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KRISTIINA KIVIMIES

AMPHETAMINE, CANNABIS AND OPIOID USE DISORDERS IN FORENSIC PATIENTS AND IN SCHIZOPHRENIA

KRISTIINA KIVIMIES

Amphetamine, Cannabis and Opioid Use Disorders in Forensic Patients and in Schizophrenia

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ABSTRACT

Schizophrenia is a severe mental disorder which is associated with considerable disability and human suffering. This thesis presents an investigation into possible differences in between amphetamine, cannabis and opioid use disorders among patients with psychosis in terms of how these disorders are associated with the risk of committing violent crime. The aim was also to estimate the prevalence of forensic patients diagnosed with psychosis prior to the index crime, and examine the correlations between psychiatric hospitalizations and amphetamine, cannabis and opioid use disorders in patients with schizophrenia. An additional objective was to obtain information on the role of opioid maintenance treatment in the treatment of patients with schizophrenia and opioid use disorder.

The data were obtained from the forensic psychiatric examination statements of all individuals (n = 206) who were involuntarily ordered to hospital treatment as forensic patients during the years 1996–1999 after having committed a violent crime (Study I and Study II). Data were gathered also from the medical files of 75 outpatients in Itäkeskus Psychiatric Outpatient Clinic, Helsinki, and of 75 inpatients in Kuopio University Hospital (Study III). The data on the use of opioid maintenance treatment among patients with schizophrenia (Study IV) included all patients with schizophrenia spectrum disorders who were undergoing involuntary treatment as forensic patients in Niuvanniemi Hospital in 2012 (n = 148).

In this study the prevalences of cannabis, amphetamine, and opioid use disorder (meaning harmful use or dependence) among forensic patients were all about 100-fold, when compared with the corresponding substance-related diagnoses among nonforensic patients. Among forensic patients, the diagnosis of psychosis was made before the index crime in over half of the cases (60%). Previous forensic mental examination could be a useful background marker among patients with psychosis who were later ordered to psychiatric treatment as forensic patients. In patients with schizophrenia, opioid use disorder is associated with significantly higher risk of hospitalization than either amphetamine or cannabis use disorder, but opioid maintenance treatment is rarely used in this subgroup.

Violent behaviour among patients with psychosis is associated with amphetamine, cannabis or opioid use disorder, but none of these substances is uniquely associated with the risk of offending. Opioid use disorder is associated with poorer outcome in patients with schizophrenia when compared to amphetamine or cannabis use disorders. Treatment of opioid use disorder requires more attention.

National Library of Medicine Classification: WM 200, WM 203, WM 275, WM 276, WM 284, WX 158, WX 205, W 740, W 860

Medical Subject Headings: Amphetamine-Related Disorders; Marijuana Abuse; Opioid-Related Disorders; Psychotic Disorders; Schizophrenia; Crime; Violence; Ambulatory Care; Hospitalization; Involuntary Treatment; Finland/epidemiology; Forensic Psychiatry; Retrospective Studies

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TIIVISTELMÄ

Skitsofrenia on vakava ja monimuotoinen psyykkinen häiriö, jolle on ominaista ajattelun tai havaitsemisen vääristymät sekä tunneilmaisujen poikkeavuudet. Psykoosisairauden oireisiin kuuluva väkivaltaisen käyttäytymisen riski on pieni, mutta kuitenkin suurempi kuin yleisväestöllä. Samanaikainen päihteiden käyttö heikentää hoitoennustetta.

Tutkimuksessa selvitettiin amfetamiinin, kannabiksen ja opioidien käyttöhäiriön yhteyttä psykoosia sairastavien henkilöiden tekemiin väkivaltarikoksiin (Tutkimus I). Lisäksi tutkittiin niiden oikeuspsykiatristen potilaiden, joiden psykoosisairaus oli diagnosoitu jo ennen väkivaltarikosta, suhteellista osuutta kaikista oikeuspsykiatrisista potilaista (Tutkimus II), miten amfetamiinin, kannabiksen ja opioidien käyttöhäiriö on yhteydessä skitsofreniapotilaiden toistuviin sairaalahoitojaksoihin (Tutkimus III) ja miten opioidikorvaushoito toteutuu opioidiriippuvaisten skitsofreniapotilaiden kohdalla (Tutkimus IV)

Tutkimusten I ja II aineisto kerättiin väkivaltarikoksiin syyllistyneiden ja tahdosta riippumattomaan hoitoon vuosina 1996–1999 määrättyjen henkilöiden mielentilatutkimuslausunnoista (n = 206). Tutkimusaineistoa kerättiin myös 75 avohoitopotilaan (Itäkeskuksen psykiatrinen klinikka, Helsinki) ja 75 sairaalahoidossa olleen potilaan (Kuopion yliopistollinen sairaala) (Tutkimus III) sekä 148 Niuvanniemen sairaalassa vuonna 2012 hoidossa olleen ja skitsofreniaa sairastavan oikeuspsykiatrisen potilaan potilasasiakirjoista (Tutkimus IV).

Tutkimustulosten mukaan amfetamiinin, kannabiksen ja opioidien käyttöhäiriö on oikeuspsykiatrisilla potilailla noin 100 kertaa yleisempää kuin päihdediagnoosien yleisyys kaikilla psykoosipotilailla. Yli puolella (60 %) oikeuspsykiatrisista potilaista psykoosisairaus on diagnosoitu jo ennen väkivaltarikosta, ja tieto aikaisemmin tehdystä mielentilatutkimuksesta auttaa psykoosipotilaan kohonneen väkivaltakäyttäytymisriskin tunnistamisessa. Skitsofreniaa sairastavilla henkilöillä opioidien käyttöhäiriöön liittyy selkeästi korkeampi riski toistuvista psykiatrisista sairaalahoitojaksoista kuin amfetamiinin tai kannabiksen käyttöhäiriöön. Opioidikorvaushoitoa on käytetty vain harvoin tässä potilasryhmässä.

Tulokset osoittavat sekä amfetamiinin, kannabiksen että opioidien käyttöhäiriön olevan yhteydessä psykoosipotilaiden väkivaltaiseen käyttäytymiseen. Opioidien käyttöhäiriö ennustaa skitsofrenian huonompaa hoitotasapainoa verrattuna amfetamiinin ja kannabiksen käyttöhäiriöön, joten siihen tulee kiinnittää erityistä huomiota.

Yleinen Suomalainen asiasanasto: amfetamiini; kannabis; opioidit; huumeiden käyttö; päihteet; väärinkäyttö; ongelmakäyttö; skitsofrenia; väkivaltaisuus; väkivaltarikokset; oikeuspsykiatria; avohoito; pakkohoito; epidemiologia; Suomi

”30-vuotiaana minulla menikin kaikki saatavilla olevat huumeet kyselemättä. Tätä jatkui 13 vuotta. Olin myös saanut skitsofreniadiagnoosin ja näin ollen olin psykoottinen sekakäyttäjä. Viinaa join ihan pirusti lopettaakseni pirin käytön. Ei se minuun tepsinyt, eikä varmasti kehenkään. Alkoholi ei korvaa huumeita eikä huumeet korvaa alkoholia. Jotakin lopettamisyrityksiä oli ja silloin en tiennyt, mihin kuuluin: mielenterveys- vai päihdepuolelle. Niin minun pompoteltiinkin kaksoisdiagnoosini kanssa paikasta toiseen. Mutta aineiden himo otti minusta yliotteen kerta toisensa jälkeen. Eikä tosiaankaan, yksinäinen raittius, riittänyt motiiviksi jatkaa selvin päin. Joten taas mentiin…”

- Stilleben (Niuvan Sanomat 2/2015)

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List of the original publications

This dissertation is based on the following original publications:

I Kivimies K, Repo-Tiihonen E, Tiihonen J. The substance use among forensic psychiatric patients. *Am J Drug Alcohol Abuse. 2012 Jul;38(4):273-7.*

II Kivimies K, Repo-Tiihonen E, Kautiainen H, Tiihonen J. Previous forensic mental examination is a useful marker indicating effective violence relapse prevention among psychotic patients. *Nord J Psychiatry. 2014 Jul;68(5):311-5.*

III Kivimies K, Repo-Tiihonen E, Kautiainen H, Maaranen P, Muhonen LH, Heikkinen M, Tiihonen J. Opioid abuse and hospitalization rates in patients with schizophrenia. *Nord J Psychiatry. 2016;70(2):128-32.*

IV Kivimies K, Repo-Tiihonen E, Kautiainen H, Tiihonen J. Comorbid opioid abuse is undertreated among future forensic patients with schizophrenia. *Submitted.*

Contents

Abbreviations

GAF	Global Assessment of Functioning
CRP	C-reactive protein
GWAS	Genome-wide association study
DALYs	Disability-adjusted life years
DSM	Diagnostic and Statistical Manual of Mental Disorders
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
HIV	Human immunodeficiency virus
ICD-10	International Classification of Diseases, tenth edition
NICE	The National Institute for Health and Care Excellence
NMDA	Anti-N-methyl-D-aspartate
OMT	Opioid maintenance treatment
SD	Standard deviation
THC	Δ 9-tetrahydrocannabinol
THL	National Institute for Health and Welfare
UNODC	United Nations Office on Drugs and Crime
WHO	World Health Organization

1 Introduction

Schizophrenia is a severe mental illness that affects the individual`s way of thinking, feelings, and behaviour. It has adverse effects on both the index individuals and people close to them, causes considerable human suffering, and has a significant impact on health and social systems, leading to substantial economic costs (Knapp et al., 2004; Lindström et al., 2007; Evensen et al., 2016).

Patients with schizophrenia have poorer outcomes than patients with other psychiatric disorders (Jobe and Harrow, 2005), and schizophrenic relapses are associated with worsening of symptoms, impaired functioning and cognitive deterioration. Patients with the condition are at risk of dropping out of school, losing their social contacts and the ability to work, and becoming homeless. Estimates of its prevalence vary, but the lifetime prevalence for nonaffective psychotic disorders in Finland was found to be 1.9%, with that for schizophrenia and schizoaffective disorder together being 1.2% (Perälä et al., 2007).

Around half of all patients with schizophrenia spectrum disorders have a history of substance use disorders during their lifetime (Regier et al., 1990; Koskinen et al., 2010; Sara et al., 2014a; Jørgensen et al., 2018). Psychiatric and substance use disorders are among the main causes of years lived with disability (Whiteford et al., 2013), so when the negative consequences of schizophrenia spectrum disorders are combined with those of substance use disorders, major health problems are likely.

Most individuals with schizophrenia never behave aggressively or violently. However, the risk of violent behaviour among this patient group is around seven times that for the general population (Tiihonen et al., 1997; Arseneault et al., 2000; Brennan et al., 2000; Wallace et al., 2004; Fazel and Grann, 2006; Soyka et al., 2007; Fazel et al., 2009a; Fazel et al., 2014). Comorbid substance abuse increases this risk considerably, and it has even been stated that the association between schizophrenia and violent crime is very weak without this comorbidity (Fazel et al., 2009b).

If an individual with schizophrenia and comorbid substance use disorder commits a violent crime, he or she will join one of the most marginalized patient subgroups. These individuals are often stigmatized not only in society but also among health professionals (Rao et al., 2009; Mittal et al., 2014). Understanding how substance use disorder affects outcomes among patients with schizophrenia, and identifying generally applicable background factors will facilitate the development of treatments for their condition and help prevent violent behaviour, thereby reducing the human suffering associated with schizophrenia.

