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Risto Ilomäki

SUBSTANCE USE DISORDERS
IN ADOLESCENCE:
COMORBIDITY,
TEMPORALITY OF ONSET
AND SOCIO-DEMOGRAPHIC
BACKGROUND

A STUDY OF ADOLESCENT PSYCHIATRIC
INPATIENTS IN NORTHERN FINLAND

UNIVERSITY OF OULU GRADUATE SCHOOL;
UNIVERSITY OF OULU, FACULTY OF MEDICINE,
INSTITUTE OF CLINICAL MEDICINE, DEPARTMENT OF PSYCHIATRY;
OULU UNIVERSITY HOSPITAL

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RISTO ILOMÄKI

**SUBSTANCE USE DISORDERS IN
ADOLESCENCE: COMORBIDITY,
TEMPORALITY OF ONSET AND SOCIO-
DEMOGRAPHIC BACKGROUND**

A study of adolescent psychiatric inpatients
in Northern Finland

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Abstract

Over 90% of addicts start substance use during adolescence. There are few studies focusing on the comorbidity and temporality of substance dependence among adolescents. The aim of this study was to investigate the comorbidity and temporality of substance use disorders, to identify the factors leading to intravenous drug dependence and to evaluate the psychotropic medication history among adolescents.

The study population comprised a sample of 508 (300 girls) 12- to 17-year-old hospitalized inpatients during a defined 5-year period. Substance use and other psychiatric disorders were identified according to DSM-IV criteria and adolescents' socio-demographic and substance use background was examined.

The main findings of the present study include the following: The most common comorbidities of alcohol and drug dependence are behavioral, depressive and phobic disorders; Phobic and behavioral disorders develop generally prior to the onset of alcohol and drug dependence; Drug dependent boys are more likely to have depression than girls (IV); In adolescence, phobic disorders may influence the development of secondary substance dependence within a few years from the onset of phobia (I); Behavioral disorders are associated with earlier initiation of daily smoking, and earlier age of onset of daily smoking is associated with an increased risk for alcohol and drug dependence (III); Adolescents with intravenous drug dependence start experiment with drugs at young age, often before the age of 10 years, and present more commonly with parental absence and troubled school background (II); Prescribed benzodiazepine medication is associated with an increased risk of sedative dependence (V).

These findings imply that psychiatric comorbidity plays a pivotal role in the development of substance use disorders in adolescence. Those adolescents who experiment with substances at a young age are at greatest risk of substance dependence and intravenous drug use before the age of 18. Family dynamics seem to play an important role in this development. The psychotropic medication history of substance-using adolescents often differs greatly from current evidence-based guidelines and is dominated by those medications that are frequently abused.

Keywords: abuse, adolescent, alcohol, dependence, drug, medication history, psychiatric comorbidity, sociodemographic factors, substance, temporality of onset

Ilomäki, Risto, Päihdehäiriöiden komorbiditeetti, ajallisuus ja sosiodemografinen tausta psykiatrisessa osastohoidossa olevilla alaikäisillä nuorilla.

Oulun yliopiston tutkijakoulu; Oulun yliopisto, Lääketieteellinen tiedekunta, Kliinisen lääketieteen laitos, Psykiatria, PL 5000, 90014 Oulun yliopisto; Oulun yliopistollinen sairaala, PL 26, 90029 OYS

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Tiivistelmä

Yli 90 % päihdeongelmaisista aloittaa päihteidenkäytön nuoruusiällä. Silti päihdehäiriöiden ja niihin liittyvän psykiatrisen sairastavuuden – komorbiditeetin ja tämän ajallisen ilmenemisen – temporaliteetin - tutkimus nuorisoväestössä on suppeaa.

Väitöskirjatutkimuksen tarkoituksena oli kartoittaa nuoruusiän päihdehäiriöiden komorbiditeetin ja temporaliteetin ominaispiirteitä, selvittää taustalla olevia sosiodemografisia tekijöitä, sekä arvioida päihdehäiriöisten nuorten reseptilääkehistoriaa päihdehäiriöiden synnyn ymmärtämiseksi.

Tutkimusaineisto koostui 508 (300 tyttöä) 12-17-vuotiaasta akuuttia psykiatrista sairaalahoitoa tarvitsevasta potilaasta. Nuorten psykiatrinen- ja päihdesairastavuus selvitettiin DSM-IV diagnoosijärjestelmän mukaisesti, sekä sosiodemografinen tausta kartoitettiin kattavasti.

Alkoholi- ja huumeriippuvaisilla nuorilla yleisimpiä komorbiditeetteja häiriöitä olivat käytös-, masennus- ja pelkohäiriöt. Pelko- ja käytöshäiriöt ilmenivät yleensä ajallisesti ennen alkoholi- ja huumeriippuvuutta. Huumeriippuvaisilla pojilla oli tyttöjä useammin masennusta (IV). Pelkohäiriöt vaikuttivat sekundaarisen päihderiippuvuuden kehittymiseen mahdollisesti jo muutamien vuosien kuluessa pelkohäiriöiden ilmenemisestä (I). Käytöshäiriöt liittyivät aikaisempaan päivittäisen tupakoinnin aloittamiseen joka liittyy edelleen sekä alkoholi- että huumeriippuvuuteen (III).

Suonensisäisen huumeidenkäytön aloittaminen nuorella iällä liittyi selkeästi vanhemmattoomaan kotiin, sekä jo ala-asteella alkaneisiin koulunkäyntiongelmien. Vaikeimmin päihderiippuvaisien nuorten päihteidenkäyttökokeilut alkoivat merkittävän nuorena, jo onnen 10 ikävuotta ala-asteella (II). Bentsodiatsepiinien reseptilääkkeekäyttö sairaalahoitoa aiemmin liittyi merkittävästi sedatiiviriippuvuuteen (V).

Löydösten perusteella psykiatrisella sairastavuudella on merkittävää rooli päihdehäiriön kehittämisessä jo nuoruusiällä. Nuoret, joiden päihdekokeilut alkavat varhain, ovat suurimmas- sa riskissä riippuvuuteen ja ajautumiseen suonensisäiseen käyttöön. Päihderiippuvaisilla nuoril- la on lisäksi taipumus sekä reseptilääkkeiden väärinkäyttöön, että kykyä näiden hankkimiseen - myös lääkärin määräämänä.

Asiasanat: alkoholi, huumeet, lääkitys, nuoruusikä, psykiatrinen komorbiditeetti, päihde, riippuvuus, sociodemografiset tekijät, temporaliteetti, väärinkäyttö

To my family

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Abbreviations

ADHD	Attention deficiency/hyperactivity disorder
ALD	Alcohol use disorders = Alcohol abuse/dependence
AMPH	Amphetamine
ANOVA	Analysis of variance
ANX	Anxiety disorders
AUDIT	Alcohol Use Disorders Identification Test
BD	Behavioral Disorders
BDZs	Benzodiazepines
CAPA	Child and Adolescents Psychiatric Evaluation
CD	Conduct disorder
CGAS	Children's global assessment scale
CI	Confidence interval
CIDI	Composite International Diagnostic Interview
DALYs	Disability adjusted life years
Delta-9-THC	Delta-9-tetra-hydro-cannabinol
DEP	Depressive disorders
DD	Drug use disorders = Drug abuse/dependence
DISC-IV	Diagnostic Interview Schedule for Children Version IV
DSM-III-R	Diagnostic and statistical manual on mental disorders, third edition - revised
DSM-IV	Diagnostic and statistical manual on mental disorders, fourth edition
ESPAD	European School Survey Project on Alcohol and Other Drugs
EuropASI	European addiction severity index
FAS	Fetal alcohol syndrome
GSMS	Great Smoky Mountains Study
HIV	Human immunodeficiency virus
HR	Hazard Ratio
ICD-10	International Classification of Disorders, tenth edition
IDD	Intravenous drug dependence
IDU	Intravenous drug use
K-SADS-PL	Schedule for affective disorder and schizophrenia for school-age children present and lifetime
MDD	Major depressive disorder
MPA	Methylphenidate

MWU	Mann-Whitney U-test
NCS	National comorbidity survey
NCS-A	National Comorbidity Survey, Adolescent supplement
NCS-R	National Comorbidity Survey - Replication
NES	National Epidemiological Survey
NESARC	National Epidemiological Survey on Alcohol and Related Conditions
NIMH	National Institute of Mental Health
OCD	Obsessive-compulsive disorder
ODD	Oppositional defiant disorder
OR	Odd's ratio
PSY	Psychotic disorders
PTSD	Post-traumatic stress disorder
RR	Risk ratio
SD	Standard deviation
SUD	Substance use disorders
SNRIs	Serotonin/Noradrenalin Reuptake Inhibitors
SSRIs	Selective serotonin re-uptake inhibitors
TCA	Tricyclic antidepressant
YAPA	Young Adult Psychiatric Evaluation
WHO	World Health Organization

List of original Publications

This thesis is based on the following publications, which are referred to in the text by the Roman numerals I-V

- I Ilomäki R, Hakko H, Timonen M, Lappalainen J, Mäkiyö T & Räsänen P (2004) Temporal relationship between the age of onset of phobic disorders and development of substance dependence in adolescent psychiatric patients. *Drug and Alcohol Dependence* (6): 327–330.
- II Ilomäki R, Kaartinen K-L, Viilo K, Mäkiyö T, Räsänen P & Study-70 workgroup (2005) Intravenous drug dependence in adolescence – what lies in the background? *Journal of Substance use* 10(5): 315–326.
- III Ilomäki R, Hakko H, Riala K, Räsänen P, Lappalainen J, Mäkiyö T, Timonen M & Study 70 workgroup (2008) Temporal association of onset of daily smoking with adolescent substance use and psychiatric morbidity. *European Psychiatry* 23(2): 85–91.
- IV Ilomäki R, Södervall J, Viilo K, Hakko H, Räsänen P & Study-70 workgroup (2008) Drug dependent boys are more depressed compared to girls: a comorbidity study of substance dependence and mental disorders. *European Addiction Research* 14(3): 161–168.
- V Ilomäki R, Ilomäki E, Hakko H, & Räsänen P (2011) Psychotropic medication history of inpatient adolescents – is there a rationale for benzodiazepine prescription? *Addictive Behaviors* 36 (1–2): 161–165.

Also, some unpublished data are presented in this thesis.

