	1.77 (0.43)[4]	0.72 (0.20)[3]

Differences between medication users and non-users were tested using the Mann-Whitney U –test for suicidal ideation and Student's t-test for other variables.

[1] SCL total = Symptom Checklist-25 (SCL) total score without suicidal ideation

[2] SCL ratio = suicidal ideation adjusted for SCL total score without suicidal ideation

[3] $p < 0.05$

[4] $p < 0.001$

Table 8. Use of antidepressant medication and suicidal ideation in diagnostic groups.

Diagnostic group	Antidepressant	Suicidal ideation mean (SD)	SCL total score[1] mean (SD)	SCL ratio[2] mean (SD)
All subjects (N=8,211)	no (n=8,100)	1.05 (0.25)**	1.34 (0.31)**	0.80 (0.16)
	yes (n=111)	1.37 (0.69)**	1.81 (0.52)**	0.76 (0.26)
Any depression (n=372)	no (n=301)	1.28 (0.64)	1.72 (0.50)	0.75 (0.25)
	yes (n=71)	1.41 (0.69)	1.85 (0.50)	0.76 (0.27)
No depression (n=7,839)	no (n=7,799)	1.04 (0.22)**	1.33 (0.29)**	0.80 (0.15)
	yes (n=40)	1.30 (0.69)**	1.74 (0.56)**	0.75 (0.23)

Differences between medication users and non-users were tested using the Mann-Whitney U –test for suicidal ideation and Student's t-test for other variables.

[1] SCL total = Symptom Checklist-25 (SCL) total score without suicidal ideation

[2] SCL ratio = suicidal ideation adjusted for SCL total score without suicidal ideation

[3] $p < 0.05$

[4] $p < 0.001$

Table 9. Use of benzodiazepine medication and suicidal ideation in diagnostic groups.

Diagnostic group	Benzodiazepines	Suicidal ideation mean (SD)	SCL total score[1] mean (SD)	SCL ratio[2] mean (SD)
All subjects (N=8,211)	no (n=8064)	1.05 (0.25)[4]	1.34 (0.31)[4]	0.80 (0.16)[4]
	yes (n=147)	1.29 (0.60)[4]	1.80 (0.49)[4]	0.72 (0.22)[4]
Psychosis (n=95)	no (n=74)	1.27 (0.63)[3]	1.67 (0.53)[4]	0.77 (0.23)
	yes (n=21)	1.67 (0.91)[3]	2.13 (0.52)[4]	0.75 (0.25)
Depression (n=372)	no (n=308)	1.27 (0.64)[3]	1.69 (0.50)[4]	0.76 (0.25)
	yes (n=64)	1.47 (0.69)[3]	1.98 (0.46)[4]	0.74 (0.26)
Epilepsy (n=132)	no (n=125)	1.10 (0.39)	1.40 (0.37)	0.80 (0.19)
	yes (n=7)	1.29 (0.49)	1.48 (0.61)	0.88 (0.09)

Differences between medication users and non-users were tested using the Mann-Whitney U –test for suicidal ideation and Student's t-test for other variables.

[1] SCL total = Symptom Checklist-25 (SCL) total score without suicidal ideation

[2] SCL ratio = suicidal ideation adjusted for SCL total score without suicidal ideation

[3] $p < 0.05$

[4] $p < 0.001$

Table 10. Use of antidepressant or benzodiazepine medication and suicidal ideation in subjects with insomnia.

SCL insomnia	Medication	Suicidal ideation mean (SD)	SCL total score[1] mean (SD)	SCL ratio[2] mean (SD)
High (score 3-4)	All subjects (n=521)	1.24 (0.58)	1.81 (0.44)	0.69 (0.22)
	Antidepressant (n=30)	1.63 (0.85)[4]	2.02 (0.53)[3]	0.78 (0.24)[3]
	Benzodiazepine (n=50)	1.36 (0.66)	2.04 (0.47)[4]	0.66 (0.22)
Low (score 1-2)	All subjects (n=7,684)	1.04 (0.22)	1.32 (0.28)	0.81 (0.15)
	Antidepressant (n=81)	1.27 (0.59)[4]	1.73 (0.49)[4]	0.75 (0.26)
	Benzodiazepine (n=97)	1.26 (0.56)[4]	1.68 (0.46)[4]	0.75 (0.22)[3]

Differences between medication users and non-users were tested using the Mann-Whitney U –test for suicidal ideation and Student's t-test for other variables.

[1] SCL total = Symptom Checklist-25 (SCL) total score without suicidal ideation

[2] SCL ratio = suicidal ideation adjusted for SCL total score without suicidal ideation

[3] $p < 0.05$

[4] $p < 0.001$

Table 11. Use of antiepileptic medication and suicidal ideation in diagnostic groups.

Diagnostic group	Use of antiepileptics	Suicidal ideation mean (SD)	SCL total score[1] mean (SD)	SCL ratio[2] mean (SD)
All subjects N=8211	no (n=8157)	1.05 (0.26)	1.35 (0.32)[3]	0.80 (0.16)[3]
	yes (n=54)	1.07 (0.33)	1.51 (0.40)[3]	0.73 (0.17)[3]
Epilepsy (n=132)	no (n=89)	1.13 (0.46)	1.39 (0.40)	0.83 (0.20)
	yes (n=43)	1.05 (0.21)	1.42 (0.35)	0.76 (0.15)
No epilepsy (n=8079)	no (n=8068)	1.05 (0.26)	1.35 (0.32)[4]	0.80 (0.16)[4]
	yes (n=11)	1.18 (0.60)	1.88 (0.38)[4]	0.62 (0.19)[4]

Differences between medication users and non-users were tested using the Mann-Whitney U –test for suicidal ideation and Student's t-test for other variables.

[1] SCL total = Symptom Checklist-25 (SCL) total score without suicidal ideation

[2] SCL ratio = suicidal ideation adjusted for SCL total score without suicidal ideation

[3] $p < 0.05$

[4] $p < 0.001$

6.2.3 Dose of medication and suicidal ideation

In the entire sample, there was no difference in suicidal ideation between subjects using high or low doses of antipsychotic medication. However, the correlations between doses of antipsychotic medication and adjusted suicidal ideation (*SCL ratio*) were different when studied in diagnostic groups (shown in Figure 3). The Spearman correlation coefficients were 0.35 (p=0.03) for schizophrenia, -0.08 (p=0.85) for other psychoses, and 0.64 (p=0.01) for the subjects without any psychosis. In the test of interaction, the associations of medication dose and adjusted suicidal ideation (*SCL ratio*) were statistically significantly different in different diagnostic groups (t=-2.46, p=0.017).

The use of high doses of antidepressant medication (*DDD ratio* value >1.00) was associated with decreased suicidal ideation compared to the use of middle or low doses (mean 1.19 vs. 1.47, p=0.018) (Appendix Table 3). High doses of antidepressant medication also associated with less depression and anxiety symptoms (mean of *SCL total* 1.65 vs. 1.89, p=0.014). There were no statistically significant differences in suicidal ideation, *SCL total*, or *SCL ratio* between different doses of benzodiazepine or antiepileptic medication.

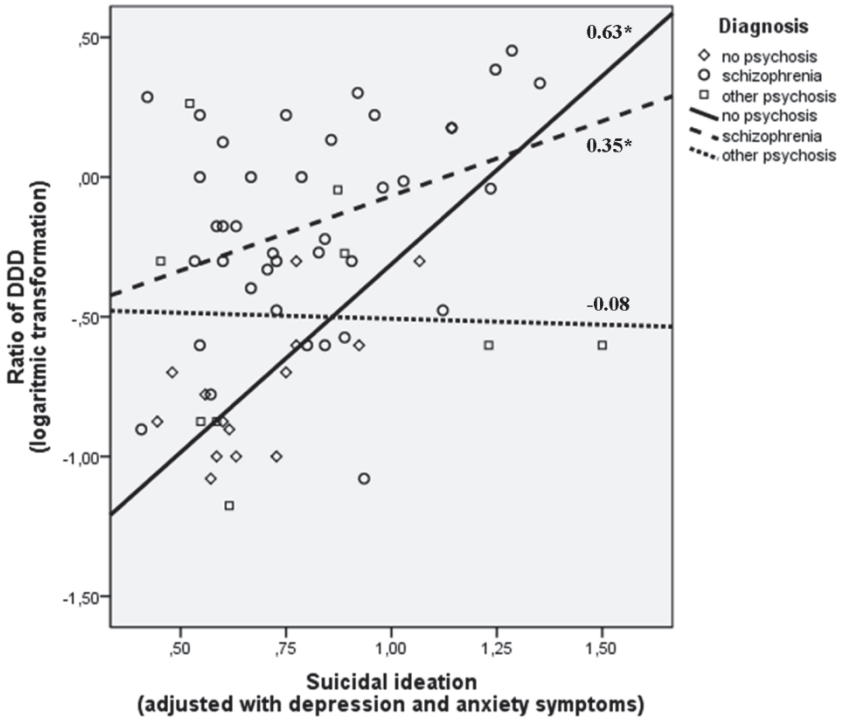

Fig. 3. Dose of antipsychotic medication and adjusted suicidal ideation in diagnostic groups.