2 Review of the literature

2.1 SCHIZOPHRENIA

2.1.1 Definition, symptoms, and prevalence

The World Health Organization (WHO) defines schizophrenia as a severe mental disorder characterized by profound disruptions in thinking and perception. It affects the language and the sense of self, and often causes psychotic experiences such as delusions and hearing voices. Consequently, it can impair an individual's overall functioning by reducing the ability to work or disrupting the studies (WHO, 2016a). Schizophrenia is a collection of signs and symptoms, and is usually defined by observed signs of psychosis (Insel et al., 2010). Its three major symptom areas are positive and negative symptoms, and cognitive dysfunction. Positive symptoms include hallucinations, delusions, and disorganized speech and thought; negative symptoms include social withdrawal, loss of motivation, emotional blunting, and scarcity of speech. Cognitive dysfunction affects attention, executive function and working memory. It has been argued that these changes in cognition are the core symptoms of schizophrenia (Picchioni and Murray, 2007; Insel, 2010; Kahn and Keefe, 2013; Kirkpatrick et al., 2014). In addition to these main symptoms, patients may have general psychiatric symptoms such as depression, anxiety, aggression, and suicidal behaviour. In Finland, the diagnostic definition of schizophrenia is based on the International Classification of Diseases, tenth edition (ICD-10) (WHO, 1995). The classification and diagnostic tool used in the United States is the Fifth Edition of the Diagnostic and Statistical Manual for Mental Disorders (American Psychiatric Association, 2013).

Schizophrenia occurs all over the world (Saha et al., 2005); its global lifetime prevalence in the human population is estimated to be about 0.7–1% (McGrath et al., 2008). However, a Danish study found that the lifetime risk of schizophrenia was almost 2% for men, and about 1.6% for women (Pedersen et al., 2014). In Finland, the lifetime prevalence of schizophrenia is 0.87%, while those of schizoaffective disorder and schizophreniform disorder are 0.32% and 0.07%, respectively (Perälä et al., 2007). However, the risk is higher in the northern and eastern areas of the country (Perälä et al., 2008). Additionally, the risk in the most urban environment is 2.4 times higher than that in the most agrarian area (Vassos et al., 2012). Schizophrenia usually starts in late adolescence or early adulthood, with a later age of onset in women (Riecher-Rössler and Häfner, 2000; Abel et al., 2010; Gogtay et al., 2011).

Schizophrenia is one of the most debilitating conditions in the world. It's most important experienced consequences stem from distress, diminished quality of life, caregiver burden, and the burden of stigma (Millier et al., 2014). Comorbid substance use disorder further complicates the situation because persons with this dual diagnosis are considered dangerous, unpredictable, and hard to talk with (Crisp et al., 2000), and drug addiction is commonly viewed as self- inflicted. The economic costs of schizophrenia are remarkable. In addition to direct costs, the condition imposes substantial burdens on social and justice systems, and causes major losses of productivity. Overall, it accounts for between 1.5 and 3 per cent of total national health care expenditure (Knapp et al., 2004). Its psychiatric costs are negatively correlated with the global assessment of function (GAF), and inpatient treatment of schizophrenia is especially costly (Ekman et al., 2013). Among mental, neurological, and substance use disorders, mental disorders account for the greatest proportion (56.7%) of disability-adjusted life years (DALYs), followed by neurological (28.6%), and substance use disorders (14.7%). Mental and substance used disorders in early adulthood are associated with a particularly pronounced increase in DALYs (Whiteford et al., 2013).

2.1.2 Etiology and risk factors

No single factor is known to cause schizophrenia; it is a multifactorial condition influenced by both genetic and environmental factors, and their interactions (Nestler et al., 2016). Moreover, despite active research, the mechanisms by which individual factors contribute to the disorder are unknown. Neurotransmitter, anatomic, and immune system abnormalities are connected to the condition's pathophysiology. The dopamine hypothesis states that the symptoms of schizophrenia are related to excessive central dopamine transmission. Another neuropathological model involves changes in the glutamate neurotransmitter system, and is based on the observation of hypofunctional glutamatergic signalling via glutamate receptors (Howes et al., 2015; Coyle et al., 2012). During the last decades there has been increasing evidence that epigenetic mechanisms as DNA methylation can be crucial in gene-environmental interaction (Schmitt et al., 2014). The brains of schizophrenic individuals may exhibit various anatomic abnormalities such as enlarged ventricles and a reduced volume in the medial temporal areas. Abnormalities may also be present in the hippocampal area (Wright et al., 2000; Tamminga et al., 2010; Mattai et al., 2011). Inflammation and oxidative stress are some other important components of schizophrenia's pathophysiology: individuals with psychosis exhibit elevated levels of cytokines and other signs of immune system activation. Additionally, a range of autoimmune diseases and autoantibodies have been linked to schizophrenia (Benros et al., 2012). Notably, anti-N-methyl-D-aspartate (NMDA) -receptor encephalitis is an underrecognized cause of psychosis that results from the formation of antibodies against NMDA receptors (Finke et al., 2012).

The typical age of onset in schizophrenia is late adolescence which is a critical period in brain development (Mueser and McGurk, 2004; Gogtay et al., 2011). The course of illness differs between patients and between the stages of illness within individual patients. Twin studies suggest that the heritability of schizophrenia is about 85% (Cardno et al., 1999; Sullivan et al., 2003). However, 85% of persons with schizophrenia have no first-degree relatives with the condition (McGlashan and Johannessen, 1996). A Swedish population-based study found that the heritability of schizophrenia was 64% (Lichtenstein et al., 2009), and genome-wide association studies (GWAS) on the disease have identified several genetic risk variants (single nucleotide polymorphisms) with weak effects (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Prenatal difficulties such as intrauterine starvation (McGrath et al., 2011), viral infections (Brown and Patterson, 2011), gestational complications (Cannon et al., 2002), and stress (Malaspina et al., 2008; Markham and Koenig, 2011) are also proven to be related to the development of schizophrenia. Biological risk factors include complications before or during birth (Preti et al., 2000), older paternal age at childbirth (Lehrer et al., 2016), seasonality of birth (Davies et al., 2003), and exposure to the protozoan parasite Toxoplasma gondii (Torrey et al., 2012). According to several studies, cannabis use is associated with an increased risk of schizophrenia (Arseneault et al., 2004; French et al., 2015; Kelley et al., 2016; Marconi et al., 2016). Also, amphetamine can be viewed as a stressor and a risk factor for the vulnerable individuals. Amphetamine may also play a role in the development of vulnerability (Bramness et al., 2012). Potential environmental risk factors include urban life (Vassos et al., 2012), childhood victimizing experiences (Bebbington et al., 2004), and bullying (Trotta et al., 2013). The incidence of schizophrenia and other psychoses is elevated in many migrant and minority ethnic groups, especially among migrants from developing countries (McGrath et al., 2004; Cantor-Graae and Selten, 2005; Morgan et al., 2010). The risk is particularly high among certain immigrant and refugee groups, notably those from the Caribbean and Bermuda, while rates are lower among immigrants from Northern Europe or East Asia (Anderson et al., 2015). On the other hand, especially for males, belonging to a minority with a high socioeconomic status can be protective against schizophrenia (Suvisaari et al., 2014).

2.1.3 Course of schizophrenia

The course and features of schizophrenia vary from person to person, and it has been claimed that no two patients with schizophrenia have the same constellation of symptoms (Buckley et al., 2009). Around half of all individuals with schizophrenia have quite good long-term outcomes (Harrison et al., 2001), but most patients have relapses with high rates of hospitalization (Almond et al., 2004; Brown et al., 2010). Relapses are associated with worsening of symptoms, impaired functioning, and cognitive deterioration. Patients are at risk of losing their social contacts, dropping out of school, losing the ability to work, and becoming homeless. Compared to patients with other psychotic or nonpsychotic psychiatric disorders, patients with schizophrenia have poorer outcomes (Jobe and Harrow, 2005). Around 50% of such patients have a chronic course and exhibit hardly any changes in their psychopathology over the long term (an der Heiden and Häfner, 2015); a Finnish study obtained a median recovery rate of 13.5% (Jääskeläinen et al., 2013). The rehospitalization rate for patients with schizophrenic psychoses after first hospitalization was 60% within 2 years, and 73.8% within 5 years (Miettunen et al., 2006). An earlier study (Robinson et al., 1999) yielded a cumulative rate for first relapse of 81.9% by the end of a 5-year follow-up period. When the association between relapse and hospitalization was investigated, the rates of both relapses and hospitalizations were found to be quite similar: during the two-year follow-up period, 37% of the patients relapsed and 26% were hospitalized (Addington et al., 2013). Short hospitalizations are recommended by guidelines, but some patients may benefit longer periods in hospital since short first hospitalization has been associated to higher risk of rehospitalizations (Miettunen et al., 2006).

Substance use worsens the course of schizophrenia (Swofford et al., 1996; Ringen et al., 2008; Turkington et al., 2009; Volkow, 2009; Kerner, 2015), and patients with this comorbidity are at risk of several other negative outcomes - notably, they face elevated risks of premature death, suicidality, and treatment noncompliance. They have more outpatient visits with positive symptoms, more missed appointments, and more rehospitalizations (Swartz et al., 1998; Swofford et al., 2000; Olfson et al., 2000; Cantor-Graae et al., 2001; Saha et al., 2007; Schmidt et al., 2011; Addington et al., 2013).

Non-adherence to antipsychotic medication is the most common factor related to relapses; other factors associated with worse outcomes include stress, psychosocial therapies, previous hospitalizations, relapses, and lack of insight (Hui et al., 2013; Olivares et al., 2013). Anxiety disorders, depression, and eating disorders are common psychiatric comorbidities. They may worsen the course of schizophrenia in many ways - for example, panic attacks can lead to paranoid symptoms, and depression can promote secondary negative symptoms (Bermanzohn et al., 2000; Buckley et al., 2009; Kouidrat et al., 2014). It has been speculated that social anxiety may be a continuum to paranoia, but a recent study indicated that social anxiety and positive psychotic symptoms are separable constructions, albeit significantly associated with one-another (Cooper et al., 2016).

The risk of death among patients with schizophrenia is around 2–3 times higher than that for the general population (Joukamaa et al., 2006; Saha et al., 2007; Brown et al., 2010; Bushe et al., 2010), and the difference in life expectancy between schizophrenia patients and the general population is over 20 years (Tiihonen et al., 2009; Laursen, 2011; Nordentoft et al., 2013). Excluding unnatural deaths, the gap is 15 years for men and 12 for women (Crump et al., 2013a). Among unnatural causes, suicide accounts for about 25% of deaths (Olfson et al., 2015); around 5% of persons with schizophrenia commit suicide (Palmer et al., 2005). Between the ages of 16 and 39, suicide accounts for 50% of all deaths among schizophrenic patients, and about 70% of suicide incidents occur within 3 years of the first outbreak of illness (Alaräisänen et al., 2009). The risks of homicidal and accidental deaths among schizophrenic patients are around twice (Crump et al., 2013b) and four times (Crump et al., 2013c) those for the general population, respectively.

Leading medical causes of premature death among persons with schizophrenia include cardiovascular, respiratory, substance-induced nonsuicidal death, and cancer (Crump et al.,

2013a; Olfson et al., 2015; Bitter et al., 2017). Negative health habits and metabolic disorders are associated with both the disease and its treatment (Millier et al., 2014). Smoking, autoimmune and gastrointestinal disorders, elevated levels of C-reactive protein (CRP), and elevated levels of antibodies to Toxoplasma gondii, Herpes simplex virus type 1, and Epstein-Barr virus are all known predictors of mortality among schizophrenia patients (Suvisaari et al., 2013; Dickerson et al., 2007; Dickerson et al., 2013; Dickerson et al., 2014; Dickerson et al., 2016; Horsdal et al., 2017). About 50% of deaths among hospitalized patients with schizophrenia are related to tobacco (Callaghan et al., 2014). The relative unadjusted risk of mortality attributable to autoimmune disorder and coincident smoking is about 18 for patients with schizophrenia relative to individuals with neither of these risk factors (Dickerson et al., 2016).