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1 Introduction

Clinical and epidemiological studies suggest that, during their lifetime, between 50% and 80% of all substance users have met the criteria for at least one other psychiatric diagnosis (Armstrong & Costello 2002). Over 90% of adult addicts start their substance use in adolescence (Sheehan *et al.* 1988). Substance use in Finnish adolescents typically begins at the age of 12 to 13 years, and substance use disorders start to emerge at the age of 14 to 15 years (Marttunen 2000). Substance use disorders are typically long-lasting, persistent, challenging to treat and have a tendency to relapse after remission. Adolescents with substance use disorder often abuse more than one substance, for example tobacco, alcohol and illegal drugs. Substance use endangers normal development in adolescence; cognitive, social and emotional development of substance-using adolescents is often severely impaired. Different forms of risk-behavior are associated with substance use, adolescents with trouble with substances may be more prone to accidents, may be sexually reckless and susceptible to abuse. Financing the substance use may lead to criminal activity and conflict with the law. Adolescents who use drugs intravenously have a high risk for fatal viral infections and are vulnerable to infections that are comparatively rare in their peers. Patients diagnosed with substance use disorder in adolescence are more often diagnosed with substance use disorder, psychiatric comorbidity and impaired social and economical functionality in adulthood. The younger the substance use starts, the more likely it is that these problems will continue into young adulthood, and the more evident is the reflection to psychosocial wellbeing and psychiatric morbidity (Marttunen 2000). In a U.S. general population sample approximately one third of adolescents with any psychiatric condition, and only one in seven adolescents with substance use disorders, receive treatment for their condition (Merikangas *et al.* 2011).

Substance use problems create a significant medical, social and economical burden, not only for those who suffer from these disorders, but also to society in general (WHO 2010). The presence of untreated psychiatric comorbidities among patients with substance use disorders is associated with poor treatment outcomes (Deas 2006). The treatment and diagnosis of comorbid psychopathology is therefore fundamental in the treatment of substance use disorders. Substance use is generally initiated in adolescence or early adulthood and is commonly accompanied by other psychiatric morbidity (Armstrong &

Costello 2002). Treatment utilization for substance use disorders among adolescents has been reported to be low (Merikangas *et al.* 2011).

Further study of the comorbidity, temporal relationship (temporality) of comorbidities and sociodemographic background of substance use disorders in adolescence would invariably result in earlier diagnosis, treatment initiation and preferable outcome.

Following an amendment to the Finnish Mental Health Act that stipulated that minors under 18 years could no longer be hospitalized within adult psychiatric wards (Aho & Huuhtanen 1992), a new acute psychiatric ward for adolescent patients was set up at Oulu University Hospital in Northern Finland. All of the adolescent psychiatric inpatients in the catchment area of Oulu University Hospital are initially treated in this unit. The STUDY-70 project was initiated in the beginning of 2001, just as the new unit began operating. A large database, consisting of the 508 patients – of whom 300 were girls and 208 boys – admitted to the unit 70 during a 5-year period between April 2001 and May 2006, was created with the aim of examining the association between various psychosocial risk factors for severe psychiatric disorders among young hospital-treated adolescents. The aim of this thesis is to investigate the risk factors for substance use disorders and the temporal association between substance use and other psychiatric disorders.

2 Review of the literature

2.1 Global burden of substance use

According to the World Health Organization (WHO 2010), the magnitude of worldwide substance use is estimated at 2 billion alcohol users, 1.3 billion smokers and between 172 and 250 million illicit drug users. Worldwide, 76.3 million men and women are diagnosed and receive treatment for alcohol use disorders and at least 15.3 million persons are being treated for diagnosed drug use disorders. Globally, it is estimated that 4.1% of healthy life years (QALYs – Quality adjusted life years, Weinstein *et al.* 2009) are lost due to tobacco, 4.0% to alcohol and 0.8% to illicit drugs. In 2002, intravenous drug use (IDU) was reported in 136 countries, of which 93 report HIV-infection among the IDU-population (WHO 2010). Treatment of drug use disorders has been evaluated as being economically beneficial. It has been estimated that, for every 5 dollars invested in drug treatment, 7 dollars are saved in health and social costs. Alcohol use by itself accounts for 4.5% of the global disease burden and is responsible for 3.8% of all deaths worldwide. Rates of alcohol-related deaths are highest in Europe and in the countries of the American continent. Illicit drug use is also a major concern for both the developed and developing world. Cannabis is the most commonly used illegal substance, accounting for an estimated 80% of illicit drug use worldwide. The next most commonly used psychoactive substances are stimulants (including amphetamine), cocaine and ecstasy. It is estimated that 15.9 million people are injecting drugs worldwide and the latest figures report intravenous use in 148 of 192 United Nations countries. Of deaths worldwide, 0.4% are attributable to intravenous drug use. The use of stimulants such as amphetamine has increased rapidly in Asia and Europe. The non-medical use of prescription sedative and analgesic medication is also thought to be considerable. (WHO 2010)

Alcohol intoxication leads to increased risk-taking and impaired judgment, which are associated with accidental injuries. Alcoholism contributes to more than 60 different disorders, including fetal alcohol syndrome (FAS), liver diseases, neurological disorders, cardio- and cerebro-vascular diseases and several cancers (WHO 2010).

The harmful and hazardous use of psychoactive substances is associated with poverty, social exclusion, health problems and criminal behavior. Intravenous

drug use is closely associated with blood-borne viruses, such as HIV and Hepatitis B and C transmission through the sharing of needles, as well as other injecting equipment. Dependence, overdose and a variety of serious mental health problems are among the main health risks associated with drug use (WHO 2010).

Adolescence is characterized by rapid biological, psychological and social changes. Late- adolescence includes major events like graduating, choosing a profession and leaving childhood home. This developmental phase requires considerable mental work, setting goals and objectives and taking both active and conscious responsibility of one's own life. Adolescence is a significant transitional phase that holds increased and continuous demands in the social, educational and occupational fields, while offering at the same time a broad stream of new attractions. The choices made during this period have life-long effects. Therefore, substance abuse arising during this developmental period is particularly injurious and deserves research attention.

2.2 Definition of substance use disorders

According to the WHO (2010), "Substance abuse refers to the harmful or hazardous use of psychoactive substances, including alcohol and illicit drugs. Psychoactive substance use can lead to dependence syndrome - a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and that typically include a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal state" (WHO 2010).

The medical classification of substance use disorders is usually based on the diagnostic criteria of ICD-10 (International Classification of Disorders, 10th edition, WHO 1992) or DSM-IV (the Fourth edition of Diagnostic and Statistical Manual of Mental Disorders, American Psychiatric Association 1994). The ICD-10 is used in clinical work especially in European countries, while the DSM-IV is more widely used by clinicians in the U.S. and is widely used in the field of research. Substance use disorders include substance abuse and substance dependence.

Both the ICD-10 and the DSM-IV classifies individuals with substance use into two distinct categories: substance use, and substance dependence. Abuse implies maladaptive use leading to failure to fulfill responsibilities at school,

work or in social life. Dependence is more severe form of abuse, often involving increase in substance use, high tolerance and strong desire to use substance despite obvious social impairments (APA 1994). Although these two categories of the DSM-IV contain extensive criteria of substance use problems, the definitions exclude individuals who are engaged in experimental or recreational use, without having handicap in their social and occupational life – the most common form of substance use in the community (Bauman & Phongsavan 1999).

2.2.1 Definition of substance abuse

The diagnostic criteria for substance abuse (harmful use) according to ICD-10 (WHO 1992) include the following: A) clear evidence that the substance use was responsible or substantially contributed to) physical or psychological harm, including impaired judgment or dysfunctional behavior, which may lead to disability or have adverse consequences for interpersonal relationships. B). The nature of the harm should be clearly identifiable (and specified). C) The pattern of use has persisted for at least 1 month or has occurred repeatedly within a 12-month period. D) The disorder does not meet the criteria for any other mental or behavioral disorder related to the same drug in the same time period.

The DSM-IV (APA 1994) defines substance abuse as a maladaptive pattern of substance use leading to clinically significant impairment of one (or more) of the following symptoms, occurring within a 12-month period: 1) Recurrent use resulting in a failure to fulfill major role obligations at work, school, or home (such as repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; or neglect of children or household). 2) Recurrent use in situations in which it is physically hazardous (e.g. driving an automobile or operating a machine when impaired by substance use). 3) Recurrent substance-related legal problems (such as arrests for substance-related disorderly conduct). 4) Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (for example, arguments with spouse about consequences of intoxication and physical fights). According to the DSM-IV, a person can be abusing a substance or dependent on a substance but not both at the same time.

2.2.2 Definition of substance dependence

The diagnostic criteria for substance dependence according to ICD-10 (WHO 1992) include that three or more of the following manifestations should have occurred together for at least 1 month or, if persisting for periods of less than 1 month, should have occurred together repeatedly within a 12-month period: (1) a strong desire or sense of compulsion to take the substance; (2) impaired capacity to control substance-taking behavior 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; (3) 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; (4) 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; (5) 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; (6) persistent substance use despite clear evidence of harmful consequences.

The DSM-IV (APA 1994) defines substance dependence as maladaptive use of a substance, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring any time in the same 12-month period: 1) Tolerance, as defined by either of the following: (a) A need for markedly increased amounts of the substance to achieve intoxication or the desired effect or (b) Markedly diminished effect with continued use of the same amount of the substance. 2) Withdrawal, as manifested by either of the following: (a) The characteristic withdrawal syndrome for the substance or (b) The same (or closely related) substance is taken to relieve or avoid withdrawal symptoms. 3) The substance is often taken in larger amounts or over a longer period than intended. 4) There is a persistent desire or unsuccessful efforts to cut down or control substance use. 5) A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects. 6) Important social, occupational, or recreational activities are given up or reduced because of substance use. 7) The substance use is continued despite knowledge of having a

persistent physical or psychological problem that is likely to have been caused or exacerbated by the substance (for example, current cocaine use despite recognition of cocaine-induced depression or continued drinking despite recognition that an ulcer was made worse by alcohol consumption).

In this thesis, DSM-IV is used exclusively. The diagnostic criteria for substance abuse and dependence according to DSM-IV are further explained in the methods section (APA 1994).

2.3 Prevalence of substance use in adolescence

Substance use usually emerges and becomes more common as adolescents get older. A longitudinal study of 1,420 U.S. general population adolescents noted that, by the age of 16 years, more than half of adolescents have reported substance use (Costello *et al.* 1999). The highest proportion of use has been reported for alcohol (54% girls and 50% of boys), followed by tobacco (14% and 17%, respectively) cannabis (11% and 15%), and amphetamine (2.8% and 2.3%). The prevalence of opioid use was reported as 1.2% for boys and 1.1% for girls among US general population adolescents, 6.3% of girls and 5.7% of boys had developed substance abuse or dependence by the age of 16. The mean onset age for substance use disorders (SUD) was 14.6 years for girls and 14.3 years for boys (Costello *et al.* 1999).

In Australian general population, the last-month prevalence of alcohol use was 36% among 12- to 15 year-old adolescents and 70% among 16- to 17 year old adolescents (White & Hayman 2006a). The lifetime prevalence for illicit drug use was 15% among 12- to 15 year-olds and 33% among 16- to 17 year-olds (White & Hayman 2006b). As seen in Figure 1 (below), the reported alcohol use among Finnish adolescents has increased constantly with age (Raisamo *et al.* 2011).