6.2.4 Type of medication and suicidal ideation

There were no statistically significant differences in suicidal ideation between distinct antidepressant, benzodiazepine, or antiepileptic medication groups. Subjects using the antipsychotic class N05AD (butyrophenone derivatives, i.e. haloperidol) had more suicidal ideation than subjects using other classes of antipsychotics (Appendix Table 2). This difference, however, was no longer significant after adjusting for other symptoms (*SCL ratio*). There was no statistically significant difference between typical and atypical antipsychotics.

6.3 Additional analyses

6.3.1 Gender and suicidal ideation

The gender differences in associations of nervous system medications and suicidal ideation are presented in Table 12. Overall, males had more suicidal ideation than females (mean 1.06 vs. 1.04, $p<0.001$), even when adjusted for other symptoms of depression and anxiety (*SCL ratio* mean 0.82 vs. 0.78, $p<0.001$). However, females had higher mean of depression and anxiety symptoms (*SCL total* mean score 1.38 vs. 1.31, $p<0.001$). The associations between nervous system medications and suicidal ideation, *SCL total* score, and *SCL ratio* studied divided by subjects' gender did not differ from those studied in the whole sample.

Both among females and males the use of antipsychotic, antidepressant, or benzodiazepine medication associated with increased suicidal ideation. There were no association between the use of antiepileptic medication and suicidal ideation among females or males. However, among males antiepileptic medication was associated with increased symptoms of depression and anxiety (*SCL total*). When suicidal ideation was adjusted for other symptoms of depression and anxiety, females using benzodiazepine medication had lower mean score of *SCL ratio* than females not using medication. Males using antipsychotic, benzodiazepine or antiepileptic medication had lower mean scores of *SCL ratio* than males not using those medications.

6.3.2 Somatic medications and suicidal ideation

As comparison to nervous system medications, also the associations between the use of analgesic or cardiovascular system medication and suicidal ideation were studied. Overall, there was no difference in suicidal ideation between subjects using analgesic or cardiovascular medication and control population (Table 13). However, subjects using somatic medication had more other symptoms of depression and anxiety (*SCL total*), resulting the adjusted suicidal ideation (*SCL ratio*) to be lower among subjects using somatic medication than among controls.

Table 12. Gender differences in use of nervous system medication and suicidal ideation

Gender	Medication	Suicidal ideation mean (SD)	SCL total score[1] mean (SD)	SCL ratio[2] mean (SD)
Female (n=4,279)		1.04 (0.25)[3]	1.38 (0.33)[4]	0.78 (0.15)[4]
	Antipsychotic (n=34)	1.47 (0.79)[4]	1.83 (0.55)[4]	0.80 (0.28)
	Antidepressant (n=62)	1.27 (0.61)[4]	1.77 (0.51)[4]	0.74 (0.27)
	Benzodiazepine (n=85)	1.29 (0.63)[4]	1.80 (0.50)[4]	0.72 (0.22)[3]
	Antiepileptics (n=27)	1.00 (0.00)	1.44 (0.32)	0.73 (0.16)
Male (n=3,932)		1.06 (0.28)[3]	1.31 (0.30)[4]	0.82 (0.16)[4]
	Antipsychotic	1.40 (0.74)[4]	1.84 (0.50)[4]	0.74 (0.21)[3]
	Antidepressant (n=49)	1.49 (0.77)[4]	1.86 (0.53)[4]	0.79 (0.24)
	Benzodiazepine (n=62)	1.29 (0.56)[4]	1.80 (0.48)[4]	0.72 (0.22)[4]
	Antiepileptics (n=27)	1.15 (0.46)	1.58 (0.46)[3]	0.74 (0.17)[3]

Differences between medication users and non-users were tested using the Mann-Whitney U –test for suicidal ideation and Student's t-test for other variables.

[1] SCL total = Symptom Checklist-25 (SCL) total score without suicidal ideation

[2] SCL ratio = suicidal ideation adjusted for SCL total score without suicidal ideation

[3] $p < 0.05$

[4] $p < 0.001$

Table 13. Use of analgesics or cardiovascular system medication and suicidal ideation.

Medication	Suicidal ideation mean (SD)	SCL total[1] mean (SD)	SCL ratio[2] mean (SD)
No analgesics (n=7596)	1.05 (0.26)	1.34 (0.32)[3]	0.80 (0.16)[3]
Analgesics (n=615)	1.07 (0.30)	1.44 (0.36)[3]	0.76 (0.17)[3]
No cardiovascular system (n=8043)	1.05 (0.26)	1.35 (0.32)[3]	0.80 (0.16)[3]
Cardiovascular system (n=168)	1.08 (0.35)	1.53 (0.42)[3]	0.73 (0.16)[3]

Differences between medication users and non-users were tested using the Mann-Whitney U –test for suicidal ideation and Student's t-test for other variables.

[1] SCL total = Symptom Checklist-25 (SCL) total score without suicidal ideation

[2] SCL ratio = suicidal ideation adjusted for SCL total score without suicidal ideation

[3] $p < 0.001$

6.4 Nervous system medications and suicide attempts and suicides in the register sample

The associations of the use of nervous system medications and suicide attempts and suicides during the follow-up (15 years for suicide attempts, and 14 years for

suicides) were studied in the register sample (N=10,799). According to the registers, antipsychotic medication was used by 183 (1.7%) subjects, antidepressant medication by 311 (2.9%) subjects, benzodiazepine medication by 268 (2.5%) subjects, and antiepileptic medication by 92 (0.9%) subjects.

Of all subjects, 83 (0.8%) had made a suicide attempt between the years 1998 and 2012, and 48 (0.4%) had died by suicide between 1998 and 2011 (Table 14). The incidence of suicide attempts was statistically significantly increased among subjects using any nervous system medication (4.2%), antipsychotic medication (4.9%), antidepressant medication (5.8%), or benzodiazepine medication (6.0%) (for all $p<0.001$). The incidence of suicides was statistically significantly increased among subjects using antipsychotic medication (1.6%, $p=0.047$), antidepressant medication (1.3%, $p=0.049$), and benzodiazepine medication (1.5%, $p=0.031$). Among those using antiepileptic medication neither the incidence of suicide attempts or suicides was statistically significantly increased (for attempts $p=0.16$, for suicides $p=1.00$).

Table 14. Use of nervous system medications and incidence of suicide attempts and suicides in the register sample.

Medication	Suicide attempts 1998-2012 n (%)	Suicides 1998-2011 n (%)
Total (N=10,799)	83 (0.8%)	48 (0.4%)
Any nervous system (n=566)	24 (4.2%)[2]	5 (0.9%)
Antipsychotics (n=183)	9 (4.9%)[2]	3 (1.6%)[1]
Antidepressants (n=311)	18 (5.8%)[2]	4 (1.3%)[1]
Benzodiazepines (n=268)	16 (6.0%)[2]	4 (1.5%)[1]
Antiepileptics (n=92)	2 (2.2%)	0 (0.0%)

Differences between medication users and non-users were tested using the Fisher's exact test.

[1] $p < 0.05$

[2] $p < 0.001$

6.4.1 Polypharmacy of nervous system medications and suicide attempts and suicides

The incidence of suicide attempts or suicides increased with the polypharmacy of nervous system medications (Table 15). The linear association (Mantel-Haenzel Chi-Square test) between the number of used nervous system medications and suicide attempts was 126.04 ($p<0.001$), and between number of nervous system medications and suicides 8.08 ($p=0.004$).