2.1.4 Schizophrenia and violent crimes

Most persons with schizophrenia are not violent, but violent behaviour may be a symptom of the disorder in a small minority of patients. The violent behaviour of persons with schizophrenia is usually targeted at family members or friends (Joyal et al., 2004; Ghoreishi et al., 2015). Most studies of violence in schizophrenia are conducted in western world settings, but the condition had similar effects in a low income rural African community (Tsigebrhan et al., 2014).

Several studies conducted in a wide range of settings have found that the risk of violent behaviour among persons with schizophrenia is greater than for the general population (Eronen et al., 1996a; Tiihonen et al., 1997; Arseneault et al., 2000; Brennan et al., 2000; Wallace et al., 2004; Fazel and Grann, 2006; Swanson et al., 2006; Fazel et al., 2009a; Soyka et al., 2007). A Swedish follow-up study indicated that the risks of committing violent crimes for men and women with serious mental disorders are 4- and 27.5-fold greater, respectively, than for the general populations of men and women (Hodgins, 1992). Moreover, schizophrenia is associated with an 8-fold increase in homicides in males and a 6.5-fold increase in women (Eronen et al., 1996b). The first cohort study to demonstrate the quantitative risk of violent crime in general was conducted by Tiihonen et al. (1997), which followed an unselected birth cohort for nearly thirty years. Their results indicated that the risk of violent offences among male schizophrenia patients was 7 times higher than that for males with no mental disorder. The risk was greatest among males with schizophrenia and coexisting substance abuse. Previous criminality associated with schizophrenia increases also the risk of violent behaviour in the future (Tiihonen et al., 1996).

Around 15% of psychiatric patients in general psychiatry have committed at least one criminal offence before their first contact with psychiatric services. Moreover, about 80% of forensic patients were treated in general psychiatric wards before committing the offence that resulted in their admission to forensic treatment (Hodgins and Müller-Isberner, 2004). Additionally, around 35% of male patients with schizophrenia started a criminal career before their first contact with the psychiatric hospital system (Munkner et al., 2003).

Perhaps the most important epidemiological study in this field is the Epidemiological Catchment Area study, which is based on a sample of 10,059 individuals. This study found that 8% of individuals with schizophrenia exhibited violent behaviour, with the incidence rising to 30% among those with comorbid substance abuse. The prevalence of violence among individuals without mental disorders was 2% (Swanson et al., 1990). In keeping with these results, a case-linkage study (Short et al., 2013) found that persons with schizophrenia were more than twice as likely to have a violent conviction compared to controls. The population-attributable risk fraction for violence in patients with severe mental disorders was 5%, suggesting that such patients commit one of 20 violent crimes (Fazel and Grann, 2006). A Swedish total population study that ran for 38 years (Fazel et al., 2014) found that about 11% of men and 3% of women with schizophrenia were convicted of a violent crime within five years of their diagnosis.

2.1.5 Risk factors for violence in schizophrenia

Most individuals with schizophrenia are not violent; in fact, many of them are rather withdrawn and prefer to be alone because of their cognitive and negative symptoms. Indeed, the negative symptoms of schizophrenia reduce the likelihood of serious violence (Swanson et al., 2006). Also, because the prevalence of schizophrenia is only around 1%, the absolute risk of violent behaviour remains low. However, violent behaviour may be a symptom of the disorder in a small minority of patients.

The MacArthur Violence Risk Assessment study, which included over 1,000 patients with mental disorders, identified several factors associated with an increased risk of violent behaviour, including prior violence, criminality, substance use disorder, and childhood experiences such as physical abuse and substance abuse by parents (Monahan, 2002). However, it should be noted that trying to predict future violence is very difficult, especially in the context of individuals with schizophrenia. The risk of aggressive behaviour differs in different levels of positive symptoms (Hodgins and Riatz, 2011), and the risk is not attributable to any one factor but to several factors that act in different phases of the disorder (Wallace et al., 2004). In a Swedish study of genetic and environmental factors of violence risk (Sariaslan et al., 2016), 67% of the correlation between schizophrenia and violent crimes was related to genetic influences that were shared with psychotic disorder, substance abuse, and violent crime.

Risk factors such as earlier violent behaviour and substance abuse have been recognized in several studies (Swartz et al., 1998; Swanson et al., 1990; Tiihonen et al., 1997; Arseneault et al., 2000; Brennan et al., 2000; Walsh et al., 2004; Amore et al., 2008; Witt et al., 2015). Aggressive behaviour may result from residence in a high-crime neighborhood (Monahan, 2002) and victimization (Swanson et al., 2006; Hodgins et al., 2007). An increased risk of violence is also associated with treatment nonadherence (Witt et al., 2013), male gender, and younger age (Amore et al., 2008; Ghoreishi et al., 2015). Other factors associated with the risk of violent behaviour are positive psychotic symptoms (Swanson et al., 2006), lack of insight, hostility, problems with impulse control (Swartz et al., 1998; Witt et al., 2013), suicidal threats (Witt et al., 2014), childhood conduct disorder, threat-control-override symptoms (patients' fears of being harmed and controlled by others), depressive symptoms (Hodgins, 2011), and psychopathy (Tengström et al., 2000). Still other studies have identified a need for special education (Walsh et al., 2004), shorter education, rural residence, unemployment, and living alone (Karabekiroğlu et al., 2016) as risk factors. Finally, there is a strong association between neurocognitive and social cognition deficits and violence (O´Reilly et al., 2015).

Relative to men with no diagnosis, the risk of committing violent crimes is elevated by a factor of around 3.6 in men with schizophrenia, and a factor of around 25 in men with both schizophrenia and comorbid alcohol use (Räsänen et al., 1998). The elevated risk of violent offending is not solely due to the comorbid substance use according to Short et al. (2013), and it has been stated that schizophrenia is only associated with violence in the absence of treatment (Keers et al., 2014). On the other hand, substance use predicts missed outpatient appointments (Coodin et al., 2004).

2.2 THE CONCEPT OF FORENSIC PSYCHIATRIC MENTAL EXAMINATION AND FORENSIC PATIENTS

In Finland, the perpetrator of a crime is not legally responsible if the crime was committed at a time when the perpetrator was suffering from a mental illness, severe mental deficiency, serious mental disturbance, or serious disturbance of consciousness that rendered them unable to understand the factual nature or unlawfulness of their act, or if their ability to control their behaviour was decisively weakened because of such a condition (criminal irresponsibility) (Finlex, 1990). During the court process, the judge may call for a report on the defendant's mental state. When this happens, the National Institute for Health

and Welfare (THL) is asked to arrange a full forensic examination, although the court will sometimes ask the THL to produce a report based on the defendant's medical records instead. THL decides whether the examination will be performed at a state mental hospital, at the forensic psychiatry unit of a university hospital, or at the prison's mental hospital (National Institute of Health and Welfare, 2015). By international standards, Finnish procedures for conducting mental examinations are considered very thorough (Eronen et al., 2010).

Mental examinations include a psychiatric assessment, psychological tests, and monitoring by nurses for one to two months. In addition, a physical health examination is performed. Possible structural abnormalities of the brain are also examined using imaging techniques. Information is collected from several sources, including information on the person's prior contacts with health care organizations. A statement is made by the physician responsible for the examination. The statement is delivered to THL, which then presents its own conclusions to the court. A patient who is evaluated as requiring psychiatric treatment waits for THL's decision at the hospital. A forensic patient is a person who has been committed to hospital for psychiatric treatment after a mental examination. Such patients are considered to have no criminal responsibility during their alleged offence(s) because of their mental illness, and their sentences are waived (Finlex, 1990; National Institute of Health and Welfare, 2017). The number of forensic mental examinations conducted each year in Finland has fallen recently. For example, 126 examinations were performed in 2007, and 96 in 2016 (National Institute of Health and Welfare, 2017).

2.3 SUBSTANCE USE

2.3.1 Amphetamines

Amphetamine was synthesized in 1887, and it was the first member in the group of central nervous system stimulants called "amphetamines". Amphetamine is one of the most potent sympathomimetic drugs. It produces the effects by increasing synaptic levels of dopamine, noradrenaline and serotonin through multiple mechanisms. The behavioural stimulant effects of amphetamine are mediated primarily through dopamine and depend on the dopamine transporter (DAT). Amphetamines inhibit dopamine reuptake by interacting with DAT so that the concentration of dopamine in the synaptic cleft increases. Amphetamines can induce symptoms of psychosis similar to those of acute schizophrenia spectrum psychosis, and so amphetamine-induced psychosis is used as a model for primary psychotic disorders (Berman et al., 2009; Bramness et al., 2012; EMCDDA, 2015a).

Amphetamine is widely regarded as a human invention, but in 1997 the compound was found in two species of Texas acacia bushes (Clement et al., 1997). The original amphetamine epidemic in the United States was created by the pharmaceutical industry and medical profession which introduced the compound as a medicine for congestion in the 1930s. A little later, amphetamine tablets were used for narcolepsy, postencephalitic Parkinsonism, and minor depression. In the 1950s, they were used to treat depression and obesity (Rasmussen, 2008).

Based on past-year use, the percentage of the global population aged 15–64 that has used amphetamine-type stimulants (excluding ecstasy) is 0.3–1.2% (UNODC, 2016). In Europe, 1.0% of young adults aged 15–34 years have a history of amphetamine use within the last year. The lifetime prevalence of amphetamine users in this age group differs markedly from country to country in Europe, ranging from 0.1% to 12.4% with a weighted average of 5.5% (EMCDDA, 2015a; Moratalla et al., 2017).

The effects of amphetamine consumption usually begin immediately if injected or smoked, or within 30 minutes if swallowed or snorted. Methamphetamine is more potent than amphetamine, but in real-world situations it is generally impossible to distinguish between their effects (EMCCDA, 2015a).

Amphetamine use can cause hypertension, tachycardia, and increased self-confidence and sociality. It also reduces appetite and fatigue, and can easily cause insomnia. Users may feel irritable, restless, anxious, and depressed. Acute amphetamine intoxication leads to agitation, disorientation, paranoia, impulsivity, and aggressive behaviour. Persistent use of amphetamine may cause neuroanatomical and neurotoxic changes, and problems with memory, decision-making, and verbal reasoning (EMCDDA, 2015a).

Almost a third of methamphetamine users experience psychosis at some point, particularly when it is question of long-term, regular, and high-dose use (Darke et al., 2008; Salo et al., 2011). The relationship between amphetamine psychosis and primary psychosis can be understood in terms of the stress-vulnerability model, with amphetamine exposure being a stressor for vulnerable individuals (Bramness et al., 2012). A prospective study conducted by McKetin et al. (2013) found that the risk of psychotic symptoms increased from a low baseline (7%) during methamphetamine abstinence to 48% during heavy use of methamphetamine. On the other hand, in a cohort of amphetamine users, demographic risk elements and earlier psychiatric morbidity were more important risk factors than amphetamine use for predicting hospitalization due to psychosis (Rognli et al., 2014).

The likelihood of aggressive behaviour in chronic users of amphetamines stems from changes in impulsivity, the presence of positive symptoms of psychosis, and the interaction of these two factors (Dawe et al., 2009). Interpersonal violence is a typical consequence of aggressive behaviour related to methamphetamine use. It has been estimated that the likelihood of violent acts increases from 10% to 60%, between times of abstinence and periods of excessive methamphetamine use (McKetin et al., 2014). Although methamphetamine use is a risk factor for violence, aggressive behaviour is not unavoidable, even in chronic methamphetamine users (Payer et al., 2011; Baskin-Sommers and Sommers, 2006). On the other hand, Martin et al. (2009) found no association between amphetamine use and violence among persons with a median age of 22 years.