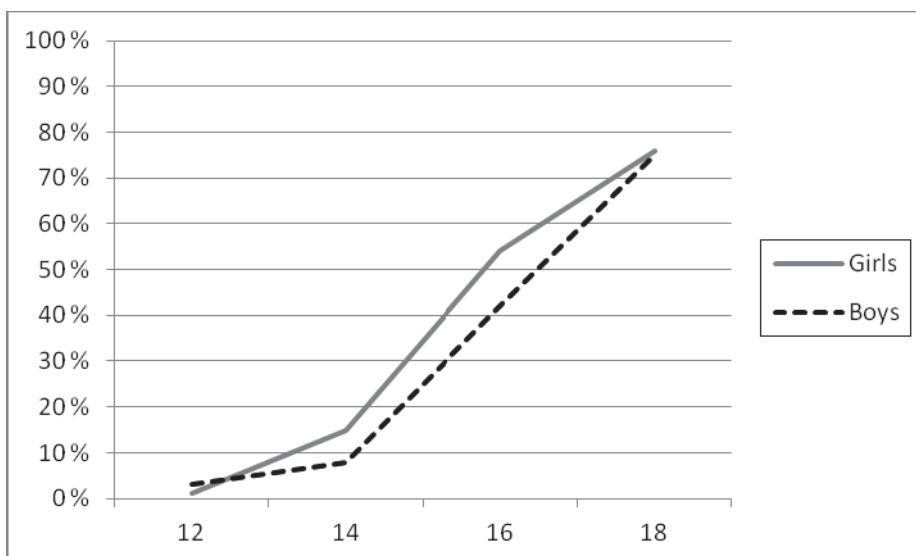


Fig. 1. Alcohol use among Finnish adolescents. The proportion of 12-, 14-, 16-, and 18-year-old adolescents who use alcohol regularly (at least once a month). Illustration by the author according to figures presented by Raisamo et al. 2011.

Even though DSM-IV (APA1994) recognizes nicotine dependence as a substance diagnosis, it is not usually accounted as a substance use disorder, and is analyzed separately, more commonly as a risk factor for other substance use disorders or other psychiatric comorbidity. Among Finnish adolescents, the prevalence of daily smoking has been reported to decline during the last two decades; in 1991 28% of boys and 24% of 14- to 18 year-olds in the general population were daily smokers. The latest, corresponding figures were 19% for boys and 16% for girls (Raisamo *et al.* 2011). Among German adolescent inpatients aged 16-17, the prevalence of regular smoking was 78% in boys and 54% in girls (Ribeiro *et al.* 2008). Among younger adolescent inpatients (mean age 13.7 years) in the U.S. the prevalence of daily smoking was lower, being 39% (Upadhyaya *et al.* 2003).

2.3.1 Prevalence of alcohol use

The prevalence of alcohol and other drug use has recently been comprehensively assessed in 35 European countries. Over 100, 000 adolescent students (mean age 15.8) participated in the European School Survey Project on Alcohol and Other Drugs (ESPAD). The proportion of Finnish adolescents who have consumed

alcohol during the last 12 months (77%) was similar to the European average (82%); the proportion of those adolescents who were drunk was reported as higher (45% vs 39%) (Hibell *et al.* 2009). Please see Figure 1. The rates of alcohol consumption in Finland have been reported as generally similar (9.3 liters of pure alcohol per capita per year) to those in Scandinavian countries - 13.1 liters in Denmark, 10.8 liters in southern and 8.4 liters in northern Sweden - yet alcohol use disorders are reported more commonly in Finland. The rates for alcohol dependency symptoms among young people (16–29 years) in these countries were 47% in Finland, 29% in Denmark and 18% in southern and 21% in northern Sweden (Bloomfield *et al.* 2010). Swendsen and colleagues (2012) recently reported that in general population, 78% of US adolescents had consumed alcohol and 47% were drinking regularly (Swendsen *et al.* 2012). Among German adolescent psychiatric inpatients, 70% of adolescents had tried alcohol. Of these 16- to 17-year-old adolescents, 74% of boys and 30% of girls used alcohol regularly (Ribeiro *et al.* 2008).

2.3.2 Prevalence of drug use

In Finland, drug use is more common in southern parts of the country, particularly the Helsinki metropolitan area (Pahlen & Marttunen 2005). In 2002 roughly one fourth of adolescents/young adults (15 to 24 years) reported lifetime use of cannabis. Even though the growth in the number of people trying illicit drugs seems to have decreased since the beginning of the decade, the proportion of abusers has grown. It has been estimated that the prevalence of drug use disorders in Finnish general population is 0.6-0.8% (Pahlen & Marttunen 2005). The prevalence of drug use disorders among young urban Finnish adults has been evaluated to be significantly higher, with one-month prevalence of cannabis use disorders reported at 2.7% (Aalto-Setälä *et al.* 2001). At the end of 1990s the prevalence of drug trials among 15- to 16-year-old adolescents had doubled: in 1999 10% of girls and 11% of boys had used drugs at least once (Ahlström *et al.* 1999). The 2003 ESPAD reported that 11% of 15- to 16-year-old Finnish 9th graders had used cannabis (Hibell *et al.* 2004): in the 2007 ESPAD this percentage had dropped to 8% of the adolescents in this age group and was reported to be considerably lower than the average of in other ESPAD countries, 19% (Hibell *et al.* 2009). The lifetime prevalence of other drug use in Finland was 3%, also lower than the ESPAD average of 6%. The lifetime prevalence of abuse of prescription medication was 7%, the same as in other ESPAD countries. Poly-

substance use of psychotropic medication and alcohol was more common among adolescents in Finland (17%) than in other European countries (9%) participating in the ESPAD in 2003 (Hibell *et al.* 2004), but this finding was not present in the ESPAD in 2007, where 9% of Finnish and 6% of other ESPAD adolescents were found to use alcohol and psychiatric medication simultaneously (Hilbell *et al.* 2009). Among U.S. adolescents of general population (Swendsen *et al.* 2012), the prevalence of drug use is significantly higher; the opportunity to use illicit drugs has been reported to be 81% and the prevalence of drug use as high as 43%. The prevalence of lifetime drug use among German adolescent inpatients was reported to be 50% and 23% of the adolescent inpatients had used drugs during the past month (Ribeiro *et al.* 2008).

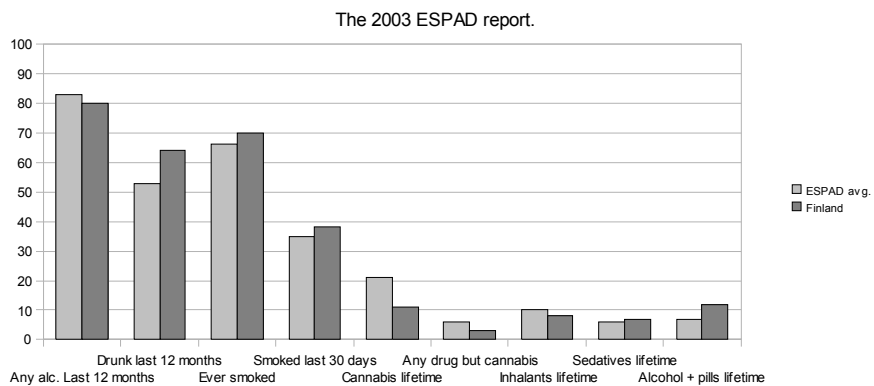


Fig. 2. Substance use rates among European 15- and 16- year-olds. European School Project for Alcohol and other Drugs, ESPAD (Illustration by the author on the basis of figures according to Hibell *et al.* 2007).

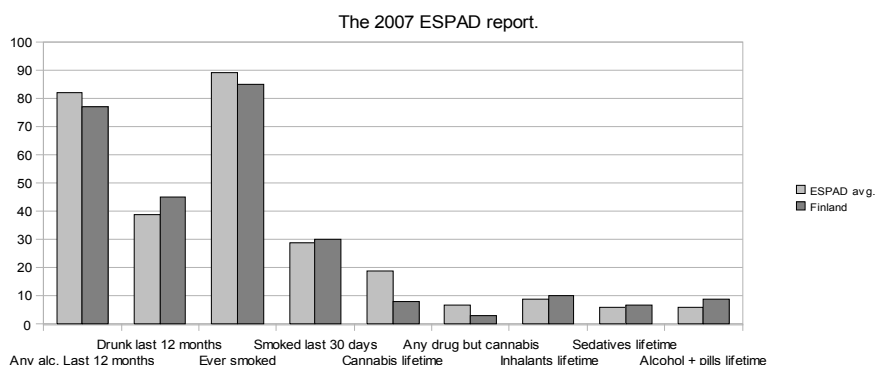


Fig. 3. Substance use rates among European 15- and 16- year-olds. European School Project for Alcohol and other Drugs, ESPAD (Illustration by the author on the basis of figures according to Hibell et al. 2009).

2.4 Prevalence of substance use disorders in adolescence

Recently published results in the Adolescent supplement of the National Comorbidity Survey (NCS-A) included 10, 123 U.S. adolescents aged between 13 and 18 years (Merikangas *et al.* 2010). It reported increased lifetime (DSM-IV) prevalences of 6.4% for alcohol abuse/dependence (ALD) 8.9% for drug abuse/dependence (DD) and 11.4% for any substance use disorder (SUD). These disorders were more frequent among males (Merikangas *et al.* 2010). Among adolescent psychiatric patients of various treatment settings the prevalence of SUD has been evaluated higher, being 25% among 13- to 17-year-olds in the U.S. Cannabis use disorders were reported to account for more than 80% of all SUD (Wu *et al.* 2011). Compared to other psychiatric disorders, SUD appeared to have a later age of onset, with a rapid increase in incidence after the age of 15 years. At the age of 18 years, the estimated risk for any SUD was 23.8%. The median age for onset for SUD was 15 years (Merikangas *et al.* 2010). Health service utilization for substance disorders is relatively low, as only 15% of adolescents with substance disorder in the U.S. general population receive treatment for it (Merikangas *et al.* 2011).

The prevalence of substance use disorders among European adolescents has been evaluated among children and adolescents by Ravens-Sieberer and co-workers (2008). They measured the prevalence of mental health problems in German general population by using a subsample of 2,863 children aged 7–17

years from a total sample of 17,641 children aged 0–17 years for the analysis (BELLA-study). For each family participating in the BELLA study, one computer-assisted telephone interview was conducted with the child and a parent. Mental health problems were identified using standardized screening instruments, constructed taking into account the diagnostic criteria of ICD-10 and DSM-IV. The BELLA-report showed a prevalence of alcohol consumption with impairment to be 0.5% among girls and 2.6% among boys. The prevalence for repeated drug use with impairment was 0.7% for girls and 1.6% for boys. The BELLA study can be criticized for its methodological limitations regarding the interviews, in addition the participation rate was 70%. Even so, this study is one of the few studies on European general population adolescent samples (Ravens-Sieberger *et al.* 2008). Niethammer and Frank (2007) studied the prevalence of substance abuse and dependence among German adolescent inpatient population. DSM-IV Substance use diagnoses were assessed by M-CIDI diagnostic interviews in this rather small clinical sample of 70 adolescents. The prevalence of alcohol use disorders was 33% among boys and 25% among girls. The prevalence of drug abuse was 9% and that of drug dependence 17%: the most common were abuse and dependence of cannabis, followed by hallucinogens and opioids. Vreugdenhill and colleagues (2003) reported a prevalence of 55% for substance use disorders among incarcerated Dutch male adolescents.