6.4.2 Diagnostic group and medication and suicide attempts and suicides

Both among subjects having and subjects not having any mental disorder, the use of any nervous system medication, use of antidepressant medication, or use of benzodiazepine medication was statistically significantly associated with increased incidence of suicide attempts (Table 18). There was no association between the use of nervous system medications and suicides among subjects having or not having any mental disorder.

6.5 Relation of suicidal ideation and suicide attempts and suicides

Reported suicidal ideation was a risk factor of later suicide attempt and suicide. Of those 351 subjects who reported suicidal ideation in 1997, 13 (3.7%) made a suicide attempt between 1998 and 2012, and 4 (1.1%) died by suicide. Of those not reporting suicidal ideation, 31 (0.4%) later made a suicide attempt and 19 (0.2%) died by suicide. The odds ratio for suicide attempt was 9.7 (95% confidence interval (CI) 5.0-18.7) and 4.8 (CI 1.6-14.1) for suicide when reporting suicidal ideation.

Table 15. Use of nervous system medication polypharmacy and incidence of suicide attempts and suicides.

Number of nervous system medication	Suicide attempts 1998-2012 n (%)	Suicides 1998-2011 n (%)
None (n= 10,233)	59 (0.6%)	43 (0.4%)
One (n= 342)	11 (3.2%)	2 (0.6%)
Two (n= 166)	6 (3.6%)	0 (0.0%)
More than two (n= 58)	7 (12.1%)	3 (5.2%)

Mantel-Haenzel Chi-Square test 126.04 ($p<0.001$) for suicide attempts, and 8.08 ($p=0.004$) for suicides.

Table 16. Use of nervous system medications and incidence of suicide attempts and suicides in diagnostic groups.

Any non-organic mental disorder	Medication use	Suicide attempts n (%)	Suicides n (%)
No	Total (n=10291)	59 (0.6%)	36 (0.3%)
	Any nervous system (n=347)	8 (2.3%)[2]	1 (0.3%)
	Antipsychotics (n=51)	0 (0.0%)	0 (0.0%)
	Antidepressants (n=188)	4 (2.1%)[1]	0 (0.0%)
	Benzodiazepines (n=153)	5 (3.3%)[1]	1 (0.7%)
	Antiepileptics (n=72)	1(1.4%)	0 (0.0%)
Yes	Total (n=508)	24 (4.7%)	12 (2.4%)
	Any nervous system (n=219)	16 (7.3%)[1]	4 (1.8%)
	Antipsychotics (n=132)	9 (6.8%)	3 (2.3%)
	Antidepressants (n=123)	14 (11.4%)[2]	4 (3.3%)
	Benzodiazepines (n=115)	11 (9.6%)[1]	3 (2.6%)
	Antiepileptics (n=20)	1 (5.0%)	0 (0.0%)

Differences between medication users and non-users were tested using the Fisher's exact test.

[1] $p < 0.05$

[2] $p < 0.001$

6.6 Psychiatric diagnosis as a covariate in prediction of suicidal ideation

As sensitivity analyses, binary logistic regression analyses were performed to ascertain the effects of nervous system medications and any mental disorder on the likelihood of having suicidal ideation. This adjustment with any mental disorder was performed instead of using *SCL ratio* to study the sensitivity. The regression models were statistically significant ($p<0.05$) for any nervous system medication, antipsychotic medication, antidepressant medication, and benzodiazepine medication, but were not for antiepileptic medication. In all these statistically significant models, both the use of medication and the diagnosis of any mental disorder increased the likelihood of having suicidal ideation. The odds ratios (and 95% CIs) were 2.0 (1.4-2.8) for any nervous system medication, 2.2 (1.3-3.9) for antipsychotic medication, 2.0 (1.2-3.2) for antidepressant medication, and 2.4 (1.6-3.8) for benzodiazepine medication.

7 Discussion

7.1 Main findings

7.1.1 The associations between nervous system medications and suicidality

The associations between antipsychotic, antidepressant, benzodiazepine, and antiepileptic medications and suicidal ideation are summarised in Table 17. In general, both antipsychotic and antidepressant medications associated with increased suicidal ideation, but also with increased severity of other symptoms of depression and anxiety. When the suicidal ideation was studied in relation to other symptoms, the associations were no longer significant. Use of benzodiazepine medication was associated with increased suicidal ideation, and increased other symptoms of depression and anxiety. When the suicidal ideation was analysed in relation to other symptoms, benzodiazepine medication associated with lower suicidal ideation. The use of antiepileptic medication associated with increased symptoms of depression and anxiety, but not with suicidal ideation. Findings of other somatic medications, i.e. analgesic and cardiovascular system medication, were similar to antiepileptic medication.

The incidence of suicide attempts and suicides was increased among subjects using antipsychotic, antidepressant, or benzodiazepine medication. There was also a significant association between the use of any nervous system medication and suicide attempts. The use of antiepileptic medication was not associated with increased incidence of suicide attempts or suicides.

Table 17. Main results of association between medications and suicidal ideation.

Medication	Suicidal ideation	Symptoms of depression and anxiety	Adjusted suicidal ideation
Antipsychotics	+ +	+ +	N.S.
Antidepressants	+ +	+ +	N.S.
Benzodiazepines	+ +	+ +	-
Antiepileptics	N.S.	+	-
Analgesics	N.S.	+ +	-
Cardiovascular	N.S.	+ +	-

+/++ statistically significantly increased with p-value <0.05/0.001

- statistically significantly decreased with p-value <0.05

N.S. not statistically significant

7.1.2 The association between polypharmacy of nervous system medications and suicidality

The polypharmacy of nervous system medications was associated with suicidal ideation, suicide attempts, and suicides. When suicidal ideation was studied in relation to severity of other symptoms, the association disappeared. This finding shows that subjects using several medications have not only increased suicidal ideation but also increased severity of other symptoms of depression and anxiety. The incidence of suicide attempts and suicides increased with polypharmacy of nervous system medication showing that subjects using several medications have also tendency for suicidal behaviour.

7.1.3 The use of nervous system medications and suicidality in diagnostic groups

Subjects with any mental disorder and using antipsychotic, antidepressant, or benzodiazepine medication had increased suicidal ideation. This association did not remain after adjusting for other symptoms of depression and anxiety, showing that the severity ratings of other symptoms were even higher than the suicidal ideation. Among subjects without any mental disorder, only the use of antipsychotic medication was associated with increased suicidal ideation. Regarding suicide attempts, a significant association between the use of any nervous system medication, antidepressant, or benzodiazepine medication, and increased incidence of suicide attempts was seen both in the subjects with or

without any mental disorder. There were no statistically significant associations between antipsychotic or antiepileptic medication and suicide attempts. The number of suicides in the follow-up was too limited to study the use of nervous system medications and incidence of suicides in different diagnostic groups reliably.

The score of suicidal ideation was significantly higher among subjects with a high score of insomnia and using antidepressant medication than among those having a high score of insomnia but not using antidepressant medication. This finding was significant even when adjusted for other symptoms of depression and anxiety.

7.1.4 The association between dose and type of nervous system medications and suicidal ideation

Among subjects with psychosis, the dose of antipsychotic medication did not correlate with suicidal ideation, but among subjects without psychosis, higher doses correlated strongly with increased suicidal ideation even when adjusted for severity of depression and anxiety symptoms. In the entire sample, the use of high doses of antidepressant medication was associated with decreased suicidal ideation and depression and anxiety symptoms compared to the use of middle or low doses. No correlation was found between the dose of benzodiazepine or antiepileptic medication and suicidal ideation. No difference in suicidal ideation was found depending on the type of antidepressant, benzodiazepine, or antiepileptic medication. Haloperidol was associated with more suicidal ideation than other antipsychotics.