The possibilities for medical treatment of amphetamine dependence are limited, and there is little evidence that any existing treatment is particularly effective. According to Srisurapanont et al. (2001), neither fluoxetine, amlodipine, imipramine, nor desipramine have any major beneficial effects on amphetamine use disorders. Naltrexone reduces cue-induced craving and subjective responses to methamphetamine (Ray et al., 2015), and naltrexone implants reduce amphetamine use (Kelty et al., 2013), including in individuals with coexisting heroin and amphetamine dependences (Tiihonen et al., 2012). Antipsychotics had no advantages over placebo with respect to psychostimulant abstinence or craving (Kishi et al., 2013). The use of psychostimulant medications (modafinil, bupropion, dexamphetamine or methylphenidate) as a substitution treatment for amphetamine dependence did not seem to be useful according to Pérez-Mañá et al. (2013).

Amphetamine stimulants are used to treat attention deficit hyperactivity disorder (ADHD), and narcolepsy. However, they have side-effects such as neurotoxicity, and are easily abused (Berman et al., 2009; Castells et al., 2011).

2.3.2 Cannabis

The generic term cannabis describes several psychoactive formulations of the plant Cannabis sativa that have anxiolytic, sedative, analgesic, and psychedelic activity. It is the most widely used illegal substance. Estimates suggest that the number of past-year users in 2015 was about 183 million (UNODC, 2017). In many countries, herbal cannabis and cannabis resin are known as marijuana and hashish. Cannabis has been used and cultivated for at least 6000 years, but the knowledge of its pharmacology is based on studies conducted at the end of the nineteenth century (Atakan, 2012). Its principal psychoactive component is Δ 9-tetrahydrocannabinol (THC). Compounds structurally similar to THC are known as cannabinoids, which include Δ 8-THC, cannabinol, and cannabidiol. Cannabidiol does not induce hallucinations or delusions as THC does, and it has been hypothesized that it has antipsychotic (Zuardi et al., 2012) and anxiolytic properties (Crippa et al., 2011).

Cannabinol binds to cannabinoid receptors on neurons. These receptors belong to the endocannabinoid system, which is located in areas of the brain effecting on pleasure, memory, thinking, focusing, movements and coordination, and time perception. THC triggers endocannabinoid receptors artificially, and disrupts the function of endogenous cannabinoids (Alger, 2013; EMCDDA, 2015b).

The potency of cannabis products depends on their THC content, and improvements in cultivation techniques over the last few decades have resulted in increases in potency. The potency of herbal cannabis can average over 10%, compared with an average of 5% for both imported cannabis resin and cannabis grown by traditional methods (EMCDDA, 2008). Overstimulation of the endocannabinoid receptors creates the feeling of being "high" and also has other effects on mental processes. Cannabis is mostly consumed by smoking, which causes its effects to appear almost immediately. If it is ingested, absorption is slower lower, and more-delayed peak THC concentrations are lower (Huestis, 2007).

Almost every system in the human body is affected when cannabis is used. Overstimulation of the cannabinoid receptors can modify their function, which together with additional alterations in the brain area may induce dependence and withdrawal symptoms when cannabis use is discontinued. The acute toxicity of cannabis is low. Although cannabis consumption produces euphoria, it can also contribute to dysphoric reactions including severe anxiety and panic, and to paranoid delusions and psychosis. Dose-related effects are more common among people new to the drug, anxious individuals, and psychologically vulnerable persons. The health risks associated with cannabis use are less pronounced than those for other substances such as heroin. However, the impact of cannabis on public health is significant because of its widespread use (Atakan, 2012; EMCDDA, 2015b; WHO, 2016b).

Synthetic cannabinoid receptor agonists are functionally similar to THC and thus mimic the effects of cannabis. They have been advertised as legal substitutes for cannabis, and constitute a broad group of psychoactive substances that is being monitored by the European Monitoring Centre for Drugs and Drug Addiction. These products have been marketed to users as herbal smoking blends since the mid-2000s (EMCDDA, 2017a).

In general, cannabis has only minor addictive potential. Data on regular use of cannabis has been used as an indicator of the prevalence of problematic use in the population. In Europe, the overall prevalence of daily or near-daily use in the adult population has been estimated to be about 1% (EMCDDA, 2015c). Cannabis dependence is difficult to predict and associated with a negative outcome (van der Pol et al., 2015), and the likelihood of dependence is increased by high levels and early onset of use (Nocon et al., 2006). The prevalence peaks between 20-24 years and is higher in males than females and in high income regions (Degenhardt et al., 2013). Uncontrolled cannabis use increases the risk of long-term health problems such as psychiatric and cardiovascular disorders. Chronic inflammatory and precancerous changes in the airways are also linked to cannabis use (Kalant, 2004; Hall and Degenhardt, 2009). The impact of cannabis use on cognitive skills is unclear, but the available evidence suggests that constant effects of THC on cognitive abilities are more evident among individuals who used the drug during the developmental stage (Verrico et al., 2014).

Individuals with both schizophrenia and a history of cannabis use have an earlier age of initiation of psychosis than patients without substance use (Koskinen et al., 2010; De Hert et al., 2011; Myles et al., 2012; van Dijk et al., 2012; Stefanis et al., 2014; Helle et al., 2016), but may be only in cannabis sensitive persons (Schimmelmann et al., 2011). A Finnish study (Niemi-Pynttäri et al., 2013) found that the eight-year cumulative risk of a schizophrenia diagnosis was 46% for persons with a diagnosis of cannabis-induced psychosis. At the population level, eliminating cannabis use could reduce the occurrence of schizophrenia by about 8% (Arseneault et al., 2004). Notably, regular use of high-potency cannabis has been associated with a heightened risk of psychosis compared to a single use or the use of low-potency cannabinol (Di Forti et al., 2015). High-potency cannabis consumption is also

related to the severity of dependence, and is more likely to affect memory impairment and paranoia (Freeman and Winstock, 2015).

The number of treatment periods in which cannabis is the primary drug has increased over the years, but most people who use cannabis do not enter treatment (EMCDDA, 2015c). Treatment for cannabis-related problems is based primarily on psychosocial approaches which combine elements of classical psychotherapy with social support and care (EMCDDA, 2015c). Preliminary studies have investigated the use of various medications with different mechanisms to treat cannabis dependence, including the cannabinoid agonist nabilone, the adrenergic agonist lofexidine, gabapentin, N-acetylcysteine, buspirone, bupropione, escitalopram, and quetiapine (Mariani et al., 2014; Balter et al., 2014; Marshall et al., 2014; Weinstein et al., 2014). In addition, buccal sprays (nabiximols) containing THC and cannabidiol have been used in substitution treatment (Allsop et al., 2014; Allsop et al., 2015). However, none of these treatments has proven very effective.

Cannabis has some therapeutic benefit as an analgesic. Dronabinol, a pharmaceutical formulation of THC, is used to treat nausea associated with cancer chemotherapy, and anorexia-related weight loss in patients with AIDS. Cannabis is also used as a medicine for multiple sclerosis, certain types of pain, and other neurological conditions (Madras, 2015; FDA, 2017). In Finland, a cannabis-based mouth spray was licensed for use in 2012 to treat multiple sclerosis patients suffering from muscle stiffness or spasms (FIMEA, 2012). In recent years, there has been a global trend towards reducing the legal penalties associated with cannabis consumption, or at least minor cannabis possession (EMCDDA, 2017b).

2.3.3 Opioids

The term "opioid" refers to any substance that binds to the body's opioid receptors, including both natural compounds and synthetic substances with opiate-like effects such as fentanyl, oxycodone and buprenorphine. Opioids are classified as agonists or partial agonists according to their effects at opioid receptors. Agonists such as morphine produce a maximal response from the receptor. Partial agonists (such as buprenorphine) bind to receptors but produce limited functional feedback no matter the amount of drug administered. The term "opiate" is used as a generic term for alkaloids extracted from the opium poppy (Papaver Somniferum). Opiates include opium, heroin, codeine, and morphine. Morphine is one of the oldest known medications: the opium poppy has been cultivated for its production since 3000 BC (EMCDDA, 2011; Pathan and Williams, 2012). A recent phenomenon is the use of new super-strong synthetic opioids such as U-47700, which was found for the first time in Finland by the Eastern Finland Police Department in a home search in 2017 (Savon Sanomat, 2017).

Heroin, which is another name for diamorphine, is an agonist of receptors that are normally activated by endogenous peptides known as endorphins. It is 2–3 times more powerful than morphine, and is related to a greater number of overdoses and fatal poisonings than any other substance. Methadone is a synthetic agonist with similar pharmacological activity to morphine. It has a long half-life that enables once a day dosing, and is primarily used as a pain killer for treating severe pain, as well as in opioid maintenance treatment (Pathan and Williams, 2012). Buprenorphine stimulates the mu receptor partially, causing similar effects to full opioid agonists such as heroin, morphine, or methadone, but with lesser intensity. Buprenorphine is also an antagonist**.** It may induce positive mood and feelings of well-being by attaching to the kappa receptor and slowing its activity, because stimulation of the kappa opioid receptor plays a role in producing symptoms (as chronic depression) associated with opioid withdrawal (Pathan and Williams, 2012). If a person using some other opioid takes buprenorphine, they may develop withdrawal symptoms due to the reduced stimulation of the receptors (Jones, 2004).

Opioids are usually abused intravenously, but also by smoking, inhaling, oral administration, or snorting. Their effects include pain relief, feelings of pleasure, decreased anxiety and tranquility, elevation of mood, and also nausea and vomiting. The induced feeling of euphoria and decreased concern for problems is often referred to as being "high". When opioids are self-administered intravenously, and sometimes when heroin or opium are smoked, the rapid increase in brain opioid levels produces an intense sensation of pleasure referred as a "flash" or "rush". Long-term effects include constipation, loss of sex drive, mental impairment, respiratory depression, nausea, suppression of the cough reflex, and hypothermia. When the use of opioids has been prolonged, discontinuation or reduction in opioid use leads to characteristic withdrawal symptoms including melancholic mood, nausea, vomiting, muscle aches, pupillary dilation, insomnia, and fever (Lowinson and Joyce, 1997).

In 2010, there were about 15.5 million opioid-dependent people worldwide (Degenhardt et al., 2014), and in 2014 the use of opium, morphine and heroin affected about 17 million people globally (UNODC, 2016). There are estimated to be around 1.3 million high risk opioid users in the European Union, and opioids are identified in 79% of fatal overdoses (EMCDDA, 2011; EMCDDA, 2017c). Among substance disorders, opioid dependence is the largest contributor of years of life lost (Whiteford et al., 2013). In 2015, almost 70% of the global burden of disease attributable to drug use disorders, were attributable to opioids (UNODC, 2017). Opioid use increases the risk of death nearly 15- fold according to a review by Degenhardt et al. (2011). In the United States, almost every aspect of the opioid overdose death epidemic worsened in 2014. For example, heroin death rates increased by 20.6% from 2013 to 2014 (Rudd et al., 2016). Opioid dependence is often compared to other lifelong disorders such as hypertension, diabetes and asthma (Leshner, 1997; McLellan et al., 2000). Pharmacological treatments for opioid dependence are based on either opioid withdrawal or agonist maintenance (WHO, 2009). The semi-synthetic competitive opioid antagonist naloxone reverses opioid overdose, and has been used in overdose treatment since the 1970s. Reducing the number of deaths related to opioid use is a global challenge, and take-home naloxone is recommended to people who are likely to witness an overdose (WHO, 2014; EMCDDA, 2016).