2.5 Prevalence of psychiatric disorders in adolescence

2.5.1 Depressive disorders

The lifetime prevalence of mood disorders in the U.S. in 13- to 18-year-old adolescents has been reported to be 14.3% in the NCS-A (Merikangas *et al.* 2010). The prevalence of mood disorders increased uniformly with age, with a twofold yearly increase from 13–14 to 17–18. At the age of 18 years the estimated risk for mood disorder was 18.2%. In this study females were twice as likely to have depressive disorders and more likely to suffer from bi-polar disorders than males. The median age of onset for mood disorders was 13 years (Merikangas *et al.* 2010). Approximately every third (38%) adolescent with mood disorders in the U.S. received treatment for their condition (Merikangas *et al.* 2011). The prevalence of depressive symptoms in the general population of German adolescents was 5.6% for girls and 5.5% for boys (Ravens-Sieberger *et al.* 2008).

and among German adolescents only 23% of those with DSM-IV depressive disorders used mental health services (Essau 2005). The prevalence of depression in general adolescent population (14–16 years) in Finland has been reported to be 11% for girls and 6% for boys (Kaltiala-Heino *et al.* 1999) and the prevalence of depression among Finnish adolescent (12–17 yrs) psychiatric inpatients to be 26% (Laukkanen *et al.* 2003).

2.5.2 Behavioral disorders

In the general population of U.S. adolescents, the lifetime prevalence of any of the behavioral disorders was 19.6% (Merikangas *et al.* 2010). The prevalence of ADHD was reported to be 8.7% with a male to female-ratio of 3:1. The prevalence of oppositional defiant disorder (ODD) was reported as 12.6% and 6.8% of the adolescents met the criteria for lifetime conduct disorder (CD). The estimated risk for behavioral disorders at the age of 18 years was 17.6% and the median onset for behavioral disorders was 11 years (Merikangas *et al.* 2010).

Results of a cohort study of ADHD in Northern Finland showed the prevalence of ADHD in adolescents to be 8.5% (Smalley *et al.* 2007). The symptoms of behavioral disorders are easily recognizable and have the highest rates of disorder-specific treatment, with 60% of adolescents with ADHD and 45% of adolescents with other behavioral disorders receiving treatment for their respective disorders (Merikangas *et al.* 2011). The prevalence of behavioral symptoms in the general population of German adolescents was 6.7% for girls and 10.7% for boys (Ravens-Sieberer *et al.* 2008). Although the prevalence of conduct and oppositional disorders in the Finnish adolescent population has not been reported, the prevalence of behavioral disorders among hospitalized adolescents in Finland has previously been found to vary from 13% to 15% (Sourander & Turunen 1999).

2.5.3 Anxiety disorders

Nearly one third (31.9%) of adolescents in the U.S. meet the criteria for lifetime anxiety disorders (Merikangas *et al.* 2010). The most common anxiety disorder is specific phobia (19.3%). Anxiety disorders are more common among females. Anxiety disorders generally occur earlier than other psychiatric disorders and there is a steep increase in early childhood as well as a more gentle increase after the age of 12. At the age of 18 years, the estimated prevalence of anxiety

disorders was reported as 26.2%. The median onset age for anxiety disorders was reported to be 6 years (Merikangas *et al.* 2010). Adolescents with anxiety disorders are not always accessing treatment since only 18% of adolescents with anxiety disorders in the U.S. and in Germany have received treatment (Merikangas 2011, Essau 2005). The prevalence of anxiety symptoms in the general population of German adolescents was 7.5% for girls and 5.2% for boys (Ravens-Sieberger *et al.* 2008). The prevalence of anxiety disorders has scarcely been studied among adolescents in Finnish general population but the prevalence of anxiety disorders in Finnish adult population has been reported as 4.1%, with no significant gender difference (Pirkola *et al.* 2005).

Lifetime prevalence of social phobia in the general population has been reported to vary from 4% to 15% in adolescents (Verhulst *et al.* 1997, Last *et al.* 1992). Lifetime prevalences of agoraphobia and simple phobia have been reported to vary from 3% to 7% and from 6% to 22%, respectively (Curtis *et al.* 1998, Magee *et al.* 1996). NCS-A showed prevalences of 9.1% for social phobia, 2.4% for agoraphobia and 19.3% for simple (specific) phobia. The 12-month prevalence of social phobia in the Finnish general population of adolescents has been reported as 3.2% (Ranta *et al.* 2009). In the U.S., only one fifth of adolescents with non-comorbid social phobia had been in contact with a mental health professional (Merikangas *et al.* 2011). The majority of studies have found the onset age of phobic disorders to be between 11 and 16 years. (Compton *et al.* 2000, Magee *et al.* 1996).

2.5.4 Other psychiatric disorders

In Finland, the prevalence of psychotic disorders among inpatient adolescents has been reported as 12% (Laukkanen *et al.* 2003). In the United Kingdom the prevalence of schizophrenia and other psychoses has been reported to have slowly declined during the last decade: the prevalence rate of psychotic disorders was reported to be 155 in 100,000 patient years of exposure in the general population in 2006, the mean onset age of psychotic disorders being 29.7 years (Frischer *et al.* 2009). The three-year prevalence of psychotic disorders in the general population of Scottish adolescents has been reported as 5.9 of 100, 000 (Boeing *et al.* 2007). Twenty percent of psychotic adolescents were not in contact with mental health services and for 80% of the psychotic adolescents the first inpatient treatment contact was in adult psychiatric wards (Boeing *et al.* 2007).

In the U.S. general population sample of adolescents (NCS-A) the lifetime prevalence for bipolar disorder was reported as 2.9%, without statistically significant gender differences (Merikangas 2010). Furthermore, the lifetime rate for disorder-specific mental health service use among adolescents with bipolar disorders was 22.2% (Merikangas *et al.* 2011).

In NCS-A the lifetime prevalence of eating disorders among adolescents was 2.7%, with girls (3.8%) diagnosed with eating disorder more often than boys (1.5%). The service utilization for eating disorders was relatively high, being 36.2% for all adolescents (Merikangas *et al.* 2011).

2.6 Psychiatric comorbidity of substance use disorders in adolescence

It has been suggested that, even within the general population, two out of every three adolescents with SUD have at least one other comorbid diagnosable psychiatric disorder (Armstrong & Costello 2002). On the basis of previous literature, Brook and colleagues (2000) presented three possible models to explain the relationship between substance use disorders and other psychiatric comorbidity; first, a psychiatric disorder precedes and affects the development of substance use disorder. Second, substance use disorder and comorbid psychiatric disorder share common etiological factors. Third, a substance use disorder precedes and affects the development of comorbid psychiatric disorder.

In a review of population-based sample studies, the Odds Ratios (ORs) for comorbidity of any psychiatric disorder with substance use disorder has been reported to vary from 3.5 to 18.6 with a median of 4.7. (Armstrong & Costello 2002). Among youths with diagnosed SUD in juvenile detention, the prevalence of other psychiatric morbidity was over 74% (Abram *et al.* 2003, Vreugdenhil *et al.* 2003). Psychiatric comorbidity has been reported to be more common among those adolescents who started substance use at a younger age (Rohde *et al.* 1996). Previous methodologically sound studies on comorbidity of substance use disorders and other psychiatric disorders in the general population and treatment population samples are presented in Tables 1 and 2, respectively, and are discussed in detail below.

Table 1. General adolescent population studies on comorbidity of Substance use disorders and other psychiatric disorders.

Authors and year of publication, country (study)	Sample size, gender distribution	Mean age (years)	Interview tool	Time frame	Informant	Prevalence of psychiatric disorders among adolescents with SUD	Disorders statistically significantly associated with SUD
<i>Essau 2011, Germany</i>	1035, ♀ 41%, ♂ 59%	14.3 years	CIDI, (DSM-IV)	Present	Adolescent	ANX 17%, PHO 9%, DEP 28%, SOMA 28%	NS
<i>Macdonald et al. 2010, US, (NAS)</i>	1868 ♀ 45%, ♂ 55%	14.8 years	Structured phone interview, (DSM IV)	6 months	Adolescent	SUD among PTSD	NS
<i>Lansford et al. 2008, US, (Child Development Project)</i>	585 ♀ 48%, ♂ 52%	Follow-up at 18 years	DIS, DSM-IV	Follow-up, lifetime. Evaluation at 18 years.	Participants	♀: 22% ♂:12% ANX 9%, DEP 10%, INT 21%, BD 28%, BD-INT 36%	INT p<0.05 BD p<0.001 BD-INT p<0.001
<i>Whitbeck et al. 2008, US/Canadian adolescents reservations /Canadian</i>	651 indigenous	10-12 and 13-15 years.	DISC-R, CIDI, DSM-IV.	Follow up, lifetime	Adolescent, parent.	CD 62%	NS
<i>Roberts et al. 2007, US, (TH 2000)</i>	4175 ♀ 49%, ♂ 51%	≤12yrs 27% 13y-15y 48% 16y-18y 25%	Computer assisted DISC-IV (DSM-IV)	12 months	Adolescent	no prevalences given	Please see table 4.
<i>Chi et al. 2006, US 2005</i>	♀ 57%, ♂ 43%	12-17 years.	Clinical (ICD-9)	1 year	Adolescent, clinical	♀: MDD 67%, Bipol 15%, ♂ MDD 58%, Bipol 18%	MDD p<0.0001

Authors and year of publication, country (study)	Sample size, gender distribution	Mean age (years)	Interview tool	Time frame	Informant	Prevalence of psychiatric disorders among adolescents with SUD	Disorders statistically significantly associated with SUD
<i>Sung et al. 2004, US, (GSMS)</i>	1420	16 years	CAPA (DSM-IV)	Prospective, follow up at 16 years.	Adolescent	-	CD (OR=1.7) ANX (OR=1.6) predict SUD at age 16.
<i>Kilpatrick et al. 2003, US, (NSA)</i>	3906 ♀ 49%, ♂ 51%	12-17 years	Modified NWS (DSM-IV)	6 months, 12 month for SUD.	Adolescent phone interview	♀: PTSD 25%, DEP 39% ♂: PTSD 14%, DEP 17%	NS
<i>Warner et al. 2001, US, (NCS)</i>	641 ♀ 45%, ♂ 55%	15-18 years	CIDI (DSM-IV)	Past year	Adolescent, Parent	No prevalences,	MOOD OR=3.0 ANX OR=1.1ns
<i>Warner et al. 2001, Puerto Rico</i>	922 ♀ 54%, ♂ 46%	15-18 years	CIDI (DSM-IV)	Past year	Adolescent, Parent	No prevalences, mood and anxiety analyzed.	MOOD OR=2.4ns ANX OR=3.2ns
<i>Costello et al. 1999, US</i>	1420 ♀ 50%, ♂ 50%	Follow-up at 16 years	CAPA, DSM-III-R	Longitudinal, Lifetime	Adolescent, parent	♀: DEP 35%, ANX 19%, BD 26% ♂: DEP 30%, ANX 5%, BD 11%	♀: BD p<0.001 ♂: DEP p<0.001
<i>Kandel et al. 1999</i>	401 ♀ 47%, ♂ 53%	14yrs 23% 15yrs 24% 16yrs 27% 17 yrs 25% 18 yrs 1%	DISC 2.3	Lifetime	Adolescent, parent	DEP 49%, ANX 16%, BD 25%	DEP: OR=4.5, ANX: OR=2.1 BD: OR=5.6

Table 2. Table 2. Results on comorbidity of substance use disorders and other psychiatric disorders in clinical adolescent population studies.