7.2 Comparison to previous studies

7.2.1 Nervous system medications and suicidality in diagnostic groups

In the present study, the use of nervous system medications was studied without selecting subjects with specific diagnoses, unlike in most previous studies. Suicidal ideation and behaviour is related not only to mood disorders, but rather to all mental disorders and many somatic disorders (Harris & Barraclough 1998). In a previous study of subjects admitted to hospital after self-poisoning, 36% of

those not having any mental disorder had previously been prescribed psychotropic medication (Prescott & Highley 1985). It is therefore important to study the association between nervous system medications and suicidality without selecting subjects from specific diagnostic categories. Also in the present study, some subjects used nervous system medications without having any mental disorder (or epilepsy) which can be considered off-label use.

In the present study, the association between off-label use of nervous system medications and suicidality was studied. Off-label use is a complex concept. It can be defined as the use of a medication for an unapproved indication, or in an unapproved age group, unapproved dose, or unapproved form of administration (Stafford 2008). The EMA and the FDA regulate prescription drug marketing, not prescribing. The physicians are allowed to prescribe drugs for non-approved indications, and sometimes the off-label prescribing may even represent the standard of care with significant level of supporting evidence. For physicians, the knowledge of on-label and off-label indications is not always easily available. It has been found that physicians' beliefs that a certain drug use was indicated on-label correlated with the level of evidence supporting such use (Chen *et al.* 2009).

Antipsychotic medication and suicidality

The association between antipsychotic medication and increased suicidal ideation was seen among those without psychosis or any mental disorder. There was no association among those who had schizophrenia or other psychosis. Also, the dose of antipsychotic medication correlated with the severity of suicidal ideation among those without psychosis, but not among those with psychosis. The use of antipsychotic medication among those not diagnosed with psychosis can be considered as off-label use. It is not known how a long-term use of antipsychotic medication affects a healthy, non-psychotic person (Maglione *et al.* 2011). It is possible that antipsychotic medication is not fully suitable for non-psychotic people and in off-label use, antipsychotic medication may have increased harmful adverse effects, such as increased suicidal ideation. Of course the present finding that off-label use of antipsychotic medication was associated with increased suicidal ideation may also be explained if antipsychotic medication was used to treat severe depression and anxiety symptoms co-occurring with suicidal ideation.

Off-label use of antipsychotic medication has increased during recent decades (Alexander *et al.* 2011, Domino & Swartz 2008, Leslie *et al.* 2009, Maglione *et al.* 2011, Pringsheim & Gardner 2014). Majority of psychiatrists asked about their

medication prescribing practices reported the use of antipsychotic medication as anxiolytics as being a reasonable practice, based mainly on their personal experience rather than the literature (El-Khayat & Baldwin 1998). There is some evidence of efficacy of off-label use of antipsychotic medication e.g. in dementia, generalised anxiety disorder, or obsessive compulsive disorder, but these results are based on small studies with short follow-up times, and in many other conditions there is no evidence of efficacy (Maglione *et al.* 2011). Adverse effects are common in off-label use of antipsychotic medication.

The data are limited considering the off-label use of antipsychotic medication and the risk of suicidality. In a previous study of the use of quetiapine in depression, the risk of suicidality did not differ between quetiapine and a placebo (Weisler *et al.* 2014). As far as it is known by the author, there are no other studies on the association between off-label use of antipsychotic medication and suicidality.

Antipsychotics block D2 receptors which causes certain side effects (Stahl 2008). Higher doses of antipsychotic medication cause more side effects that detract from the quality of life and may cause anhedonia and depressiveness that may result in increased suicidality (Adrianzen *et al.* 2010, Ernst & Goldberg 2004, Mihanovic *et al.* 2010). The lower dopaminergic activity found in people with depression has been reported to associate with suicidality (Roy *et al.* 1992). In the present study, among non-psychotic subjects, the higher doses of antipsychotic medication associated with increased suicidal ideation, even when adjusted with symptoms of depression and anxiety. Higher D2 receptor occupancy is associated with negative symptoms and depression, and individuals with a lower dopamine levels at baseline have an increased risk of such responses (de Haan *et al.* 2004). The lower baseline dopamine levels in non-psychotic subjects, and the related increase in dysphoric responses, may be one explanation for this finding.

Antidepressant medication and suicidality

In the present study, antidepressant medication was associated with increased suicidal ideation among those without depression, but not among those with depression. Subjects using antidepressant medication without having received a diagnosis of depression might have other, more severe, mental disorders which may explain their higher suicidal ideation, and higher symptoms of depression and anxiety. Especially bipolar disorder and borderline personality disorder have previously been associated with increased suicidality. In bipolar disorder, the

suicide mortality is 8% (WHO 2014). Antidepressant medication, especially as monotherapy, may increase the suicidality of people with bipolar disorder by inducing mixed or manic episodes, e.g. when used after misdiagnosed as depression (McElroy *et al.* 2006). Of people with borderline personality disorder, up to 10% die by suicide and 60-70% make suicide attempt (Black *et al.* 2004, Oldham 2006). The comorbidity of mental disorders, especially depression and substance use disorder increases the risk. Antidepressant-induced suicide-related events are more common among adolescents with borderline personality disorder than with adolescents without the disorder (Kuba *et al.* 2011), suggesting that borderline personality disorder may play a role in increased suicidality when using antidepressant medication. In the present study bipolar disorder or borderline personality disorder were not studied separately from other mental disorders.

When studying those not having any mental disorder in the present study, there was no difference in suicidal ideation between those using and those not using antidepressant medication. Among people with depression and comorbid substance use disorder there was no difference in suicidal ideation between subjects using or not using antidepressant medication that is consistent with previous studies (results shown in original publication II). The risk of suicidality is increased in substance use disorders, especially when comorbid with other mental disorders, e.g. depression (Suokas *et al.* 2011, Davis *et al.* 2012). However, the outcomes of antidepressant medication, including suicidality outcomes, seem to be similar in depression despite whether a subject has a concomitant substance use disorder or not (Davis *et al.* 2012).

In a recent study, those who had persistent suicidality during the 12-weeks treatment of depression were more likely to use antidepressant medication compared to those who resolved their suicidality during the treatment (Seo *et al.* 2014). Additionally, more than one third of those who responded to antidepressant treatment had persistent suicidality, suggesting that improvement of depressive symptoms may not result improvement of suicidal ideation (Seo *et al.* 2014). These findings are contrary to present findings showing that subjects using antidepressant medication with suicidal ideation had also more severe symptoms of depression and anxiety, which might be due the differences in study design and samples. In another study, the subjects with more severe symptoms of depression were more likely to use antidepressant medication than subjects with less severe symptoms, and when controlling for the severity of symptoms, the risk of suicide

attempt or suicide reduced by 20% among those using antidepressant medication (Leon *et al.* 2011).

The FDA's black box warning of potential emergence of suicidality in children and adolescents using antidepressant medication (Laughren 2006) can be considered also as a warning against off-label use. The efficacy and safety of antidepressant medication has been studied primarily in adult samples, and the use of medication in other age groups can therefore be considered as off-label use. In the present study, all the subjects were aged 31 years old, and therefore the effect of age could not be studied.

The previous literature is limited in addressing the association between the dose of antidepressant medication and suicidal ideation. In the present study, subjects using high doses of antidepressant medication had less suicidal ideation and symptoms of depression and anxiety than subjects using lower doses. The dose of antidepressant medication correlates with the indication for medication, and the lower doses might be prescribed for other diagnoses than depression. It is possible that in these other indications, e.g. in insomnia, bipolar disorder, or borderline personality disorder, the antidepressant medication has harmful effects or does not have effect good enough on symptoms, e.g. suicidal ideation. It is also possible that antidepressant medication has a protective effect on suicidal ideation only when used with high doses (in the present study, daily dose higher than the average dose, DDD-ratio > 1).

Benzodiazepine medication and suicidality

In studies showing an association between the use of benzodiazepine medication and increased suicidality (Mallon *et al.* 2009, Voaklander *et al.* 2008), the findings are most likely to be at least partly confounded by the indication for medication and the severity of psychiatric symptoms of subjects using benzodiazepines. In the present study, subjects using benzodiazepine medication had increased severity of depression and anxiety symptoms together with increased suicidal ideation. Supporting the present study, in a large population-based study with an over ten-year follow-up, the use of benzodiazepine medication associated with an increased risk of severe anxiety and depression symptoms, even when the severity of baseline symptoms and potential confounders were controlled for (Nordfjaern 2012). In the present study, there was no evidence that use of benzodiazepine medication might increase suicidal ideation when studied in relation to other symptoms. However, in a previous

study the use of sedative-hypnotics was associated with an increased risk of suicidal ideation, plans, and attempts, even when adjusted for demographic characteristics, physical and mental disorders, and sleep disturbances (Brower *et al.* 2011). This might be due the differences in study design and sample, e.g. in Browen *et al.* (2011) the suicidality was adjusted for presence of mental disorders, unlike in the present study where the severity of symptoms was taken into account.