The prevalence of psychosis has been found to be lower among abusers of opioids than abusers of amphetamine and cannabis (Dalmau et al., 1999). In a review, Maremmani et al. (2014) highlighted the antipsychotic effectiveness, anticraving capability, and effectiveness of opioids on the psychopathological level.

Opioids are effective at treating pain in the short and medium term, but there is a lack of evidence supporting their use for chronic pain. However, opioids remain the gold standard to which all other analgesics are compared (Pathan et al., 2012).

2.3.3.1 Opioid maintenance treatment

Opioid maintenance treatment (OMT), which is also known as opioid replacement or opioid substitution treatment, means the use of evaluated opioid agonists, full or partial, by professionals in recognized medical practices to opioid-dependent individuals in order to achieve defined treatment goals (WHO, 2009). Opioid maintenance treatment involves a combination of psychosocial and pharmacological methods, including opioid maintenance treatment and opioid withdrawal treatment. It is given to opioid-dependent individuals whose drug use has not been successfully terminated by other treatments. The aim of maintenance treatment is rehabilitation and abstinence or reduction of harmful consequences such as criminality, use of illegal opioids, intravenous opioid use, and overdose risk (NICE, 2007a; WHO, 2009).

The available pharmacological treatments for opioid dependence include methadone, buprenorphine and heroin. Methadone and buprenorphine are both sufficiently long-acting to be dosed once a day. Also, unlike shorter-acting agents such as heroin, they are not associated in the same way with risks of intoxication or withdrawal. Their use is supported

by a strong evidence base, and they are on the WHO model list of essential medicines (WHO, 2017). Opioid maintenance treatment effectively reduces illicit opioid use as well as both all cause and overdose mortality (Degenhardt et al., 2009). The mortality risk for patients undergoing maintenance treatment is less than a third of that for opioid users not undergoing such treatment (Sordo et al., 2017), and optimal buprenorphine-naloxone dosing and psychosocial support may reduce intravenous use of patient`s own or illicit opioid maintenance medication (Launonen et al., 2016).

Opioid maintenance treatment is not suitable for all patients and should only be used as one element of a patient's rehabilitation. Contraindications and precautions to opioid agonist maintenance treatment include decompensated liver disease, acute asthma, and other conditions involving respiratory insufficiency (WHO, 2009). There is a potential risk of respiratory problems during the initiation of methadone treatment, which is increased by interactions between methadone and other respiratory depressants such as alcohol and benzodiazepines (O'Donnell and Vogenberg, 2011). Pharmacological studies suggest that buprenorphine is probably safer than methadone, but its intravenous use is associated with fatal overdoses (Whelan and Remski, 2012).

In Finland, opioid maintenance treatment programmes became available in 1997 in response to the increasing number of HIV infections and abuse of opioids and other drugs (Hakkarainen and Tigerstedt, 2005). The number of clients undergoing treatment has mirrored changes in legislation. In 2012, there were approximately 13–15,000 problem opioid abusers in Finland (0.24–0.28% of the population) (Ollgren et al., 2014), and the coverage of opioid maintenance treatment was 16–19% (Selin et al., 2015). Globally, only 10% of people who need opioid agonist maintenance treatment is receiving it (WHO, 2009; WHO, 2014).

Finland was the first European country to adopt the buprenorphine-naloxone combination in 2004 (EMCDDA, 2017d). This combination (Suboxone) includes buprenorphine and the opioid antagonist naloxone in a 4: 1 ratio (Pharmaca Fennica, 2018). Naloxone has no clinically significant effects when used sublingually as prescribed, but its opioid antagonism can induce withdrawal effects if it is administered intravenously. It therefore reduces the risk of abuse of the combination therapy (Orman et al., 2009). In Finland, buprenorphine is much more commonly used with naloxone than without; in 2015, buprenorphine-naloxone combination was used in 62%, methadone in 35%, and buprenorphine in 2% of cases (Partanen et al., 2017). The prescribed use of buprenorphine is more common in Finland than in other Nordic countries, and buprenorphine abuse is the most common reason for seeking opioid maintenance treatment (Selin et al., 2015).

Injectable heroin is a potential second-line treatment for heroin addicts for whom earlier treatments (e.g. oral buprenorphine or methadone) have brought no benefits (EMCDDA, 2012). In the future the pharmacological treatments for drug dependence may include for example anti-craving medications, formulations with ultra-long -action, and drug vaccinations (Reed et al., 2015).

2.3.3.2 Opioid antagonists

As a competitive opioid receptor antagonist, naltrexone cuts off the euphoric effects of opioids. Oral naltrexone has been available since the 1980s, but it is considered rather ineffective because of patients' poor adherence to the treatment. However, it can be used for patients who are committed to achieving abstinence. Long-lasting and injectable naltrexone became available in 2010, and these sustained release naltrexone formulations have shown beneficial abstinence-promoting effects in various treatment settings (Krupitsky et al., 2011; Kunøe al., 2014). Naltrexone increases the risk of overdose if the patient resumes using illicit opioids because it reduces opioid tolerance (Sullivan et al., 2007). Additionally, the mortality rate for oral naltrexone is higher than that for methadone (Gibson and Degenhardt, 2007). Naltrexone is licensed for use as an adjunctive prophylactic

treatment for formerly opioid-dependent persons who have remained opioid free for at least a week (NICE, 2007b; WHO, 2009).

2.3.4 Definition of substance use disorders

In European countries, the diagnostic criteria for substance use disorder, i.e harmful use and dependence, are based on the International Classification of Diseases, tenth edition (ICD-10), which is the standard diagnostic instrument for epidemiological, health management, and clinical purposes (WHO, 1995). ICD-10 was initiated in WHO Member States in 1994, and in Finland in 1996. It is currently under revision; ICD-11 is expected to be published in 2018 (WHO, 2018; National Institute of Health and Welfare, 2011). In the United States, diagnoses are based on The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), which is the classification and diagnostic tool of the American Psychiatric Association and was most recently updated in 2013. In DSM-5, the DSM-IV classifications of substance abuse and substance dependence are united into a single condition that ranges from mild to severe (Hasin et al., 2013). The term "substance abuse" is in widespread use especially in North America, and it refers generally to problems of psychoactive substance use. It is not used in ICD-10. The term "substance misuse" is defined as use of a substance for a purpose not consistent with legal or medical guidelines, as in the non-medical use of prescription medications (WHO, 2006).

According to ICD-10, harmful use (F1x.1) is defined as psychoactive substance use that causes damage to health. The damage may be physical (e.g. a hepatitis infection contracted following injection) or mental (e.g. depression after heavy drinking). A diagnosis of harmful use includes:

- "clear evidence that the substance use was responsible for (or substantially contributed to) physical or psychological harm, including impaired judgement or dysfunctional behaviour
- the nature of the harm should be clearly identifiable (and specified)
- the pattern of use has persisted for at least one month or has occurred repeatedly within a twelve-month period
- the disorder does not meet the criteria for any other mental or behavioural disorder related to the same drug in the same time period (except for acute intoxication)"

Harmful substance use is usually not approved by others and is commonly associated with various social consequences. The fact that the use of a specific substance is criticized by other people or may have caused socially negative events such as an arrest or marital crisis is not in itself evidence of harmful use.

In 1964, the term "dependence" was introduced by a World Health Organization Expert Committee to replace "addiction" and "habituation". According to ICD-10, dependence (F1x.2) is a physiological, behavioural, and cognitive phenomenon in which the substance use takes a much higher priority than other behaviours; the defining characteristic of a dependence syndrome is an overriding urge to take the psychoactive drug. The substance of dependence may be alcohol, tobacco, or some other substance that may or may not be legally prescribed (WHO, 1995).

According to the ICD-10 diagnostic criteria for research, a diagnosis of dependence can usually be made if three or more of the following signs of dependence have been present together at some time during the previous year:

- "a strong desire or sense of compulsion to take the substance
- impaired capacity to control substance-taking behaviour in terms of its onset, termination, or levels of use, as evidenced by: the substance being often taken in larger amounts or over a longer period than intended; or by a persistent desire or unsuccessful efforts to reduce or control substance use;
- a physiological withdrawal state when substance use is reduced or ceased, as evidenced by the characteristic withdrawal syndrome for the substance, or by use of

the same (or closely related) substance with the intention of relieving or avoiding withdrawal symptoms
- evidence of tolerance to the effects of the substance, such that there is a need for significantly increased amounts of the substance to achieve intoxication or the desired effect, or a markedly diminished effect with continued use of the same amount of the substance
- preoccupation with substance use, as manifested by important alternative pleasures or interests being given up or reduced because of substance use; or a great deal of time being spent in activities necessary to obtain, take, or recover from the effects of the substance
- persistent substance use despite clear evidence of harmful consequences, as evidenced by continued use when the individual is actually aware, or may be expected to be aware, of the nature and extent of harm"

2.3.5 Amphetamine, cannabis and opioid use in Finland

The use of illicit substances increased markedly in Finland in 1960s, and again in the 1990s (Partanen and Metso., 1999). Over the last decade, the use of all major illegal substances increased again among the adult general population. Polydrug use is common. The most commonly used illicit drug is cannabis, and opioids such as illegally sold buprenorphine and amphetamines have been the main substances associated with high-risk use. In general, Finland is not a notable target for drug trafficking, and the Finnish drug market has been fairly stable. However, the use of methamphetamine is growing. Since 2012, Helsinki and Turku have participated in the Europe-wide annual wastewater campaigns, and in 2016, a further 12 cities joined the campaign. The campaign provides data on drug use based on the levels of different illicit drugs and their metabolites in sources of wastewater, and an increase in methamphetamine concentration was found in Helsinki and Espoo over the 2014–2016 period (EMCDDA, 2018). Home growing of cannabis and its professionalization are rapidly increasing, and it has become easier to get new psychoactive substances via the internet. Finnish narcotics legislation is based on international conventions and the Finnish Narcotics Act (Finlex, 1993). Finnish drug policy rests on total prohibition and the assumption that criminalization reduces the use of illegal drugs. Finland also has a policy of harm reduction that focuses on minimizing harm to individuals, the community, and society. Available harm reduction interventions include needle and syringe programs, testing for infectious diseases, and vaccinations, but not take-home naloxone programs, drug consumption rooms, or heroin-assisted treatments (EMCDDA, 2017d).

Cannabis use is mainly concentrated among young people; about 14 % of persons aged 15-34 years used cannabis in the last year (EMCDDA, 2017c). A public survey from 2014 found that 19% of persons aged between 15 and 69 have tried cannabis (National Institute for Health and Welfare, 2016). Cannabis is used mainly in its herbal forms.

According to a register-based study, the number of problem amphetamine users was 11,000-18,000, and the number of problem opioid users 13,000–15,000 in 2012 (Ollgren et al., 2014). Buprenorphine is the most common (41%) reason for seeking treatment for problem drug use; only 2% of drug users take heroin as their primary drug (National institute for Health and Welfare, 2016). Since 2001, heroin has been largely replaced by buprenorphine, which typically originates from Lithuania, France, or Norway. Amphetamines originating in Western Europe are brought to Finland via Estonia, Lithuania, Sweden, and Russia.

The rate of drug-induced mortality among persons aged 15–64 was 43.1 deaths per million in 2015, the European average being 20.3 deaths per million. However, comparisons between different countries must be made with caution because of variation in reporting systems and other issues. Most of the drug-induced deaths in that year involved buprenorphine, usually in combination with other psychoactive substances such as alcohol or benzodiazepines (EMCDDA, 2017c).