Authors and year of publication, country	Sample size, gender distribution	Mean age (years)	Interview tool	Time frame	Informant	Treatment setting	Prevalence of psychiatric disorders among adolescents with SUD (♀/♂)	Disorders statistically significantly associated with SUD
<i>Essau 2011</i> , Germany	374 substance abuse treatment patients ♀ 56%, ♂ 44%	16.0	CIDI (DSM-IV)	Present	Adolescent	Outpatient	ANX 22%, PHO, 12%, DEP 29%	NS
<i>Wu et al. 2011</i> , United States	1423 Psychiatric patients ♀ 31%, ♂ 69%	2-12 yrs (7%) 13-17 yrs (93%)	Electronic health record database (DSM-IV)	Lifetime	Adolescent, Medical records on treatment visits by medical professionals	Outpatient and Inpatient	MOOD:49%/29% ANX: 19%/9% CD: 26%/19% ADHD: 12%/21% PSY: 4.1%/4.3%	ANX OR=2.1, ADHD OR=2.8, CD OR=2.0, PSY OR=0.3, MOOD OR=0.9
<i>Langenbach et al. 2010</i> , Germany	151 substance abuse treatment patients ♀ 25%, ♂ 75%	17.0	CIDI, K-SADS (DSM-IV-TR)	Lifetime	Adolescent and parent	Inpatient	DEP 22%, ANX 27%, CD 60%, SOMA15%	only w/ SOMA
<i>Lehto-Salo et al. 2009, Finland</i>	77 patients with BD ♀ 42%, ♂ 58%	12-18	SCID-I, K-SADS-PL (DSM-IV)	Lifetime	Adolescent and parent	Institutionalized (Reform School, Inpatient)	SUD among BD, ♀:63%, ♂:27%	Among ♀ BD more prevalent than ♂ BD
<i>Soutullo et al. 2009</i> , Spain	38 patients with Bipolar disorder ♀ 21%, ♂ 79%	13.9	K-SADS-PL (DSM-IV)	Lifetime	Adolescent	Outpatient	18% SUD among Bipolar disorders	NS

Authors and year of publication, country	Sample size, gender distribution	Mean age (years)	Interview tool	Time frame	Informant	Treatment setting	Prevalence of psychiatric disorders among adolescents with SUD (♀/♂)	Disorders statistically significantly associated with SUD
<i>Steinbuechel et al. 2009, US</i>	105 patients ♀/♂? with Bipolar disorder	13.6	K-SADS-E, SCID (DSM-IV)	Present	Adolescent	Outpatient	32% SUD among NS Bipolar disorder	NS
<i>Chan et al. 2008, US</i>	1 (<15yrs) 916 ♀ 34%, ♂ 66%	<15	GAIN, (DSM-IV)	Past Year	Adolescent	Various; inpatient, outpatient, residential, intervention...	CD 72%, ADHD 64%, DEP 53%, ANX 25%	DEP OR=5.6, ANX OR=4.6, BD OR=3.2, DEP OR=5.6, ANX OR=4.9, BD OR= 4.8.
<i>Ribeiro et al. 2008, Germany</i>	432 psychiatric inpatients SUD patients ♀ 46%, ♂ 54%	13.7	Structured Questionnaire (DSM-IV)	Lifetime	Adolescent	Inpatient	BD 28%	♀ OR 6.4 ♂ OR 2.5 s
<i>Salbach-Andreare et al. 2008, Germany</i>	101 anorexia patients ♀ 100%	15.2	SIAB, CIDI (DSM-IV)	Present	Adolescent	Inpatient & outpatient	9% SUD among Anorexia	NS
<i>Hodgins et al. 2007, Sweden</i>	178 substance misusers ♀ 54%, ♂ 46%	♀: SUD 17.8, non-SUD 15.8 ♂: SUD 16.4, non-SUD 17.7	K-SADS, SCID (DSM-IV)	Present	Adolescent and parents	Outpatient	PSY 20% / 30%, MDD 70% / 48%, sPHO 45% / 13%, PTSD 20% / 9%, EAT 40% / 0%, CD 70% / 74%.	♀: PSY, MDD, CD p<0.05 ♂: PSY, MDD, CD p<0.05

Authors and year of publication, country	Sample size, gender distribution	Mean age (years)	Interview tool	Time frame	Informant	Treatment setting	Prevalence of psychiatric disorders among adolescents with SUD (♀/♂)	Disorders statistically significantly associated with SUD
<i>Lubman et al. 2007, Australia</i>	100 substance abusers ♀ 47%, ♂ 53%	19.4	SCID I-P (DSM-IV)	Lifetime	Adolescent	Outpatient	MDD 46%, Panic disorder 15%, PTSD 35%	w/ PTSD and current panic disorder
<i>Chinet et al. 2006, Switzerland</i>	85 substance users ♀ 35%, ♂ 65%	17.1	BDI, ADAD (DSM-IV)	Present	Adolescent	Res/In/outpatient 27%/15%/26%, Other 32%	Decrease in DEP associates with decreased SUD.	NS
<i>Karlsson et al. 2006, Finland</i>	218 mood disord. patients ♀ 82%, ♂ 18%	16.4	K-SADS-PI SCID II by a clinician (DSM-IV)	Lifetime	Adolescent	Outpatient	SUD among DEP: ♀ 58% / ♂ 55%	NS
<i>Cornelius et al. 2004, US</i>	116 with Alcohol use disorders ♀ 35%, ♂ 65%	16.8	SCID (DSM-IV)	Present	Adolescent	Outpatient	MDD 43%	NS
<i>Kelly et al. 2004, US, (PAARC)</i>	503 with SUD ♀ 37%, ♂ 63%	16.6	K-SADS, SCID (DSM-III-R, DSM-IV)	Lifetime, current for SUD	Adolescent and parent	Inpatient + residential 54%, Outpatient 34%, Other 12%	DEP 48%, CD 69%, PHO 18%	NS
<i>Rowe et al. 2004, US</i>	182 drug abuse clinic ♀ 18%, ♂ 82%	15.0	DISC (DSM-III-R)		Adolescent and parent	Outpatient	CD 69%, ADHD 28%, DEP 30%, ANX 38	NS

Authors and year of publication, country	Sample size, gender distribution	Mean age (years)	Interview tool	Time frame	Informant	Treatment setting	Prevalence of psychiatric disorders among adolescents with SUD (♀/♂)	Disorders statistically significantly associated with SUD
<i>Sakai et al.</i> 2004, US	847 psychiatric patients ♀ 16%, ♂ 84%	16.1	CIDI-SAM, DISC, CARI (DSM-IV)	Lifetime	Adolescent	Residential + outpatient	MDD 39%	MDD p<0.01
<i>Fiskenscher & Novins</i> 2003, US	89 substance abuse treatment ♀ 35%, ♂ 65%	13 to 15 16 to 18	DISC-IV-Y, CIDI-I-SAM (DSM-IV, DSM-III-R)	Past year	Adolescent	Residential	CD 74%, ADHD 18%, MDD 15%, PTSD 10%	NS
<i>Jaycox et al.</i> 2003 US, (PETS- A) Substance treatment prog.	1044 substance users	15.8	GAIN (DSM-IV)	3 months	Adolescent	Residential n=577 Outpatient n=511	CD 66%, ADHD 50%	NS
<i>Vreugdenhil et al.</i> 2003, Netherlands	204 100% ♂ in SUD treatment	16.4	DISC (DSM-IV)	Lifetime	Adolescent	Juvenile detention	BD 76%, DEP/ANX 13%	OR 7.0 for BD
<i>Latimer et al.</i> 2002, US	135 in SUD treatment ♀ 25%, ♂ 75%	15.7	DICA-IV (DSM-IV)	Lifetime	Adolescent and parent	Outpatient	gender ♂ vs ♀: BD 77% / 94% MDD 44% / 17% BiPol 2.9% / 4.0%	BD OR=5.7 MDD OR=0.24
<i>Molina et al.</i> 2002, US	395 with Alcohol use disorders ♀ 37%, ♂ 63%	16.8	K-SADS and SCID (DSM-III-R, DSM-IV)	Lifetime	Adolescent and parent	Inpatient and outpatient 88%, other 12%	CD 73%, ADHD 30%	CD and non-alcohol SUD

Authors and year of publication, country	Sample size, gender distribution	Mean age (years)	Interview tool	Time frame	Informant	Treatment setting	Prevalence of psychiatric disorders among adolescents with SUD (♀/♂)	Disorders statistically significantly associated with SUD
<i>Robbins et al. 2002, US</i>	167 in SUD treatment ♀ 13%, ♂ 87%	15.6	DISC-PS, ADAD & unstructured (DSM -III-R, DSM-IV)	Current	Adolescent parent	Outpatient	CD 55%, siPHO 28%, soPHO 31%, aPHO 28%, MDD 30%	Racial differences.NS
<i>Tims et al. 2002, US</i>	600 cannabis abusers ♀ 17%, ♂ 83%	16.0	GAIN (DSM-IV)	Past year	Adolescent	Outpatient	CD 53% ADHD 38%	CD ADHD
<i>Grella et al. 2001, US</i>	992 in SUD treatment ♀ 31%, ♂ 69%	40% 15 60%≥16	DISC-R and CIDI-SAM (DSM-III-R)	Lifetime for PD, Adolescent current for SUD	Adolescent	Inpatient + Residential 76%, Outpatient 24%	CD 59% MDD 15% ADHD 13%	NS
<i>Hannesdottir et al. 2001, Iceland</i>	92 in detoxification treatment ♀ 39%, ♂ 61%	17.2	Medical specialist interv. (DSM-IV)	Past year	Adolescent	Inpatients admitted for detoxification treatment	CD 44% MDD 28% PTSD 11% ANX 6%	NS
<i>Wise 2001, US</i>	91 in SUD treatment ♀ 33%, ♂ 67%	15.4	Interview, child psychiatrist (DSM-IV)	Past Year	Adolescent	Residential, substance abuse treatment	MDD24% CD 24% ADHD 11%	NS

PubMed searches were made for terms substance use, comorbidity, adolescence (for Table 1.), inpatient, outpatient (additionally for Table 2.) were made.

Methodologically sound studies from 2000 to 2012 were selected.