Antiepileptic medication and suicidality

In the present study, there were no association between the use of antiepileptic medication and suicidal ideation, suicide attempts, or suicides in any diagnostic group. In a previous large population-based study, the use of antiepileptic medication did not associate with increased risk of suicide-related events among people with epilepsy or bipolar disorder, but associated among people with depression or those without epilepsy, depression or bipolar disorder considered as off-label use (Arana *et al.* 2010). In another study, there were no statistically significant differences in suicide-related behaviour between elderly subjects using antiepileptic medication for new-onset epilepsy and for other indications (VanCott *et al.* 2010), supporting the present findings. Though the present study did not find association between antiepileptic medication and suicidal ideation among those without epilepsy, among them an association between antiepileptic medication and increased severity of depression and anxiety symptoms was found.

In the antiepileptic medication meta-analysis of FDA, the risk of suicidal behaviour was found to be higher than the risk of suicidal ideation (US Food and Drug Administration). One explanation is that antiepileptic medication might be associated with increased depression and anxiety resulting impulses of suicidal acts, instead of merely suicidal ideation. Contrary to findings of present study, in FDA's study the highest risk of suicidality was revealed in the epilepsy indication subgroup, compared to psychiatric indications, or other indications.

In the present study, the different epilepsy types or seizure-related factors, e.g. seizure frequency, were not studied separately. Previously it has been suggested that suicidal ideation might not be associated with the epilepsy type or severity (Hecimovic *et al.* 2012).

7.2.2 Insomnia, nervous system medication and suicidal ideation

For safe and effective treatment of mood disorders, it is essential to identify those who might be at higher risk of suicidal ideation. The findings of the present study suggest that individuals with insomnia might be vulnerable to suicidal ideation while using antidepressant medication. Previously insomnia has been associated with increased suicidal ideation as it may decrease quality of life, and by that mechanism lead to increased suicidality (Lee *et al.* 2010). The association between insomnia and suicidality might be independent of depression and anxiety symptoms, especially in borderline personality disorder and chronic pain (Winsper & Tang 2014).

Benzodiazepine medication was associated with increased sleeping difficulties even when adjusted for severity of them at baseline in a previous large population-based cohort study (Nordfjaern 2012). Suggested by previous literature and the present findings, benzodiazepine medication is associating to increased symptoms of depression and anxiety, including insomnia. However, subjects with high insomnia and using benzodiazepine medication were not especially vulnerable to suicidal ideation.

7.2.3 Polypharmacy of nervous system medications and suicidality

The association between polypharmacy of nervous system medications and suicidality has also been found in previous studies. The use of multiple medications increases the risk of medication-related adverse events and drug interactions (NASMHPD 2001). Of those subjects admitted to hospital after self-poisoning and using any prescribed drugs, 31% used multiple psychotropic drugs, and the use of psychotropic polypharmacy was associated with repeated self-poisonings (Prescott & Highley 1985). Of subjects with bipolar disorder, those who had history of suicide attempt were more likely to use more than three psychotropic drugs than those who did not have a previous suicide attempt (Goldberg *et al.* 2009).

In the present study, the subjects using several antipsychotic medications had increased suicidal ideation compared to those using only one medication. This finding, however, was no longer significant after adjustment for severity of depression and anxiety symptoms. In a previous Finnish study on polypharmacy on people with schizophrenia, those using two or more concomitant antipsychotic medications did not have increased suicide mortality compared to those using

only one medication (Tiihonen *et al.* 2012). In that study, all-cause and suicide mortality rates were lowest among those people with schizophrenia that use both antipsychotic and antidepressant medication compared to those not using these medications (Tiihonen *et al.* 2012). In the present population-based study, the association between polypharmacy of nervous system medications and suicidality were not studied separately in people with schizophrenia. Here the use of concomitant antipsychotic and antidepressant medication associated with increased suicidal ideation.

In the present study, subjects using both antipsychotic and benzodiazepine medication had increased suicidal ideation. Previously, people with schizophrenia using concomitant benzodiazepine medication with antipsychotic or antidepressant medication had higher mortality, including suicide mortality, than those not using concomitant benzodiazepine medication (Tiihonen *et al.* 2012). This is in line with present findings of the use of concomitant benzodiazepine and antipsychotic medication, but here an increased suicidal ideation among those using concomitant benzodiazepine and antidepressant medication was not found. This might be due the differences in study samples, as Tiihonen and colleagues studied only people with schizophrenia and their mortality (Tiihonen *et al.* 2012). However, in another population-based cohort study, the concomitant use of benzodiazepine and antidepressant medication associated with increased risk of suicide attempt when compared to either antidepressant or benzodiazepine medication alone (Neutel & Patten 1997).

As this was a cross-sectional and non-randomised study, it was not possible to investigate the causal relationships between the polypharmacy of nervous system medications and increased suicidality. The associations seen here are more or less confounded by the severity and amount of underlying conditions that can cause suicidality by themselves.

7.3 Mechanisms of nervous system medication predisposing to suicidal ideation and behaviour

The mechanisms by which nervous system medications relate to increased suicidality are still unclear. The present study was not able to study causal relationships between nervous system medications and suicidality. It is possible that the associations found here might be due to different prescription practises for individuals that have suicidal tendency before initiation of medication. It is also possible that some individuals are more vulnerable to suicidal ideation and

behaviour, and do not respond to medication as expected, or might even generate new suicidal ideation or behaviour after starting the medication.

The nervous system medications can paradoxically worsen the mood of some individuals, or they can have undesired side effects, such akathisia and sleep disturbances, that decrease quality of life and by that mechanism increase suicidal tendency (Mihanovic *et al.* 2010). The discontinuation symptoms related to irregular use of nervous system medications may also contribute to increased anxiety and suicidality (Valuck *et al.* 2009).

Antipsychotics block D2 receptors which causes certain side effects, e.g. akathisia, anhedonia, dysphoria, or depressiveness, that may result in increased suicidality (Stahl 2008). The higher D2 receptor occupancy in mesocorticolimbic dopamine system is associated with more severe dysphoria and other side effects (Voruganti & Awant 2004). The higher receptor occupancy is seen with high-potency antipsychotics (usually typical antipsychotics), antipsychotics with predominant D2 blocking effects, and higher doses of antipsychotics. The dysphoric-depressive responses are known side effects of antipsychotic medication despite the diagnosis they are used for (Voruganti & Awant 2004), and it remains unknown how the blockade of D2 receptors affects the brain of non-psychotic individuals. However, it should be noted that only a few of individuals using antipsychotic medication experience dysphoria, suggesting that blockade of D2 receptors is not the only cause of dysphoria or suicidality, but some individuals might have innate (genetic) vulnerability to these responses. The vulnerability may be due the variations in dopaminergic function or modulation of dopaminergic activity by serotonin, acetylcholine, or other neurotransmitters (Voruganti & Awant 2004).

Antidepressants are suggested to have short-term activating effect, giving an individual some energy before improving the mood and by that mechanism increasing suicidal impulses. Antidepressants are suggested to cause asynchronous cognitive and psychomotor activation that may even increase suicidal ideation, and they may act on suicidality more slowly than on other symptoms (Mihanovic *et al.* 2010). Antidepressants may also increase the intensity of already present suicidal predictors such as dysphoria, anxiety, impulsiveness, aggression, agitation, and restlessness (Mihanovic *et al.* 2010). Abnormalities in the functioning of serotonergic system, e.g. serotonin receptors that are targets of antidepressants, are supposed to be involved in the pathogenesis of suicidality (Tsai *et al.* 2011), and these abnormalities might explain why antidepressants increase suicidality in some individuals. Multiple

pharmacogenetic studies have been conducted in recent years to identify the genetic vulnerability to antidepressant-induced suicidality (Tsai *et al.* 2011). Associations between antidepressant-induced suicidality and genes involved in neuroprotection, transcription, glutamatergic and noradrenergic neurotransmission, inflammatory and stress response, and synthesis of glycoproteins have been reported (Brent *et al.* 2010).