2.3.6 Substance use in schizophrenia

About half of all patients with schizophrenia have a substance use disorder relating to a substance other than tobacco (Regier et al., 1990; Swofford et al., 2000; Mueser et al., 2000; Barnes et al., 2006; Addington and Addington, 2007; Buckley et al., 2009; Sara et al., 2014a, Karpov et al., 2017). However, it has been speculated that there might be a descending trend in the lifetime prevalence of alcohol use disorder in patients with schizophrenia, which was found to be about 20% in a meta-analysis of Koskinen et al., 2009). Among patients with psychotic disorders in general, the lifetime prevalence of illicit drug use is about 1.5-fold higher than in the general population (60% vs. 42%) (Ringen et al., 2008). According to another Norwegian study, the lifetime prevalence of substance use among psychotic inpatients (excluding those with psychotic disorders associated with substance use) is about 63% (Helseth et al., 2009).

Substance use among individuals with psychotic disorder is markedly higher than in population controls, and this association extends over substances, races, age-groups, and sex-groups (Hartz et al., 2014). The 15.5-year cumulative hazard rate from substance-induced psychosis (relating to cannabis, stimulant, opiate, and multiple drug use) for a diagnosis of schizophrenia is about 18%, and the mean time of transition from substance-induced psychosis to a diagnosis of schizophrenia is about 13 years. However, over 50% of patients who made such a transition did so within 2 years. Risk factors include male gender, younger age, and longer duration of first hospitalization (Alderson et al., 2017).

The most frequently abused substances among patients with schizophrenia (tobacco excluded) are alcohol, cannabis, and amphetamines (Cantor-Graae et al., 2001; Margolese et al., 2004; Barnes et al., 2006; Addington, 2007; Helseth et al., 2009). Cannabis use and its relationship to schizophrenia have been actively studied in recent years, but the effect of cannabis on the course of schizophrenia is still unclear. Patients with schizophrenia and cannabis exposure may be more vulnerable to THC than the general population (D'Souza et al., 2004), and cannabis can be a component that leads to schizophrenia when combined with other factors (Castle, 2013; Murray et al., 2017). About 65% of patients with schizophrenia report lifetime use of cannabis (Barnes et al., 2006).

Cannabis use disorders are more common in young, male, and first-episode patients. The median lifetime prevalence of disorders related to cannabis use in schizophrenia patients is 27%, so around one in four patients with schizophrenia has been diagnosed with cannabis use disorder (Koskinen et al., 2010). At first-episode psychosis, the prevalence of cannabis use has been estimated to be about 35% (Myles et al., 2016).

The prevalence of stimulant use disorder in patients with psychosis varies in different studies, and is associated with regional differences (Sara et al., 2015). The lifetime use of stimulants among schizophrenia patients is about 40% (Barnes et al., 2006), and the prevalence of stimulant disorder in this group is around 14%. Stimulant disorders are roughly ten times more common in persons with schizophrenia or early psychosis compared to the general population, and over 80% of patients with a stimulant disorder also have cannabis disorders. A follow-up study of patients after admission for psychoses found that patients with stimulant disorders alone have a higher incidence of self-harm, infectious diseases, and non-mental health admissions than patients with cannabis disorders alone (Sara et al., 2014a). A diagnosis of stimulant disorder before the first psychosis admission predicts rehospitalizations (Sara et al., 2014b).

The lifetime rate of opioid use among patients with schizophrenia is about 12% (Barnes et al., 2006). Compared to the whole treatment population in substance abuse treatment units, a significantly lower proportion of patients with schizophrenia had problems with heroin (5% vs. 18%). Persons with schizophrenia also had lower incidences of non-heroin opioid problems (7% vs. 15%) (Chiappelli et al., 2018).

There are multiple potential reasons for increased substance use in psychosis (Gregg et al., 2007). Patients with comorbid substance use disorder have been found to have higher substance sensitivity and sensation-seeking traits, and they may try to alleviate their

symptoms by self-medication (Bizzarri et al., 2009). Younger age, male gender, conduct disorder, and antisocial personality disorder are often associated with comorbid substance use (Mueser et al., 1999; Cantor-Graae et al., 2001; Duke et al., 2001; Donoghue et al., 2014; Stefanis et al., 2014). The co-occurrence of schizophrenia and substance use disorder is partly attributed to shared polygenic likelihood, which is more likely to be a general risk for substance use disorder than a specific risk for specific substance use disorders (Hartz et al., 2017). It has been suggested that the genetic risk factors for schizophrenia (especially within neural systems that contribute to the risk for both psychosis and addiction) make patients vulnerable to substance use. This vulnerability may arise before the psychotic symptoms. Increased substance use in adolescence may both enhance the risk for developing a substance use disorder, and it can also be an additional risk factor for the appearance of psychotic symptoms (Khokhar et al., 2018). However, there is no evidence of a special subgroup of schizophrenia that is especially strongly characterized by substance use (Buckley et al., 2009).

Most patients with psychosis and comorbid substance use disorder do not receive appropriate treatment (Weaver et al., 2001). They are not identified by treatment services, and they do not receive special intervention (Weaver et al., 2003) which should be a combination of case and medical management and include possible opioid maintenance treatment if needed (Kern et al., 2014).

2.3.7 Comorbid serious mental and substance use disorder, and the criminal justice system

Persons with serious mental disorder and comorbid substance use disorder are overrepresented in the mental health and substance abuse treatment systems, but also in the criminal justice system (Baillargeon, 2010). Persons who have this comorbidity are more likely to be arrested, incarcerated, and to commit acts of violence. They are also more likely to be reincarcerated within a year of discharge when compared to those with only a mental or substance use disorder (Messina et al., 2004). In the United States, the prevalences of serious mental illnesses are 3–4 times higher in prisons than in the general population, and the estimates of current and lifetime prevalence of schizophrenia vary from 2 to 6.5% (Prins et al., 2014). In jails, the prevalence of current serious mental illness for men was 15% and for women 30% (Steadman et al., 2009). The vast majority (approximately 75%) of forensic patients in Australia have a lifetime substance abuse or dependence disorder. They have more criminal histories and higher level of risks and needs when compared with patients with only major mental illness (Ogloff, 2004).

This comorbidity of mental and substance use disorder is related to violent offending, juvenile records, imprisonment, and drug use preceding the index crime. Presence of co-occurring antisocial personality disorder increases the rate and severity of offending and necessitates effective treatments (Putkonen et al., 2004; Ogloff et al., 2015). The impact or lack of mental health and substance use treatment access has been stated to affect to the prevalence of mental illnesses in prisons (Peters et al., 2015). In Finnish prisons, there has been a rapid 10-fold increase in psychotic disorders during the years 2005–2016, and comorbid substance use disorders were detected in only 40% of these prisoners. There was a rapid process of deinstitutionalization in the 1990s in Finnish mental care, and it has been stated that more specialized services for persons with severe mental disorder are now needed (Jüriloo et al., 2017). However, during the deinstitutionalization of psychiatric services life expectancy among people with mental disorders increased faster than among general population (Westman et al., 2012), and it has been argued that the focus should be on community services, not just on mental health services (Putkonen et al., 2018).

2.3.8 Summary of the literature

Several studies have demonstrated that about half of all patients with psychosis have problems with substance use. This comorbidity is associated with many poorer outcomes,

including higher mortality rates. Although the risk of violent behaviour in patients with psychosis is small, it is higher than in the general population. Comorbid substance use disorder is apt to increase this risk. The effects of cannabis use among persons with psychosis have been investigated in several studies, but there have been only few studies on the effects of opioid use disorder even though opioid use is a rapidly increasing worldwide problem. The potential benefits and drawbacks of opioid maintenance treatments are currently unclear, and it is not known how extensively such treatments are used in this patient group. Also, very little is known about the possible correlations between hospitalizations and the use of different illegal substances in patients with schizophrenia. Because substance use disorders have important effects on outcomes among patients with schizophrenia, there is a need for further research in this area.

Several factors are associated with an increased risk of violent behaviour among persons with psychotic disorder. Risk assessment tools are used in clinical settings, but their predictive accuracy is variable, and they can be time consuming to use.

3 Aims of the study

1. To estimate the lifetime prevalence of amphetamine, cannabis, and opioid use disorders among patients in a forensic setting.

2. To identify a background marker among patients with psychosis who were later ordered to involuntary psychiatric treatment as forensic patients.

3. To estimate correlations between psychiatric hospitalizations and amphetamine, cannabis and opioid use disorders in patients with schizophrenia.

4. To estimate the prevalence of opioid maintenance treatment in patients with schizophrenia and comorbid opioid use disorder.

4 Subjects and methods

4.1 GENERAL BACKGROUND OF THE STUDIES

Study I and Study II were based on data of forensic patients obtained from the National Authority of Medicolegal Affairs. In Study I, the data were compared with information from Statistics Finland including all patients with both a psychotic disorder and substance use disorder diagnoses, and with information on substance use in the Finnish general population from Finnish studies.

Study III included data from the medical files of outpatients with schizophrenia in a public psychiatric outpatient clinic, and of inpatients with schizophrenia in a University psychiatric hospital.

In Study IV, the study population consisted of all patients with schizophrenia spectrum disorders who were undergoing involuntary treatment as forensic patients in Niuvanniemi Hospital in 2012.

4.1.1 Study I: Amphetamine, cannabis, and opioid use disorders among forensic psychiatric patients

The forensic psychiatric examination statements for individuals who were ordered to involuntary psychiatric treatment as forensic patients with a psychotic disorder during the years 1995–1999 in Finland were reviewed. The individuals in question were accused of violent crimes such as homicide, attempted homicide, aggravated assault, rape, or arson. All of them had undergone a pretrial forensic psychiatric examination. Diagnoses, earlier crime records, possible amphetamine, cannabis or opioid use disorder (ICD-10), general socio-demographic information, and the violent crimes that prompted the forensic psychiatric examination were investigated. The information was gathered retrospectively from the forensic examination statements.

In 1995–1999, a total of 206 persons were ordered to undergo hospital treatment after forensic examinations in Finland. Six of these individuals were excluded because of insufficient information (i.e., there was not enough information in the forensic psychiatric examination statements), and ten because they were accused of non-violent crimes (e.g. thefts, burglaries, or drug offences), so the final study population consisted of 190 subjects.

Data were gathered from the National Hospital Discharge Register for the year 1998, covering all patients who had a diagnosis of a psychotic disorder (ICD-10: F20-29 schizophrenia, schizotypal disorder or delusional disorder), and comorbid amphetamine, cannabis or opioid use disorder. Information about the Finnish population for the same year was obtained from Statistics Finland, and information on substance use in the Finnish population was drawn from Finnish studies. The year 1998 was chosen because it was the year for which information on the use of the substances in question was available, and it was acceptably close to the temporal midpoint of the study period (1995–1999). Ethical approval for this study was received from the Finnish Ministry of Social Affairs and Health.

4.1.2 Study II: Previous forensic examination as a background marker among patients with psychosis and the risk of future violent behaviour

Like Study I, this work focused on patients ordered to involuntary hospital treatment in Finland between 1995 and 1999 after forensic mental examination. There were 206 such patients in total, but one was excluded due to insufficient information (i.e., there was not enough information in the forensic mental examination statement), and ten due to being accused of non-violent crimes, so the final sample consisted of 184 individuals.

Ethical approval for the study was granted by the Finnish Ministry of Social Affairs and Health.