Psychiatric diagnoses: DEP=Depressive disorders, MDD=Major depressive disorder, ANX=Anxiety disorders, PTSD=Post-traumatic stress disorder, BD=Behavioral disorders, BiPol=Bipolar Disorder CD=Conduct disorder, ADHD=Attention deficiency/hyperactivity disorder, PHO=Phobic disorders, ODD=Oppositional defiant disorder, siPHO=Simple Phobia, soPHO=Social Phobia, aPHO=Agoraphobia, SOMA=Somatoform disorders, INT=Internalizing disorder=Combined Anxiety or Depressive disorder, BD-INT=Comorbid Behavioral and Internalizing disorder

Tools: BDI=Beck's depression index, CAPA=The Child and Adolescent Psychiatric Assessment, CIDI=Composite International Diagnostic Interview, CIDI-SAM=CIDI-Substance Abuse Module, DICA-IV=Diagnostic Interview of Children and Adolescents - 4th edition, DISC=Diagnostic Interview Schedule for Children, DISC-R=DISC – Revised, GAIN=Global Appraisal of Individual Needs, K-SADS-PL=Kiddie-Schedule for Affective Disorder and Schizophrenia for school-age children – Present and Lifetime, K-SADS-E=Kiddie-Sads, Epidemiological version. SIAB=Structured Inventory for Anorectic and Bulimic Syndromes for DSM-IV, SWAN=Strengths and Weaknesses of ADHD-Symptoms and Normal Behavior, YAPA=Young Adult Psychiatric Assessment

Diagnostic systems: DSM-IV=Diagnostic and Statistical manual for Mental disorders, fourth edition, DSM-III-R=DSM - third edition - revised.

Studies: CARL=Colorado Adolescent Rearing Inventory, DATOS-A=Drug Abuse Treatment Outcomes Studies for Adolescents, GSMS=Great Smoky Mountains Study, NAS=National Adolescent Survey, NFBC 1986=Northern Finland Birth Cohort 1986, NSA=National Survey of Adolescents, NWS=National Women's Study, PETS-A=Persistent Effects of Treatment Study for Adolescents, TH 2000=Teen Health 2000.

The development of psychiatric comorbidity in substance use disorders and other psychiatric disorders in adolescence continues into adulthood (Marttunen 2000) and the comorbidity is well studied in adult samples (Hasin *et al.* 2007, Hasin & Kilcoyne 2012, Schuckit 2006, Compton *et al.* 2000, Magee *et al.* 1996).

The studies presented in the Tables 1 and 2 present SUD comorbidity combining different substance use disorders. Roberts and colleagues (2007) studied separately the comorbidity of alcohol and drug abuse and dependence with other psychiatric disorders among a population-based sample of adolescents. The results for psychiatric comorbidity from this rather representative population based sample are seen below in Table 3. Mood disorders were significantly associated with only alcohol abuse and any substance abuse. None of the anxiety disorders studied, were statistically significantly associated with SUD. Behavioral disorders were significantly associated with all of the substance use disorders studied and adjusting with other psychiatric disorders emphasized these findings. Roberts and co-workers (2007) reported that 5.3% of the adolescents had been diagnosed with substance use disorder. Although the study represents the comorbidity in general population, and the study population is relatively large, it is somewhat flawed by the small total number of adolescents with comorbid substance use diagnoses and psychiatric disorders, resulting in wide confidence intervals of the ORs. It is clear that behavioral disorders in adolescence are a pivotal element of comorbidity (Roberts *et al.* 2007).

Table 3. Lifetime comorbidity of substance use disorders and other psychiatric disorders among adolescents in general population.

Comorbid Disorder	Alcohol use disorders		Drug use disorders	
	Abuse OR (95%CI)	Dependence OR (95%CI)	Abuse OR (95%CI)	Dependence OR (95%CI)
Mood Disorders	7.8 (3.9-15.6)	12.3 (4.8-31.7)	6.3 (3.6-11.0)	5.1 (2.4-10.9)
Controlled OR	11.7 (5.2-26.5)	5.3 (0.7-40.1)	7.4 (3.5-15.4)	2.9 (0.6-12.9)
Anxiety Disorders	0.7 (0.2-2.0)	2.8 (1.0-7.6)	0.7 (0.3-1.5)	2.2 (1.2-4.3)
Controlled OR	0.5 (0.1-1.9)	0.8 (0.1-5.6)	0.6 (0.3-1.6)	1.0 (0.4-2.8)
Behavioral Disorders	7.9 (4.5-14.0)	12.6 (5.5-28.5)	9.7 (6.4-14.8)	14.0 (8.4-23.4)
Controlled OR	6.1 (3.1-11.8)	9.4 (3.6-24.3)	8.4 (5.4-13.9)	15.0 (8.6 – 26.2)

The figures according to Roberts *et al.* (2007). Adjusted OR's for other psychiatric diagnoses.

2.6.1 Comorbidity with Depressive disorders

The comorbidity of depression with drug use disorders is more widely studied than any other comorbidity in drug use disorders. In the general population the prevalence of depression has been shown to increase from 5.0% in abstaining adolescents to 23.8% in youths who used alcohol regularly and 24.1% in youths who used illicit drugs at least once a year (Kandel *et al.* 1997). Armstrong and Costello (2002) comprehensively reviewed the psychiatric comorbidity of substance use, abuse and dependence among adolescents. In their review article of 15 community sample studies, 10 in the U.S., 2 in Canada, 2 in New Zealand and 1 in Taiwan (n=315 to n=1,710), from 1987 to 2000, the concurrent depression among adolescents with substance use disorders (SUD) was estimated to range from 11.1% to 32% with a median of 18.8%. The majority of studies reported the risk for depressive disorders among adolescents with ORs between 1.5–2.5 (median 2.2) and lifetime ORs 1.5–4.5 (median 3.3). The comorbidity of depressive disorders among adolescents with SUD has been reported to be even higher, 49% in a population-based and 58% in a clinical sample of adolescents (Clark *et al.* 1997).

Couwenbergh *et al.* (2006) reviewed studies on psychiatric comorbidity of SUD in adolescents and young adults treated for SUD in either outpatient or inpatient settings or juvenile detention centers. They included 9 U.S. studies and 1 Icelandic study conducted between 1998 and 2004, with sample sizes ranging from 89 to 992. They reported a variation of 3% to 48% and a weighted mean prevalence of 26% of mood disorders among adolescents with SUD. The comorbidity of SUD and depressive disorders has been found to relate to earlier age of onset and more severe substance use (Rohde *et al.* 1996). As shown in adult depression, secondary depression is not as likely to remit after treatment for substance use (Deas 2006). The presence of comorbid SUD and depression contributed to increased rates of adolescent suicide (Deas 2006). Among the general population of U.S. adolescents, the likelihood for comorbid mood disorders among alcohol dependent adolescents was 12-fold and among drug dependent adolescents 5.1-fold as compared to those without SUD (Roberts *et al.* 2007). Wu and co-workers (2011) reported also a high prevalence of mood disorders (49% for girls and 29% for boys) among adolescents with SUD in treatment population sample. However, this finding did not reach statistical significance in multivariate model (OR=0.9). Chan and colleagues (2008)

reported a 5.6-fold risk for depressive disorders among treatment population of adolescents with SUD.

2.6.2 Comorbidity with Behavioral Disorders

As reviewed by Armstrong and Costello (2000), comorbidity with Behavioral Disorders (Attention-Deficiency/Hyperactivity Disorder [ADHD], Oppositional Defiant Disorder [ODD], Conduct Disorder [CD]) and SUD has been widely documented in community samples. The median prevalence of Behavioral Disorders was reported as 7.0–8.0% in the absence of substance use and 46.0% in the presence of substance use disorder. The risk for Behavioral Disorders (BD) was four-fold among SUD adolescents. Even though the association was clear, there was no clear indication of any gradient of comorbidity with increasing severity of substance use. This may reflect the wide range of the developmental stages of the participants in the studies reviewed. (Armstrong & Costello 2002)

Couwenbergh and colleagues' (2006) review article reported a weighted mean prevalence of 64% for CD and 74% for BD among adolescents receiving treatment for SUD. Among young SUDs in juvenile detention, a one-year prevalence of BD is reported to be 90% (Vreugdenhil *et al.* 2003). The data on previous review studies show an ascending trend in comorbidity rates of BD and SUD from community to clinical and finally to juvenile justice samples (Armstrong & Costello 2002, Couwenbergh *et al.* 2006).

The presence of early-onset conduct disorder strongly predisposes an adolescent to developing substance use disorder (Deas 2006). Among adolescents, conduct disorder usually precedes the development of the substance use disorder. Female adolescents with conduct disorder have a worse course of substance use than males and also progress more quickly to substance use than male adolescents. ADHD is frequently associated with substance use and is practically always primary in onset (Deas 2006). However, adolescents with and without ADHD have been reported to develop alcohol or drug use disorders at the same rate (Biederman *et al.* 1997), whereas presence of CD greatly increased the comorbidity of ADHD and SUD (Wilens *et al.* 2003).

Recently, Copeland and colleagues (2009) studied which childhood and adolescent psychiatric disorders predicted young adult psychiatric disorders in a follow-up of the general population. Conduct disorder in childhood (OR=2.5), in addition to substance use disorders (OR=2.8), were the only psychiatric diagnoses

that predicted later substance use disorders. However, the finding on CD was not statistically significant after adjustment for other psychiatric diagnoses (Copeland *et al.* 2009).

Brook and colleagues (1998) suggested that the connection between ADHD and substance use disorders is probably mediated through the influence of comorbid conduct disorder. August and colleagues (2006) reported that ADHD without a comorbid externalizing disorder is not associated with an increased risk of drug abuse. On the other hand, ADHD with a comorbid externalizing disorder, primarily oppositional defiant disorder, was associated with an elevated risk of drug use (August *et al.* 2006). It has been demonstrated that, among treatment-seeking adolescents who used substances, those with behavioral disorders had a less favorable prognosis compared to those with mood or adjustment disorders (Deas 2006).

More recent studies on SUD and behavioral disorders have shown the prevalence of behavioral disorders among adolescents with SUD to vary from 28% to 62% in the general population (Lansford *et al.* 2008, Whitbeck *et al.* 2008) and from 60% to 72% among clinical samples (Langenbach *et al.* 2010, Chen *et al.* 2008). Lehto-Salo and colleagues (2009) studied the prevalence of lifetime comorbidity of SUD among adolescents with behavioral disorders in a Finnish population of institutionalized adolescents in correctional school. They reported the prevalence of SUD to be 63% among girls and 27% among boys with behavioral disorders. An increased likelihood of alcohol dependence (OR=12.6) and drug dependence (OR=14.0) has been reported among adolescents with behavioral disorders in the general U.S. population (Roberts *et al.* 2007). Chan and co-workers (2008) reported a 3.2-fold OR for comorbidity of externalizing problems (ADHD and CD) and substance use disorders below the age of 15 years and a 4.8-fold OR at ages between 15 and 17 years in a clinical adolescent population sample of substance users in the U.S. (Chan *et al.* 2008).