Benzodiazepines are reported to increase impulsivity and aggression (Weisman *et al.* 1998, Lane *et al.* 2005). The higher levels of neurotransmitter GABA have been associated with increased impulsivity and suicidality (Lee *et al.* 2009), and by enhancing the GABA functions benzodiazepines may therefore increase suicidality. However, the association between benzodiazepines and suicidality has not been sufficiently studied, and there is not enough evidence to formulate proper hypotheses regarding their association.

The previous data are limited on how the polypharmacy of nervous system medications affects in the brain. The evidence on safety and efficacy of certain nervous system medications are based on studies of monotherapy of drugs. It is unknown if the association between polypharmacy and increased suicidality seen in the present study could be explained with biological mechanism by which polypharmacy increases the suicidality. Surely, the more medications in use, the more harmful side effects there might be. In the polypharmacy of nervous system medications these adverse side effects on suicidality can be additive, as e.g. the D2 blockade of antipsychotics can cause dysphoria and the GABA enhancing of benzodiazepines can cause impulsivity, both leading to increased suicidality. Also, harmful pharmacodynamic and pharmacokinetic interactions, cumulative neurotoxicity, medication errors, excessive dosing, and off-label use of medications are possible mechanisms to increased suicidality in polypharmacy (Stahl 2008).

7.4 Somatic medications and suicidal ideation

There has been debate whether some medications for somatic disorders might increase the risk of suicidality (Thomas *et al.* 2014). As comparison to nervous system medications, also the use of analgesic or cardiovascular system medications was studied in the present study. There was no association between somatic medications and suicidal ideation, but those using somatic medications had more symptoms of depression and anxiety than control population.

The presence of pain condition has been found to associate with suicidal ideation and behaviour even after adjusting for mental disorders (e.g. mood disorders and psychological distress), and other medical and demographic covariates (Braden & Sullivan 2008). The lifetime prevalence of suicidal ideation is about 20% in chronic pain (Tang & Crane 2006). The chronic pain conditions have also been associated with increased depression and anxiety (Gerrits *et al.* 2015). Of analgesic medications, opioids have been associated with increased risk of suicidal ideation and behaviour, but this is mainly due their non-medical use (Kuramoto *et al.* 2012).

Heart disease has also been associated with increased depression and anxiety (Scott *et al.* 2010). The subjects with coronary artery disease had about two-fold risk of suicide compared to controls in a previous study from Northern Finland (Mainio *et al.* 2010). The risk of suicide is increased after myocardial infarction in subjects with or without mental disorders (Larsen *et al.* 2010). In a study of subjects with coronary artery disease, depression and anxiety symptoms were risk factors of suicidal ideation (Nascimento *et al.* 2015). However, the literature is limited on how medications for heart diseases associate with the risk of suicidal ideation and behaviour.

In the present study, only the use of analgesic or cardiovascular system medications was studied, and not the presence of pain conditions or cardiovascular system diseases. The use of these somatic medications was not associated with increased suicidal ideation.

7.5 Strengths and limitations

7.5.1 Methodological discussion

The prevalence of suicidal ideation depends on the method of assessing it (Vuorilehto *et al.* 2014), and there is no globally accepted standard measure recommended for population-based studies (Batterham *et al.* 2014). In the present study, the severity of suicidal ideation was measured by one question from Hopkins Symptom Checklist-25 (SCL) questionnaire measuring symptoms of depression and anxiety, which might not have optimal sensitivity and specificity for suicidal ideation. In a recent systematic review, none of the comprehensive measurement scales for suicidality was found to be optimal for population-based studies of adults, but Beck Scale for Suicide Ideation (BSSI) and Adult Suicidal

Ideation Questionnaire (ASIQ) were promising (Batterham *et al.* 2014). However, for large population-based samples, the comprehensive measures need more financial and human resources, and training or special professional qualifications, than brief measures. Of the brief measures, Depressive Symptom Index Suicidality Subscale (DSI-SS), Suicidal Behaviors Questionnaire-Revised (SBQ-R), and Suicidal Ideation Attributes Scale (SIDAS) had good potential for population-based studies (Batterham *et al.* 2014). DSI-SS and SBQ-R both consist of four items and were developed to be brief screeners of suicide risk in general health settings or clinical or non-clinical settings. SIDAS consists five items and was developed for population-based research, focusing on Internet-based research. The SCL questionnaire used in this study was not developed for assessing suicidality as a separate phenomenon, and it is validated only for screening psychiatric disorders, also in the NFBC 1966 (Veijola *et al*. 2003).

In general, suicidal ideation is more severe and more uncommon symptom than the other symptoms of depression and anxiety, and therefore, when comparing the mean scores of suicidal ideation and other items of depression and anxiety questionnaire, the less severe symptoms were more common than suicidal ideation. Using the *SCL ratio* may be rather conservative method as studying the suicidal ideation in relation to other symptoms of depression and anxiety. The results showing this adjusted suicidal ideation to be lower among subjects using a certain medication do not show that the medication protects from suicidal ideation. Results suggest that the medication is associated with relatively less suicidal ideation than with other symptoms, as the medication associates also with more severe symptoms of depression and anxiety. Previously, e.g. the severity of depressive symptoms, comorbid depression and anxiety disorder, insomnia, anhedonia, or feeling of inferiority have been suggested to be risk factors of suicidal ideation (Lee *et al.* 2010, Spijker *et al.* 2010). Therefore the severity of symptoms should be assessed for identification of those at greater risk of suicidal ideation.

The *SCL ratio* was selected as adjustment method instead of using multivariate analyses (e.g. ordinal regression) due the small sample sizes in some groups. However, binary logistic regression analyses were performed to ascertain the effects of any nervous system medications and any mental disorder on the likelihood of having suicidal ideation as sensitivity analyses for *SCL ratio*. The results of these sensitivity analyses were similar to those results of *SCL ratio*.

It should be noted that several bivariate analyses were performed and thus some of the statistical significances might have occurred by chance. However,

most of the significances were with p-value <0.001, which may minimize the issue.

The statistical power of the study was limited in some sub-group analyses. The number of suicide attempts and suicides in the follow-up was too limited to reliably study the use of nervous system medications and their incidence in different diagnostic groups. For instance, there were only five subjects using any nervous system medication who died by suicide during the 14-year follow-up. Also when studying suicidal ideation, some diagnostic groups were too limited to reach statistical power, e.g. when studying associations between benzodiazepine medication and suicidal ideation among people with epilepsy, instead of current 7 people using benzodiazepine medication, 28 people would have given the power of 80%.

7.5.2 Strengths of the study

The main strength of the present study was the unselected, population-based birth cohort data that enabled studying the use of nervous system medications and suicidality in a real-world setting, regardless of the indication for medication. The birth cohort data are naturalistic, non-manipulative, and non-experimental, and thus suitable for analysing associations between medications and suicidality outcomes with minimal selection and other biases. It was possible to adjust the suicidal ideation with the severity of depression and anxiety, and study the associations between medication use and suicidal ideation and behaviour in different diagnostic groups. In addition to questionnaire data, there were also broad register data enabling studying also those who did not answer the postal questionnaire. Haapea *et al.* (2010) have shown the questionnaire data on medications to be reliable and consistent with the register data of the same birth cohort. It is also a strength that clear majority (76%) of cohort members answered the questionnaire, and the total sample sizes were very large, over 8,000 in questionnaire data and nearly 11,000 in register data. The follow-up time for suicide attempts and suicides was long, up to 15 years.

The use of nervous system medications has previously been studied mainly in selected diagnostic groups, but in this sample also subjects without any mental disorders but using nervous system medication were included. Clinical trials are often considered as the golden standard of studying the safety and efficacy of medications, but e.g. clinical trials of antidepressant medication generalize poorly to the real world (Zimmerman *et al.* 2005). There has been a concern about poor-

quality reporting of harms in clinical trials (Ioannidis *et al.* 2004). Especially the reporting of suicidal ideation as an adverse effect in antidepressant medication trials is more inaccurate than reporting of suicides and suicide attempts (Maund *et al.* 2014). Subjects for clinical trials are usually selected, and the observation time is too short. The design adopted in the present study is preferred when studying the long-term side effects of various forms of medication (Wang *et al.* 2011).