4.1.3 Study III: Hospitalization rates in patients with schizophrenia and comorbid amphetamine, cannabis, or opioid use disorder

The study population initially consisted of 150 patients who were previously diagnosed with schizophrenia according to ICD-10. All data were collected from the medical files of 75 outpatients in a public psychiatric outpatient clinic (Itäkeskus Psychiatric Outpatient Clinic, Helsinki) and 75 inpatients in a University psychiatric hospital (Kuopio University Hospital, Kuopio). The sample was constructed by adding the first six or seven patients admitted to each clinic in each month of 2010 until the quota of 75 patients from each environment was reached. The diagnoses, substance use history, and psychiatric treatment history of each patient were gathered, together with general socio-demographic information. In addition, the subjects' ICD-10 codes at discharge were checked. The psychiatric medical files were investigated to determine whether each subject satisfied the diagnostic criteria for harmful use or dependence of amphetamine, cannabis, or opioids according to the ICD. In most cases, no urine screen data were available. Of the 150 patients initially included in this study, four were excluded because of insufficient information (i.e., there was not enough information about substance use or psychiatric treatment history in the medical files). Ethical approval was obtained from the National Institute for Health and Welfare, the Research Ethics Committee of the Kuopio University Hospital, and the committee of the City of Helsinki Health Centre.

4.1.4 Study IV: Opioid maintenance treatment among forensic patients with schizophrenia and opioid use disorder

The study population of 148 individuals included all patients with schizophrenia spectrum disorder undergoing involuntary treatment as forensic patients in Niuvanniemi Hospital in 2012. Diagnoses and socio-demographic information were collected from the hospital's medical registers as forensic examination statements and patient files, and opioid use disorder was defined as either harmful use or dependence according to ICD-10. The study population was compared with the available information from the persons using substance abuse services. According to that information, 565 of the 1860 persons (30.4%) using those services were receiving maintenance treatment. The study was approved by the National Institute for Health and Welfare.

5 Results

5.1 STUDY I

According the forensic psychiatric examination statements for individuals who were ordered to involuntary psychiatric treatment as forensic patients, the prevalences for cannabis, amphetamine, and opioid use disorders were 22.1%, 14.7%, and 4.7%, respectively. The risk ratios (forensic patients vs. other patients with psychosis) were 105.44 for amphetamine, 122.83 for cannabis, and 94.90 for opioid use disorder.

Cannabis use disorder was 1.5-fold (95% CI 0.97–2.31) more common than amphetamine use disorder among forensic patients, and 1.3- fold (95% CI 0.81–2.16) more common among non-forensic patients. The prevalences of cannabis-related diagnoses were 4.7- fold (95% CI 2.34–9.32) more common than opioid use disorders among forensic patients (95% CI 2.34–9.32), and 3.7-fold (95% CI 1.84–7.44) more common among non-forensic patients. Of the final study population of forensic patients, 172/190 (90.5%) were male, 116/190 (61%) had schizophrenia, 26/190 (14%) delusional psychoses, 14/190 (7%) schizoaffective disorders, and 26/190 (14%) other psychoses.

5.2 STUDY II

A total of 96 subjects of the 184 patients (52.2%) had a prior criminal record (covering all crimes, including minor offenses), and 26 (14.2%) had previously undergone at least one forensic mental examination. The diagnosis of psychosis was made before the index crime or crimes in 110 cases of 184 (59.8%). A total of 22 of those 110 patients (20.0%) had already undergone at least one earlier forensic mental examination (12.0% of the total study population), and 61 of the 110 patients (55.5%) had a criminal record.

Ten of those 22 patients (45.5%) who had received a diagnosis of a psychotic disorder before the index crime had been in psychiatric inpatient treatment following their earlier forensic mental examination. Nine of these ten were released to psychiatric outpatient care, and one patient commit a new crime while still in hospital treatment and underwent a new forensic mental examination. Ten patients (45.5%) went to prison after the forensic mental examination. Seven of the 22 patients (31.8%) had undergone two prior forensic mental examinations. Of the 22 patients, two patients (9.0%) were found not guilty by reason of insanity, but they were also not considered to require psychiatric hospital treatment after the forensic mental examination (Figure 1). Twenty-one of the 22 patients (95.5%) had a schizophrenia spectrum diagnosis (ICD-10: F20–25).

Seventy-four of the 184 subjects (40.2%) had not been diagnosed with a psychotic disorder prior to their forensic mental examination. The frequencies of amphetamine, cannabis, and opioid use disorders among patients diagnosed with a psychotic disorder before the index crime were very similar to those among patients whose first diagnosis of psychosis occurred during the forensic mental examination for the index crime.

Of the study population of 184 forensic patients, 112/184 (61%) had schizophrenia, 28/184 (15%) delusional psychoses, 13/184 (7%) schizoaffective disorders, 7/184 (4%) affective disorders, and 24/184 (13%) other psychoses.

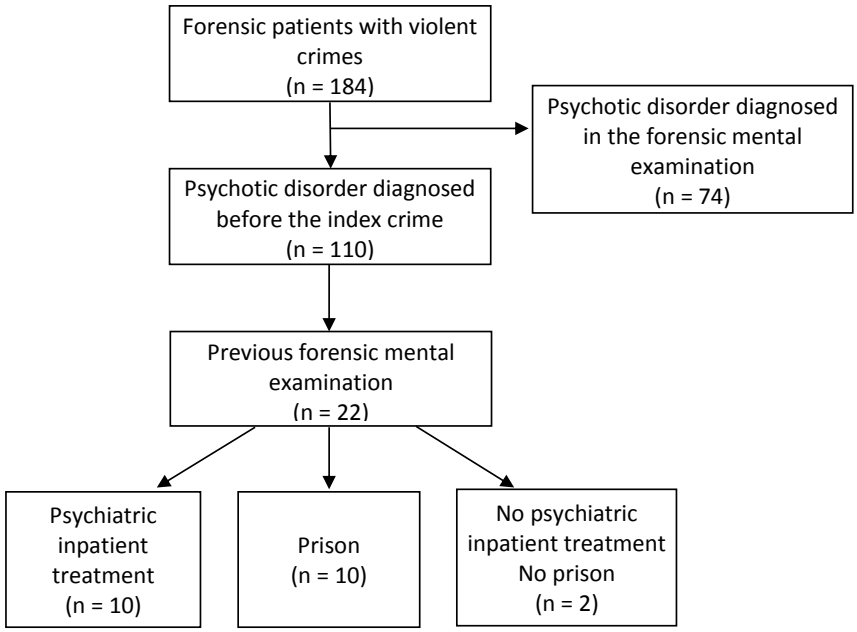

Figure 1. A flow chart of the study population (Study II).

5.3 STUDY III

The final study sample included 146 patients, and nine of them (6.2%) had a history of harmful use or dependence on more than one of the studied substances.

Among patients with schizophrenia and harmful use or dependence on any substance under study (amphetamine, cannabis and/or opioid), the number of hospitalizations was 1.51-fold greater (95% CI 1.30–1.76) than that for non-users ($p < 0.001$). The incidence rate ratio for hospitalizations was 2.9 (2.47–3.63) for opioid use disorder compared to those with no harmful use of opioids or opioid dependence, 2.0 (1.71–2.41) for amphetamine use disorder, and 1.6 (1.33–1.84) for cannabis use disorder. The risk of hospitalizations was significantly higher for harmful use or dependence according to ICD-10 on opioids than for harmful use or dependence on amphetamines ($p < 0.001$) or cannabis ($p < 0.001$). Among patients with polysubstance use disorder, the incidence rate ratio for hospitalizations was 2.3 (1.91–2.76).

The mean ages of the 64 men and 82 women were 25 (SD ± 7) years and 26 (SD ± 9) years. Of the 146 subjects in the cohort, sixteen (10.9%) had a history of harmful use or dependence on cannabis, thirteen (8.9%) on amphetamine, and six (4.1%) on opioids (Figure 2). Of opioid use disorders, three subjects used buprenorphine and one used heroin; no information was available regarding the main opioid used by the remaining two opioid-dependent subjects. The medical files indicated that none of the subjects had been prescribed opioids.

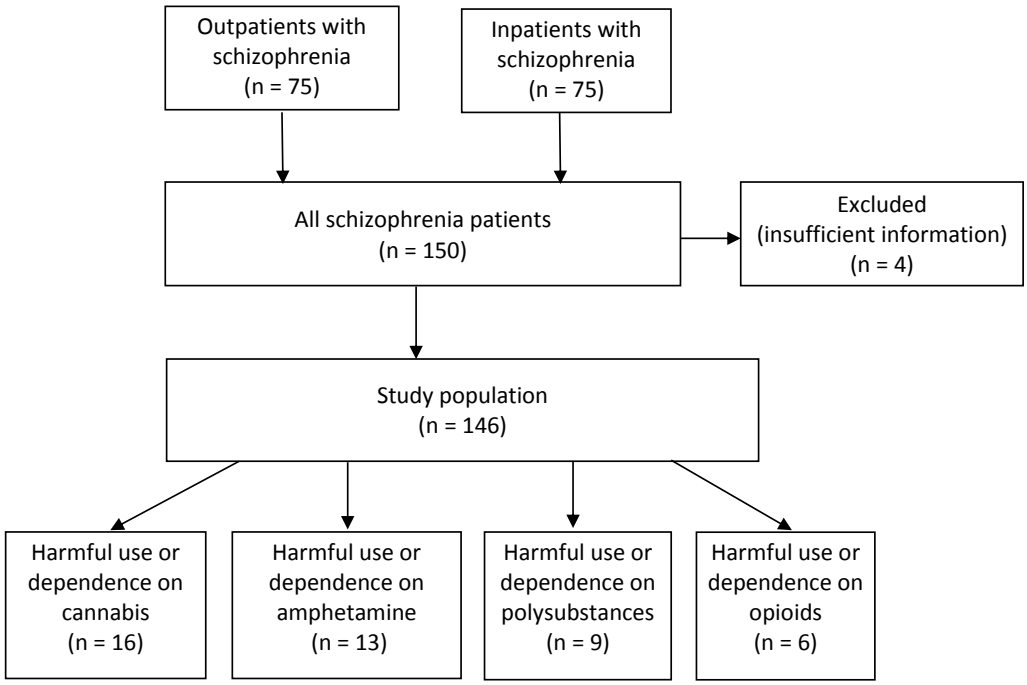

Figure 2. A flow chart of the study population (Study III).

5.4 STUDY IV

Of the study population, 23/148 (15.6%) had a history of harmful opioid use or dependence according to ICD-10, and 2/23 (8.7%) had received opioid maintenance treatment (95% CI = 1.1–28.0). Because dependence and harmful use can be challenging to distinguish from each other based on information collected retrospectively, these two categories were combined. The corresponding proportion among all patients with harmful use/dependence using substance abuse treatment services was 565/1860 (30.4%) (95% Cl: 28.3–32.5). The fraction of patients receiving maintenance treatment was significantly lower among the cohort of forensic patients ($p = 0.022$).

The cohort of forensic patients consisted of 148 persons, of whom 141 (95.3%) were male, 83 (56.1%) had paranoid, 30 (20.3%) undifferentiated, 5 (3.4%) hebephrenic, and 6 (4.1%) some other type of schizophrenia. A total of 24/184 (16.2%) had a schizoaffective disorder. The mean age of the sample was 42.8 years, and the mean age at the time of offense was 30.9 years.

6 Discussion

This thesis presents an investigation into possible differences in between the prevalence of the three most commonly used illicit substances (amphetamines, cannabis and opioids) among patients with psychosis in a forensic setting. The goal was to find potential differences in between these substances in terms of how their use is associated with rehospitalizations of patients with schizophrenia. Another goal was to obtain information on the role of opioid maintenance treatment in the treatment of patients with schizophrenia and comorbid opioid use disorder. An additional objective was to identify an easily used background marker among patients with psychosis who were later ordered to involuntary psychiatric treatment as forensic patient.