2.6.3 Comorbidity with Anxiety disorders

Studies on the comorbidity of anxiety disorders and SUD in population-based adolescent samples have shown variable results. The prevalence of anxiety disorders among SUD adolescents has been reported to range from 7% to 40% (Armstrong & Costello 2002). The median prevalence was reported as between 16.2% and 18.2%, and in the majority of the studies referred by Armstrong and

Costello (2002) the ORs were reported to be close to 1 (i.e. there was not a significant increase or decrease in comorbidity).

In another review of studies of adolescents treated for SUD, the weighted median prevalence for comorbid anxiety disorder was as low as 7% (Couwenbergh *et al.* 2006). On the other hand, the presence of social phobia increased the risk for alcohol dependence two-fold in an adolescent sample of female twins (Nelson *et al.* 2000). In recent studies in the general adolescent population, the prevalence of anxiety disorders was reported as being 13% to 17% (Copeland *et al.* 2009, Essau 2011). In recent clinical population studies, a higher prevalence of anxiety disorders has been reported among adolescents with substance use disorders, being 22% to 27% (Essau 2011, Langenbach *et al.* 2010, Chan *et al.* 2008). Roberts and colleagues (2007) reported a 2.8-fold OR for anxiety disorders among alcohol dependent and 2.2-fold OR for anxiety disorders among drug dependent adolescents in general population. The likelihood for co-occurring anxiety disorders has been reported as 4.9-fold in adolescent substance treatment population (Chan *et al.* 2008). Also, Sung and colleagues' (2004) prospective study showed that anxiety disorders predicted the development of SUD with 1.6-fold risk.

2.6.4 Comorbidity with other psychiatric disorders

Even though tobacco and alcohol are commonly used among psychotic adolescent patients (Barkus & Murray 2010), the prevalence of comorbidity of psychotic disorders and SUD has been reported to be lower than among the other psychiatric disorders discussed above (Wu *et al.* 2011). Wu and colleagues (2011) reported that among out- and inpatient adolescents with SUD the prevalence of psychotic disorders was 4.1% for girls and 4.3% for boys. They also found that, as compared to other psychiatric disorders, psychotic disorders had weaker association with SUD (OR=0.3). On the other hand, among Swedish outpatient adolescents with SUD the prevalence of comorbidity was higher (20% for girls and 30% for boys) and psychotic disorders were significantly associated with SUD (Hodgins *et al.* 2007). Cannabis is the most frequently used illicit drug among psychotic patients. However, heroin and morphine use are not reported to be higher in patients with schizophrenia (Barkus & Murray 2010).

Administration of delta-9-tetra-hydro-cannabinol (Delta-9-THC), the major psychoactive compound of cannabis, produces a transient psychosis-like state in

healthy volunteers. It has been suggested that those who are prone to psychosis and use cannabis at youth are at greatest risk for subsequent psychosis (Frisher *et al.* 2009). Frisher and colleagues (2009) studied the prevalence of psychotic disorders in the general population and, as cannabis use has become more common, hypothesized that the prevalence of psychoses would also rise. Surprisingly, they found that the prevalence rate of psychotic disorders declined from 1995 to 2006. This trend did not support their original hypothesis of an association between increased cannabis use and psychotic disorders. Amphetamine is also reported to induce psychotic symptoms, and continuous methamphetamine use has been reported to produce symptoms similar to those seen in paranoid schizophrenia (Barkus & Murray 2010).

Adolescent-onset of bipolar disorder, often initially diagnosed as depressive disorder, is a substantial risk factor for substance use disorder (Deas 2006). The prevalence of SUD among adolescents with bipolar disorders in treatment populations in Spain and the U.S. has been reported to vary from 15% to 32% (Soutullo *et al.* 2009, Steinbuechel *et al.* 2009, Chi *et al.* 2005). Adolescents with substance use disorders are more likely to have bipolar disorder than adolescents without substance use disorders. Additional risks for substance use disorder among bipolar adolescents include male sex, family history of substance use as well as mixed mania (Deas 2006).

Lifetime post-traumatic stress disorder (PTSD) has been showed to have a statistically significant relationship with lifetime SUD (Swendsen *et al.* 2010). Among general population of adolescents the prevalence of PTSD has been reported to be 22% to 25% among girls with SUD and 12% to 14% among boys with SUD (Macdonald *et al.* 2010, Kilpatrick *et al.* 2003). Among SUD treatment populations the prevalence of PTSD has been found to vary from 9% to 35% (Hodgins *et al.* 2007, Lubman *et al.* 2007, Fiskenscher & Novins 2003, Hannesdottir *et al.* 2001) Other psychiatric disorders that have been statistically significantly associated with substance use disorders among adults include dysthymia, speech and language impairment, anorexia nervosa, bulimia nervosa and tic disorders (Hasin *et al.* 2007, Compton *et al.* 2007, Armstrong & Costello 2002, Root *et al.* 2010, Blinder *et al.* 2006).

2.6.5 Prospective studies on comorbidity in substance use disorders

The literature presented above is based on cross-sectional studies. Prospective analyses of comorbidity in psychiatric disorders and substance use are rare. Swendsen and co-workers (2010) recently completed prospective investigations on mental disorders as risk factors for substance use, abuse and dependence. They used data gathered in a U.S. national comorbidity survey (NCS) with follow-up a decade later (NCS-2). The data of the study population were gathered in 48 U.S. states among non-institutionalized civilian population of both genders and aged between 15 and 54 years. Psychiatric diagnoses were assessed with CIDI, which is based on DSM-III-R and DSM-IV. The overall response rate was 88%. Swendsen and colleagues (2010) reported that, during the 10-year follow-up period, the occurrence of DSM-IV nicotine dependence was 10%, of alcohol dependence 1% and of drug dependence 0.2%. In NCS-2, baseline *mood disorders* were associated with subsequent alcohol (OR=1.8) and drug dependence (OR=2.1). Of specific diagnoses, only the association with bipolar disorders reached statistical significance (OR=3.6 for alcohol and OR=5.1 for drug dependence). Baseline *anxiety disorders* were associated with subsequent alcohol (OR=3.2) and drug dependence (OR=3.5). Of specific anxiety disorders, social phobia (OR=3.3 and 2.8, respectively), PTSD (OR=3.2 and 3.9) and separation anxiety (OR=2.7 and 3.0) disorders were associated with onset of both alcohol and drug dependence. *Behavioral disorders* were associated with subsequent alcohol (OR=2.8) and drug dependence (OR=4.6). Psychotic disorders were not analyzed and the Odds ratios were from bi-variate analyses (Swendsen *et al.* 2010). Swendsen and colleagues (2010) also evaluated the influence of psychiatric comorbidity on progression of substance use. It was evident that the psychiatric comorbidity affected the trajectory of substance use development, from use to abuse among users, and from abuse to dependence among abusers.

Copeland and colleagues (2009) evaluated which childhood and adolescent psychiatric disorders predicted morbidity later in adulthood. They used data gathered in the Great Smoky Mountain Study (GSMS), a longitudinal study initiated to study the development of psychiatric disorders in rural and urban youths. The sample consisted of a selection of 20,000 children (n=1,420) living in North Carolina in the United States. The subjects and their parents were interviewed personally or by phone using the Child and Adolescents Psychiatric Evaluation (CAPA) and later the Young Adult Psychiatric Evaluation (YAPA) to

obtain DSM-IV diagnoses. Data were collected initially from 9-, 11- and 13-year-old children, with 11 periods of follow-ups so far, the oldest youth being 21 at the last follow-up. Although quite a few psychiatric diagnoses in childhood and adolescence were predictive of other morbidity later in young adulthood, the disorders predictive of later substance use disorders were few. Namely, previous SUD in adolescence (adjusted OR=2.7) and conduct disorder at an even younger age at childhood (unadjusted OR=2.5) were predictive of young adulthood SUD. Anxiety, mood and other behavioral disorders evaluated in this study did not statistically significantly predict SUD and, after adjusting for these other psychiatric disorders, the findings regarding conduct disorders' predictive value lost statistical significance (Copeland *et al.* 2009).

2.6.6 Gender differences in comorbidity of substance use disorders

Among adolescents with drug use disorders, rates of ADHD and CD have been reported to be statistically significantly higher among boys, even though high rates are also reported among girls (Latimer *et al.* 2002). The prevalence of depressive disorders has been reported higher among drug-abusing girls than boys (Latimer *et al.* 2002). It has also been shown that the risk for comorbid anxiety disorders is greater among girls with SUD than boys with SUD (Chander *et al.* 2002). These results among adolescents are in line with results from adults; drug dependent women have presented greater comorbidity with depression, mania, phobias and PTSD, whereas men have presented higher rates of antisocial personality disorder and ADHD (Zilberman *et al.* 2003). Opposite findings were found among Finnish adolescents in correctional school by Lehto-Salo and colleagues (2009): the prevalence of SUD among girls with behavioral disorders (63%) was statistically significantly higher than among boys (27%). It appears that treatment setting can affect the findings on gender difference, as Latimer and colleagues (2002) reported that among adolescents in substance use treatment in the U.S. boys were 5.7-fold more likely to have comorbid CD and 0.2-fold less likely to have comorbid MDD. Rates of dysthymia, double depression, and bipolar disorder have been reported to be equivalent between drug dependent adolescent boys and girls (Latimer *et al.* 2002).

2.7 Temporality of substance use disorders and other psychiatric comorbidity

2.7.1 Temporality with depressive disorders

There are few studies on the temporal association (*i.e.*, temporality, Bradford-Hill 1965) of substance use disorders and associated psychiatric comorbidities in adolescents and even fewer studies on temporality among inpatient populations. While it is evident that substance use is related to increased rates of depression and that depression increases substance use, the timing of onset of substance use and depressive disorders is unclear, although it has been suggested that gender relates to the temporality of depression and substance use disorders (Deas 2006). Furthermore, depression has been suggested to be primary to alcohol dependence among girls and, vice versa, secondary among boys (Clark *et al.* 1997). The median onset age of depressive disorders among general population adolescents was reported as being 13 years and 15 years for SUD (Merikangas *et al.* 2010).

2.7.2 Temporality with behavioral disorders

Longitudinal studies have suggested that behavioral disorders predict substance disorders in adolescence; the onset age in conduct disorder is usually found to precede the onset age in substance use disorders (Haesly *et al.* 2002, King *et al.* 2004, Costello *et al.* 1999, Deas 2006). Among U.S. general population adolescents, the median onset age for behavioral disorders and SUD has been reported as 11 and 15 years, respectively, (Merikangas *et al.* 2010).

2.7.3 Temporality with anxiety disorders

The temporality of anxiety disorders and substance use disorders varies depending on the type of anxiety disorder. For example, phobic disorders are mainly found to precede the development of subsequent substance dependence (Merikangas *et al.* 1998), whereas substance use disorders generally precede panic disorder (Marquez *et al.* 2003). Adolescents suffering from anxiety disorders may use substances for self-medication of anxiety disorder and mask the anxiety until the disorder becomes clinically evident through treatment of substance use (Deas 2006). Among Finnish general population, anxiety disorders

have been found to precede substance use (Fröjd *et al.* 2011). Anxiety symptoms usually precede the onset of substance use in adolescents by approximately 2 years (Deas 2006). The median onset ages for anxiety and substance use disorders were 6 and 15 years in the U.S. general population sample (Merikangas *et al.* 2010).