7.5.3 Limitations of the study

There were several limitations in the present study. One main limitation is that the data were collected more than a decade ago, and many new nervous system medications have been introduced since 1997. At the time of the present study, only minority of subjects used atypical antipsychotics, when nowadays the use of them has become more common. Only eight subjects used clozapine. Also, the newer antiepileptics were used to a lesser extent than nowadays. In the questionnaire sample, no respondent stated they used lithium, and therefore associations between lithium and suicidal ideation could not be studied.

Subjects receiving nervous system medications were heterogeneous and at different phases in their illness and treatment, which may have affected the results. The exact purpose of medication was not known. The mean daily doses of antipsychotic and antiepileptic medications were rather low when compared to clinical samples. In general, it should be noted that suicidal ideation, suicide attempts, or suicides were rather rare phenomena in this population-based sample.

The sample sizes were small in some sub-groups studied, e.g. the amounts of subjects with bipolar disorder or borderline personality disorder were limited and therefore they could not be studied separately from other mental disorders. Bipolar disorder, borderline personality disorder, or many other diagnoses that have previously been associated with increased suicidality, were not asked separately in postal questionnaire. The exact history of mental disorders, e.g. the time spent in a depressive phase, was not known. The comorbidity of substance use disorders and mental disorders was studied only in original publication II.

The present study was mainly cross-sectional as studying the associations of present use of medication and present suicidal ideation. The duration of using nervous system medications or cumulative dose of medications were not known. Causal relationships between medication use and suicidality could not be studied. Of those using nervous system medications according to registers, only 64% answered the questionnaire. It is also possible that selected attrition may affect the

results, as those with nervous system medication participated less often than those without medications. Unidentified or residual confounding is a limitation on population-based research, however, in this study the use of nervous system medications was studied in different diagnostic groups and suicidal ideation was adjusted with severity of depression and anxiety symptoms.

In the present study, suicidal ideation was measured only by one question of SCL questionnaire, and even though SCL questionnaire is valid and reliable in measuring the symptoms of depression and anxiety, it is not designed for measuring suicidal ideation specifically. Previously it has been found that the agreement between different definitions of suicidal ideation is not very high, and the prevalence of suicidal ideation depends on the means of measuring the suicidal ideation (Valtonen *et al.* 2009, Vuorilehto *et al.* 2014). In measuring the severity of depression and anxiety, the self-reported SCL might be more inaccurate than clinical measures.

The data on suicide attempts may not be entirely comprehensive. It is possible that not all treated suicide attempts were registered which is most probable in the outpatient care registers in the present study. Information on suicide attempts where subject did not receive treatment in a health care facility were not available.

8 Conclusions

8.1 Main conclusions of the study

The use of antipsychotic, antidepressant, or benzodiazepine medication was associated with increased suicidal ideation, suicide attempts, and suicides. However, there was also an association with increased severity of depression and anxiety symptoms with all nervous system medications. When these other symptoms were taken into account, the use of antipsychotic, antidepressant, or benzodiazepine medication was no longer associated specifically with increased suicidal ideation. These results suggest that the use of these medications is not only associated with increased suicidal ideation, but also with other symptoms. Use of antiepileptic medication did not associate with increased suicidal ideation, suicide attempts, or suicides.

The polypharmacy of nervous system medications was related to increased suicidality. The greater number of nervous system medications the subjects were using, the higher the suicidal ideation score, along with a higher prevalence of suicide attempts and suicides. However, regarding suicidal ideation, the association of polypharmacy and ideation disappeared when adjusted for the severity of depression and anxiety symptoms.

The increased incidence of suicide attempts and suicides associating with nervous system medication could not be detected by the diagnosis of mental disorder. The suicidal ideation was increased for those using antipsychotic medication without any mental disorder. Particularly among those who did not have psychosis, the high doses of antipsychotic medication associated with increased suicidal ideation even when other symptoms were taken into account. Among those who had insomnia the use of antidepressant medication associated with increased suicidal ideation also when other symptoms were taken into account.

8.2 Implications of the study

The association between nervous system medications and suicidal ideation may be confounded by the severity of depression and anxiety symptoms. Although the medication associates with increased suicidal ideation, the association with other

symptoms was also strong, and therefore it could not be stated that medication associates to suicidal ideation as a specific symptom apart from other symptoms.

As a clinical implication of the study, those who are especially vulnerable to suicidal ideation, suicide attempts, and suicides while using a nervous system medication, cannot be detected by their clinical diagnosis. As the severity of depression and anxiety symptoms associates with suicidal ideation, an assessment of the severity of those symptoms might be beneficial in detecting those vulnerable to suicidal ideation. However, the current study was able to identify groups who might be at higher risk of suicidal ideation in particular, i.e. non-psychotic people using high doses of antipsychotic medication, and people with insomnia using antidepressant medication. These groups should be monitored continuously with extra caution in case of suicidality.

The polypharmacy of nervous system medications is associated with increased suicidal ideation, suicide attempts and suicides. The safety and efficacy of such medication polypharmacy has not been properly studied, and the polypharmacy might even have harmful effects. Health professionals should be careful when prescribing multiple nervous system medications. It seems that when using polypharmacy of nervous system medications, increased suicidal ideation occurs together with increased severity of other symptoms of depression and anxiety, and surveillance of these symptoms might be beneficial in detecting those vulnerable to suicidal ideation.

8.3 Implications for further research

Although some aspects of the association between the use of nervous system medications and suicidal ideation, suicide attempts, and suicides have been studied and discussed in the present thesis, there are still many aspects that have not yet been concluded. This epidemiological study provides many insights for future research.

In the present study, the severity of suicidal ideation was adjusted with the severity of depression and anxiety symptoms by forming a ratio of these. This method showed that the severity of suicidal ideation was closely related to the severity of other symptoms. In future studies, it would be useful to take into account the severity of depression and anxiety when studying suicidality, and not only the diagnoses of mental disorders. However, further studies are needed with additional methods for taking the symptom severity into account.

It remains to be seen whether the findings of association between polypharmacy of nervous system medications and suicidal ideation and behaviour can be confirmed in future studies. Further studies are also needed to confirm the results of present study showing that especially those without psychosis but using antipsychotic medication with high doses, and those with insomnia and using antidepressant medication, might be in increased risk of suicidal ideation regardless of the severity of their depression and anxiety.

Since 1997, many new nervous system medications have been introduced, and it is important to study the associations of these new medications and suicidal ideation, suicide attempts, and suicides. Especially the newer nervous system medications are used increasingly off-label, and their associations with suicidal outcomes are not fully known. These topics could be studied in future also by using the new follow-up data and national registers collected in the Northern Finland Birth Cohort 1966.

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Appendix

8.4 The ATC codes of nervous system medication

N03 ANTIEPILEPTICS

N03A ANTIEPILEPTICS (III)

N03AA Barbiturates and derivatives

N03AB Hydantoin derivatives, *e.g.* N03AB02 phenytoin

N03AC Oxazolidine derivatives

N03AD Succinimide derivatives

N03AE Benzodiazepine derivatives, *e.g.* N03AE01 clonazepam

N03AF Carboxamide derivatives, *e.g.* N03AF01 carbamazepine

N03AG Fatty acid derivatives, *e.g.* N03AG01 valproic acid

N03AX Other antiepileptics, *e.g.* N03AX12 gabapentin

N05 PSYCHOLEPTICS

N05A ANTIPSYCHOTICS (I)

N05AA Phenothiazines with aliphatic side-chain, *e.g.* N05AA01 chlorpromazine

N05AB Phenothiazines with piperazine structure, *e.g.* N05AB03 perphenazine

N05AC Phenothiazines with piperidine structure

N05AD Butyrophenone derivatives, *e.g.* N05AD01 haloperidol

N05AE Indole derivatives

N05AF Thioxanthene derivatives

N05AG Diphenylbutylpiperidine derivatives

N05AH Diazepines, oxazepines, thiazepines and oxepines, *e.g.* N05AH02 clozapine

N05AL Benzamides

N05AN Lithium

N05AX Other antipsychotics, *e.g.* N05AX08 risperidone

N05B ANXIOLYTICS (III)