The studies presented in this thesis supported earlier findings of the high prevalence of substance abuse among patients with psychosis (Regier et al., 1990; Koskinen et al., 2010; Sara et al., 2014a; Jørgensen et al., 2018) when compared to general population (Ollgren et al., 2014; National institute for Health and Welfare, 2016; EMCDDA, 2017d). A history of problematic substance use has been found to be highly prevalent among offenders with psychotic illness and severe violent crime, and substance abuse has a strong mediating effect on the risk for violent offending in schizophrenia (Fazel et al., 2009a). For example, in a study of Yee et al. (2011), the history of hazardous alcohol intake or the use of any illicit drug was present in almost all cases (95%), and according the study of Kudumija et al. (2014), alcohol addiction is the strongest violent offending predictor.

The increased risk of violent offending has not been attributed only to the effects of comorbid substance abuse in patients with schizophrenia (Short et al., 2013), but in forensic settings, about 25% of patients with schizophrenia and comorbid substance abuse are found to be violent offenders, compared to only 7% of patients without this comorbidity (Rice et al., 1995). In females, schizophrenia is a particularly strong risk factor for violence (Short et al., 2013), but when the psychosocial history of homicidal offenders was explored, there was no gender differences in the prevalence of substance abuse or psychiatric diagnoses (Putkonen et al., 2011).

This is the first study exploring amphetamine, cannabis and opioid use disorders among forensic patients with a serious mental illness and violent crimes. Amphetamine use has been associated with the possibility of violent outbursts (Lowinson et al., 1997; Håkansson and Jesionowska, 2018), and it could be expected that amphetamine users would be overrepresented. However, in the study presented herein (Study I), there were no substantial differences in the relative prevalences of amphetamine use disorders between forensic and non-forensic patients with a psychotic disorder. Cannabis use disorder was more common than amphetamine or opioid use disorder among forensic patients with a severe psychotic illness. Also, prevalences of amphetamine and opioid use disorders were higher in this patient group than estimated from the comparison group, but the corresponding difference in the prevalences of cannabis use disorder was small.

According to earlier findings, the distribution of psychotic illness has been found to be high among abusers of amphetamine and cannabis in contrast to the lower prevalence of psychosis among abusers of opioids (Dalmau et al., 1999), and opioids are described to be the only sedative drugs that have anti-psychotic effect (Maremmani et al., 2014), and so with this sample of forensic patients caution must be applied, as the findings might not be transferable to all patients with psychosis.

The burden of violent behaviour highlights the importance of preventive interventions, and successful preventive efforts may improve the life of many persons. In the etiology of violent behavior among patient with schizophrenia, genetic and early environmental risk factors have an important role (Fazel et al., 2009b). According to a meta-analysis of Nielssen

et al. (2010), approximately 4 in 10 homicides committed by persons with a psychotic disorder occur before treatment. This is in line with the finding in the study presented herein. In this study, the diagnosis of psychosis was made before the violent crime in 60% (110/184) of the cases, but violent crimes included also attempted homicide, aggravated assault, rape and arson.

Conviction for a violent crime before the diagnosis of schizophrenia may be the strongest predictor of future convictions for such crimes (Witt et al., 2015). There is a group of high-risk patients with severe chronic schizophrenia, which is not detected or treated properly (De Tribolet-Hardy et al., 2016). The scope for primary prevention of aggressive behaviour among persons with psychotic disorders such as schizophrenia is limited, but secondary prevention might be possible. Different risk assessment tools are used in clinical and criminal settings, but their predictive accuracy is variable. They might identify low risk individuals with high levels of accuracy, but they cannot be used as sole determinants (Fazel et al., 2012). Also, the tools are usually developed in individuals without psychosis (Singh et al., 2011), and are often time consuming to use. A prediction score for risk of committing violent crime in individuals with schizophrenia or bipolar disorder was developed by Fazel et al. (2017). It was based on routinely collected factors, and helps to identify especially those who are at low risk of violent offending. The strongest predictors in 12 months are conviction of previous violent crime, male sex, and age. According the study presented herein, previous forensic mental examination can be a useful background marker among psychotic patients indicating effective violence relapse prevention. It can be used easily in daily clinical work to help recognize members of high-risk subgroup (Study II). These patients, who have a diagnosis of psychotic disorder and have undergone forensic mental examination, need special monitoring of symptoms, substance abuse, medication compliance, and aggressive or antisocial behaviour.

Hospitalization rates have been used to assess the overall effectiveness of psychiatric care systems (Durbin et al., 2007), and readmissions can be considered an indicator of relapse in schizophrenia (Olivares et al., 2013). At least in Finland, patients with schizophrenia are primarily readmitted to psychiatric hospitals because of relapses. Substance use disorders have a significant impact on the hospitalization rates of patients with schizophrenia (Schmidt et al., 2011; Addington et al., 2013), but to date, it is not known whether or not there are differences between different substances and their associations with the number of hospitalizations. As stated in several publications (Margolese et al., 2004; Barnes et al. 2006; Addington et al., 2007), patients with schizophrenia had cannabis use disorder most frequently according to the study presented herein, but as a novel finding it was found out that harmful use or dependence of opioids in patients with schizophrenia was associated with higher risk of hospitalization than either harmful use or dependence of amphetamine or cannabis (Study III).

Although considerable research has been devoted to the nature of the relationship between cannabis use and schizophrenia, rather less attention has been paid to other specific substances. The burden of disease consequent of drug dependence is highest when it is question of opioid dependence (UNODC, 2017), and patients diagnosed with opioid use disorder and schizophrenia belong to the costliest group of all patients with opioid abuse (Shei et al., 2015). However, there is only limited number of previous studies about opioid maintenance treatment among patients with schizophrenia and comorbid opioid abuse. The findings presented here (Study IV) indicate that at least in this subgroup of forensic patients with schizophrenia, such treatments are rarely used for patients with schizophrenia and comorbid opioid use despite the WHO's recommendation that opioid maintenance treatments should be available in different settings (WHO, 2009). Evidence-based medications for opioid dependence can be used successfully in patients with severe mental disorder as schizophrenia (Robertson et al., 2018), but on the other hand, it has been described that the retention rate in opioid maintenance treatment among patients with schizophrenia at 12 months is less than 10%, and about 55% of the patients have illicit

opioid use during the treatment (Guerra et al., 2006). Compared to other patients, these patients are more likely to have been homeless and to have had a recent psychiatric hospitalization (Marienfeld and Rosenheck, 2015).

In an Iranian descriptive study of 100 patients with schizophrenia, as much as 50% of patients had opioid dependence disorder based on DSM-IV criteria. This high prevalence of dependence is probably influenced by the easy access and low price of opioids in Iran, but it was speculated that patients with schizophrenia may use opioids as self-medication to reduce positive symptoms (Ghaffarinejad et al., 2009). This theory may be relevant only for patients who progressed from psychotic disorder to drug addiction, not vice versa (Maremmani et al., 2011).

In the study presented herein, only about 9% (2/23) of forensic patients with schizophrenia and comorbid opioid use disorder had received opioid maintenance treatment. In comparison, the estimated proportion of problem opioid users undergoing maintenance treatment suggests a treatment coverage rate of about 50% in the European Union (EMCDDA, 2010). In Finland, opioid maintenance treatment is typically initiated in inpatient units, after which the clients are transferred to social outpatient services or health centers (EMCDDA, 2017d). The coverage of maintenance treatment in Finland may vary between different regions, and there is no other monitoring system or register of clients in treatment but data collection on a voluntary and anonymous basis by the centers for prevention and treatment of addiction (Partanen et al., 2017). About 2,400 patients were receiving opioid maintenance treatment at the end of 2011 according a survey of all units providing medication-assisted detoxification and maintenance treatment for opioid dependence (Partanen et al., 2014), but according the information of maintenance treatment collected by THL, the number of persons in opioid maintenance treatment in 2011 was 565. This information did not cover all the units offering substance abuse services (Forsell, 2012).

The latest estimate of persons with problem opioid use in Finland is 13,000–15,000 from the year 2012 (EMCDDA, 2017d). According a recent study, the number of clients in opioid maintenance treatment has increased being about 30% higher in 2015 than in 2011 (Partanen et al., 2017). Although there is a decline in the nonmedical use of prescription opioids at least in the Unites States, recent prevalence rates of opioid users indicate a notable increase in heroin use (Marsh et al., 2018). So, it could be expected that the overall number of opioid users is not going to diminish in the near future.

7 Limitations

The primary limitation of these studies is their retrospective design and care should be taken when interpreting the results. Data were originally collected for other purposes. There maybe also unknown potential confounders. Basic categorical variables were used, but not matching. Inclusion to the studies was restricted to clear categories (forensic and schizophrenia patients). The forensic psychiatric statements present the results of thorough psychiatric investigations and are generally considered reliable information sources. Moreover, the statements are independently evaluated by THL, and are all prepared using the same standards, which improves their homogeneity. As such, the data in the forensic psychiatric statements can be considered comprehensive and of sufficient quality.

There are only estimates of the prevalence of amphetamine, cannabis, and opioid use in Finland, and no exact information about the use of these substances in 1998 is available. Additionally, substance use disorder diagnoses presumably underestimate actual usage levels. Among psychotic persons, the prevalence of substance use and substance use disorders is probably much higher than that recorded in national hospital discharge statistics. However, it can be assumed that this underestimation applies equally to all illicit substances. It is thus unlikely that missing information would bias the results because it would be missing for incidental reasons. Considering all studies herein, the diagnoses of harmful use or dependence (amphetamine, cannabis, and opioids) were made based on the subjects' psychiatric medical files, and the fulfilment of the ICD-10 diagnostic criteria was checked. In most cases no urine screen data were available. All data were collected by the same person, so inter-rater reliability was not an issue.

There is no comprehensive statistics of the use of substance abuse services in Finland. It has been voluntary for the treatment places to participate to the information collection organized by THL, and it has been estimated that the available information has covered only about third of the users of those services (Forsell, 2012). So, the information of persons with opioid use disorder and their treatment is quite incomplete. However, in this study, it was presumed that the information available was representative enough since information from different substance abuse services is not described to be missing from systematic reasons.

The categories of dependence and harmful use can were combined (Study IV), and so it is theoretically possible that among forensic patients with opioid use disorder there were also patients with only harmful use of opioids, not dependence.

8 Conclusions and future directions

The general consequences of the possible violent offending resulting from a psychotic disorder affect not only the patient and the index victim but people around them, resulting in enormous human suffering and having long-standing consequences for health, social and criminal systems. These forensic patients with violent behaviour constitute a small but important subgroup of the most stigmatized patients. The studies herein show that violent behaviour among patients with psychosis is associated with amphetamine, cannabis or opioid use disorder.

According to this study, opioid use disorder is associated with poorer outcome in patients with schizophrenia when compared to amphetamine or cannabis use disorder. However, little is known about the impact of possible opioid maintenance treatment in this patient group. Coordination of mental health care and substance disorder services is essential for successful treatment, and more attention to possible opioid use disorder among patients with severe psychotic disorder should be given when planning comprehensive treatment. This is of special importance because the use of different types of opioids is a growing problem worldwide.

Previous forensic examination appears to be an easily checked background marker among patients with psychosis who were later ordered to psychiatric treatment as forensic patients.

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KRISTIINA KIVIMIES

Psychotic disorders like schizophrenia are associated with considerable disability and human suffering. Most individuals with psychoses never behave aggressively, but compared to general population, the risk of violent behaviour is higher in this patient group. Comorbid substance use disorder is known to increase this risk. This thesis presents an investigation into possible differences in between amphetamine, cannabis, and opioid use disorders among patients with psychosis in a forensic setting, and among patients with schizophrenia in general psychiatry.

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