N05BA Benzodiazepine derivatives (III), *e.g.* N05BA01 diazepam

N05C HYPNOTICS AND SEDATIVES (III)

N05CD Benzodiazepine derivatives, *e.g.* N05CD07 temazepam

N05CF Benzodiazepine related drugs, e.g N05CF01 zopiclone

N06 PSYCHOANALEPTICS

N06A ANTIDEPRESSANTS (II)

N06AA Non-selective monoamine reuptake inhibitors, *e.g.* N06AA09 amitriptyline

N06AB Selective serotonin reuptake inhibitors, *e.g.* N06AB03 fluoxetine

N06AF Monoamine oxidase inhibitors, non-selective

N06AG Monoamine oxidase A inhibitors, *e.g.* N06AG02 moclobemide

N06AX Other antidepressants, *e.g.* N06AX11 mirtazapine

N06C PSYCHOLEPTICS AND PSYCHOANALEPTICS IN COMBINATION (I, II)

N06CA Antidepressants in combination with psycholeptics, *e.g.* N06CA01 amitriptyline and psycholeptics

Table 1. Characteristics of participants and non-participants of the questionnaire.

Characteristics	Participants (n=8,211) n (%)	Non-participants (n=2,588) n (%)
Female	4,279 (80.6%)	1,033 (19.4%)
Male	3,932 (71.7%)	1,555 (28.3%)
Antipsychotics	94 (51.4%)	89 (48.6%)
Antidepressants	210 (67.5%)	101 (32.5%)
Benzodiazepines	156 (58.2%)	112 (41.8%)
Antiepileptics	55 (59.8%)	37 (40.2%)
Suicide attempt before 1997	50 (68.5%)	23 (31.5%)
Suicide attempt 1998-2012	44 (53.0%)	39 (47.0%)
Suicide 1998-2011	23 (47.9%)	25 (52.1%)

Table 2. Type of nervous system medication and suicidal ideation.

Medication	Suicidal ideation mean (SD)	SCL total score[1] mean (SD)	SCL ratio[2] mean (SD)
Antipsychotics (n=69, 0.8%)			
Typical (n=54, 78.3%)	1.31 (0.61)	1.75 (0.44)	0.75 (0.24)
Atypical (n=14, 20.3%)	1.79 (1.05)	2.14 (0.67)	0.80 (0.27)
N05AA (n=9, 13.0%)	1.33 (0.71)	1.88 (0.46)	0.71 (0.27)
N05AB (n=25, 36.2%)	1.24 (0.44)	1.71 (0.42)	0.73 (0.18)
N05AC (n=19, 27.5%)	1.63 (0.90)	1.84 (0.53)	0.86 (0.30)
N05AD (n=7, 10.1%)	2.14 (1.22)[3]	2.20 (0.66)[3]	0.95 (0.37)
N05AF (n=9, 13.0%)	1.11 (0.33)	1.59 (0.35)	0.71 (0.16)
N05AH (n=8, 11.6%)	2.00 (1.20)	2.13 (0.81)	0.89 (0.26)
N05AL (n=1, 1.4%)	1.00 (0.00)	1.17 (0.0)	0.86 (0.00)
N05AX (n=7, 10.1%)	1.57 (0.79)	2.18 (0.47)	0.70 (0.22)
Antidepressants (n=111, 1.4%)			
N06AA (n=25, 22.5%)	1.40 (0.65)	1.86 (0.53)	0.75 (0.19)
N06AB (n=77, 69.4%)	1.38 (0.73)	1.78 (0.52)	0.77 (0.27)
N06AG (n=6, 5.4%)	1.17 (0.41)	1.91 (0.63)	0.64 (0.18)
N06AX (n=10, 9.0%)	1.20 (0.42)	1.85 (0.34)	0.66 (0.22)
Benzodiazepines (n=147, 1.8%)			
N03AE (n=8, 5.4%)	1.13 (0.35)	1.80 (0.51)	0.64 (0.14)
N05BA (n=82, 55.8%)	1.30 (0.62)	1.87 (0.47)	0.70 (0.22)
N05CD (n=34, 23.1%)	1.24 (0.50)	1.75 (0.46)	0.72 (0.21)
N05CF (n=39, 26.5%)	1.38 (0.67)	1.80 (0.54)	0.77 (0.25)
Antiepileptics (n=54, 0.7%)			
N03AA (n=2, 3.7%)	1.00 (0.00)	1.17 (0.11)	0.86 (0.08)
N03AB (n=2, 3.7%)	1.00 (0.00)	1.63 (0.35)	0.63 (0.14)
N03AE (n=8, 14.8%)	1.13 (0.35)	1.80 (0.51)[3]	0.64 (0.14)
N03AF (n=33, 61.1%)	1.09 (0.38)	1.43 (0.36)	0.77 (0.16)[3]
N03AG (n=17, 31.5%)	1.00 (0.00)	1.46 (0.34)	0.72 (0.16)

Differences between medication users and non-users were tested using the Mann-Whitney U –test for suicidal ideation and Student's t-test for other variables.

[1] SCL total = Symptom Checklist-25 (SCL) total score without suicidal ideation

[2] SCL ratio = suicidal ideation adjusted for SCL total score without suicidal ideation

[3] $p < 0.05$

Table 3. Dose of nervous system medication and suicidal ideation.

Medication dose	Suicidal ideation mean (SD)	SCL total score[1] mean (SD)	SCL ratio[2] mean (SD)
Antipsychotics[4]			
Low dose (n=28)	1.29 (0.54)	1.79 (0.46)	0.73 (0.24)
High dose (n=34)	1.65 (0.92)	1.93 (0.57)	0.82 (0.25)
Antidepressants[5]			
Low dose (n=25)	1.48 (0.82)	1.94 (0.63)	0.75 (0.25)
Middle dose (n=49)	1.47 (0.77)	1.86 (0.53)	0.79 (0.30)
High dose (n=31)	1.19 (0.40)[3]	1.65 (0.39)[3]	0.74 (0.21)
Benzodiazepines[6]			
Low dose (n=47)	1.23 (0.52)	1.78 (0.44)	0.70 (0.20)
Middle dose (n=53)	1.34 (0.73)	1.78 (0.59)	0.75 (0.22)
High dose (n=36)	1.33 (0.54)	1.84 (0.40)	0.73 (0.26)
Antiepileptics[7]			
Low dose (n=18)	1.17 (0.51)	1.65 (0.48)	0.71 (0.18)
Middle dose (n=16)	1.00 (0.00)	1.35 (0.31)	0.77 (0.16)
High dose (n=15)	1.07 (0.26)	1.46 (0.32)	0.75 (0.15)

[1] SCL total = Symptom Checklist-25 (SCL) total score without suicidal ideation

[2] SCL ratio = suicidal ideation adjusted for SCL total score without suicidal ideation

[3] $p < 0.05$

[4] Subjects were classified into low or high dose categories based on the median value (0.50) of the defined daily dose (DDD) ratio. Differences between medication users and non-users were tested using the Mann-Whitney U –test for suicidal ideation and Student's t-test for other variables.

[5] Low, middle, or high dose based on the value 1.00 of DDD ratio (Low <1.00, middle =1.00, high >1.00). Kruskal-Wallis test for suicidal ideation and One-way ANOVA for other variables.

[6] Low, middle, or high dose based on tertiles of DDD ratio (0.75 and 1.00).

[7] Low, middle, or high dose based on tertiles of DDD ratio (0.40 and 0.60).

Original publications

I 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 Clin Exp 27: 476-485.

II Rissanen I, Jääskeläinen E, Isohanni M, Koponen H, Joukamaa M, Alaräisänen A & Miettunen J (2014) Use of antidepressant medication and suicidal ideation - the Northern Finland Birth Cohort 1966. Hum. Psychopharmacol Clin Exp 29: 559-567.

III Rissanen I, Jääskeläinen E, Isohanni M, Koponen H, Ansakorpi H & Miettunen J (2015) Use of antiepileptic or benzodiazepine medication and suicidal ideation - the Northern Finland Birth Cohort 1966. Epilepsy Behav: doi:10.1016/j.yebeh.2015.03.001.

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