2.8 Social risk factors of substance use

Social risk factors for substance use disorders among adolescents can be divided into family, community, personal/developmental and peer factors according to Comerici & Schwebel (2000), (Table 4).

Table 4. Why adolescents use drugs.

Factors	Description
Family	<p>Chaotic family and lack of supervision</p> <p>Parental permissiveness and preoccupation</p> <p>Parental rigidity and authoritarianism</p> <p>Family role modeling of substance abuse</p> <p>Drugs available and used in the home</p> <p>Physical and/or sexual abuse</p> <p>Biogenetic factors</p>
Community	<p>Availability of drugs</p> <p>Chaotic community, poverty, inadequate schools, and lack of supervision</p> <p>Media influence</p> <p>Modeling observed adult behavior</p> <p>Drug use and pressure to use by peers</p> <p>Rite of passage/pubertal rite</p>
Personal and Developmental	<p>Curiosity</p> <p>Underlying emotional illness/behavior disorder</p> <p>School failure</p> <p>Desire to feel better (self-medication)</p> <p>Sense of rebelliousness</p> <p>Need for autonomy and independence</p> <p>Risk taking and reckless temperament</p> <p>Desire to look older</p> <p>Need for improved self-esteem</p>

Factors	Description
Peer	Performance facilitation – academic/sports/other
	Acquisition of desired image as portrayed by the entertainment and advertising media
	Perception of limited options for the future
	Need to be accepted and to belong
	Peer drug use, antisocial behavior and pressure to use
	Social isolation and/or boredom
	Lack of attachment

Table according to Comerici & Schwebel 2000

2.8.1 Family risk factors

Family dynamics seem to play an important role in adolescent substance use. Parental divorce before the age of 18, parental discord, family disruption, family history of alcohol problems, parental nondirectiveness, negative communication, inconsistent parental discipline, low level of family bonding, high levels of family conflicts and lack of closeness have been identified as risk factors for adolescent substance use (Griffin & Botvin 2010, Pilowsky *et al.* 2009, Swadi 1999). Also, it seems that, rather than the presence of any specific childhood adverse event, the accumulation of these events seems to be most robustly associated with substance dependence (Pilowsky *et al.* 2009). Positive family relationships with good involvement and attachment appear to discourage the initiation of drug use (Swadi 1999). Contact with drug users, in the form of parental drug use, has been associated with a 19-fold OR with drug dependence among Brazilian outpatients (Ferigolo *et al.* 2009).

The increased alcohol and drug use among the adolescent offspring of alcoholic and drug-using parents is well studied and reported. Adolescents with alcoholic fathers have been reported to have steeper growth in substance use over time than adolescents without alcoholic fathers. Lowered parental supervision has been associated with earlier initiation of substance use. Parental alcoholism fosters early adolescent substance use through stress and negative affective feedback, and also through severe impairments in parental supervision. Parental modeling of substance use is likely to affect substance use in the offspring (Griffin & Botvin 2010, Swadi 1999).

Adolescent risk factors for excessive alcohol use were assessed in a recent prospective longitudinal study using a Finnish general population sample

(n=1,471, 45% males, 55% females) by Huurre and colleagues (2010). All 16-year-olds in one Finnish city completed questionnaires at school (response rate 70%), and were followed up by postal questionnaires at the age of 32. The alcohol use disorders identification test (AUDIT) was used to assess alcohol use in adulthood. Almost all of the sociodemographic variables assessed were related to increased drinking and therefore multivariate logistic regression analyses were used. In males, experience of parental divorce (OR=2.0) was a strong predictor for excessive alcohol use in adulthood.

Both adverse events in childhood/adolescence and poor parental supervision increase the likelihood of associations with undesirable community networks that encourage substance use (Botvin & Griffin 2010, Swadi 1999). Another mediating mechanism is that children with parents who have substance use problems are more vulnerable to other psychiatric morbidity and thereby to substance use disorders (Swadi 1999). The influence of parental substance use on adolescent SUD is strongest at the age of school entry/childhood before adolescence. Bereavement, unwanted pregnancy, major illnesses, and sexual victimization both in childhood and adolescence are all more common among adolescent substance users. (Swadi 1999).

2.8.2 Community and school risk factors

The availability of substances, the general attitude towards substances and observed adult behavior in the community play an important role in the development of adolescent substance problems (Comerci & Schwebel 2000).

School background also provides an insight into the development of SUD. It has been shown that those adolescents who are not engaged in school, fail to develop or maintain relationships with their teachers or who fail academically are at greater risk of engaging in substance use (Griffin & Botvin 2010). On the other hand, those who maintain active involvement in their community institutions are less likely to use illicit substances (Griffin & Botvin 2010).

2.8.3 Peer influence

As reviewed by Swadi (1999); peer influences seem, by most accounts, to have a great impact on adolescent substance use behavior. Peer drug use has been universally identified as the single most likely factor to predict concurrent drug

use. Initiation and continuation of drug use is more likely in a social setting where other adolescents of the same age group are also using illicit drugs. About a tenth of adolescent solvent/illicit drug users have been reported to have been pressured into drug taking by their friends (Swadi 1999), not to mention those adolescents who are experiencing passive peer pressure. Even the effects of social, family and individual risk factors for alcohol abuse seem to be partly mediated by their effects on peer affiliations in adolescence. The rate of development of drug use can also be influenced by peer groups. Adolescents with drug-using peers show a steeper growth in substance use compared with adolescents without drug-using peers and the influence of peer groups is strongest during adolescence. (Swadi 1999).

Residential status has also been associated with risk for substance use; those living alone have been reported to have the highest prevalence of substance abuse (Ilhan *et al.* 2009). Adolescents with substance use disorders have significantly weaker perceived attachment to parents, but significantly higher attachment to peers compared to adolescents without any psychiatric disorders (Essau 2011). Peer drug use has been associated with a 6.4-fold OR with adolescent drug dependence (Ferigolo *et al.* 2009). Huurre and co-workers (2010) analyzed a variety of social risk factors among Finnish adolescents and suggested that leisure time spent daily among friends (OR=1.6) and heavier drinking habits (OR=2.6) were the strongest predictors for excessive alcohol use in adulthood.

2.8.4 Social risk factors and substance use trajectory

Many of the socio-demographic risk factors have been identified as significant predictors for dependence when examined by the stage of use, even though they were not significantly associated with onset of dependence. Thus, it has been suggested that different socio-demographic risk factors have highly specific associations with different stages in the substance use trajectory (Swendsen *et al.* 2009). Swendsen and colleagues (2009) showed that occupational status of student or unemployment/disabled was associated with alcohol dependence regardless of the stage of use at baseline (non-use/non-abuse/abuse). Nicotine dependence was associated with increased alcohol dependence only among those who did not use alcohol or were non-abusive users – in other words, those who already abused alcohol did not have an increased risk for alcohol dependence due to nicotine dependence. Younger age was found equally predictive of drug

dependence regardless of the baseline use, but low education was found to be predictive of drug dependence only among baseline non-users or non-abusers. Also, the predictive value of alcohol abuse to drug dependence was evident only among those participants who had not used drugs. Metropolitan/urban residence was associated with higher risk for drug dependence among those who were already drug abusers (Swendsen *et al.* 2009).

2.9 Progression of substance dependence - Gateway theory

The “Gateway” theory is based on a rational assumption that drug initiation may follow a normative sequence, beginning with tobacco and alcohol use, followed by cannabis, then other illicit drugs in per-oral and smokable forms, and finally drugs used intravenously (Kandel *et al.* 1992). There are sound studies that both support (Degenhardt *et al.* 2007, Ellgren *et al.* 2006, Agrawal *et al.* 2004) and reject (Reinarman *et al.* 2004, Tarter *et al.* 2006) the Gateway theory. Degenhardt *et al.* (2009) recently used the data gathered in a National Comorbidity Survey Replication (NCS-R, n=9282) to evaluate the Gateway theory and its application and validity in real life. NCS-R is a nationally representative household survey of the U.S. adult population. Subjects were interviewed face-to-face using Composite International Diagnostic Interview (CIDI) and diagnosed using DSM-IV criteria. It was reported that, overall, only 5.2% of the participants initiated substance use in an order that contradicted the Gateway theory. The most common contradiction was the initiation of other illicit drugs before cannabis (3.7%), followed by cannabis before tobacco and alcohol use (1.6%). Younger age and early onset of internalizing disorders were identified as predictors for contradictions of the Gateway theory (Degenhardt *et al.* 2009). Substances earlier in the “gateway” sequence predicted later drug use. However, the strength of the associations differed across countries: the cannabis use among Dutch young adults is less strongly associated with later illicit drug use than among young adults in Belgium, Spain and the U.S. – countries where selling cannabis is illegal (Degenhardt *et al.* 2010). It has been suggested that the common liability model, the likelihood that someone will proceed to the use of illegal drugs, determined not by the preceding use of a particular drug but instead by the user’s individual tendencies and environmental circumstances, could predict adolescent substance use better than the Gateway theory (van Leeuwen *et al.* 2011).

According to Swendsen and colleagues (2008), the development of alcohol and drug use can be divided into six stages: 1) opportunity to use, 2) use of substance, 3) substance abuse, 4) substance dependence, 5) remission from abuse, 6) remission from substance dependence. Although progress has been made in reducing incident cases of disorder onset among drug users, greater advances may be achieved by preventing the transitions across the drug use trajectory (Swendsen *et al.* 2008).

2.9.1 Progression of substance use

The age at which initial stages of substance use (opportunity to use and use of substance) are reached is strongly associated with abuse and dependence. Those adolescents who start substance use at a young age increase the use swiftly and progress to dependence more rapidly (Swendsen *et al.* 2008). Swendsen and colleagues analyzed the NCS-R data on US adults and found that the median age of first opportunity to use drugs was 16 years, and the median onset for the subsequent use/abuse/dependence each occurred prior to the age of 20 years. The median age of remission from abuse was 26 years (with a median of five years from the initiation of abuse) and 30 years (7 years) from dependence. Half of the drug users continued to use illicit substances for 3 years before the development of abuse, but the transition from abuse to dependence generally took less than 1 year (Swendsen *et al.* 2008).

Swendsen and colleagues (2008) reported that among a sample of 9,282 U.S. adults, 72.4% had had an opportunity to use drugs. Sixty-one per cent of those who had had the opportunity to use drugs had used them at least once. Eighteen per cent of those who had used drugs had developed abuse. Thirty-eight per cent of those who had developed abuse had subsequently developed dependence. Eighty-four per cent of those with abuse and 86% of those with dependence had reached remission at some point in their life. Please see Figure 4 below for referral percentages for the total general population. (Swendsen *et al.* 2008).

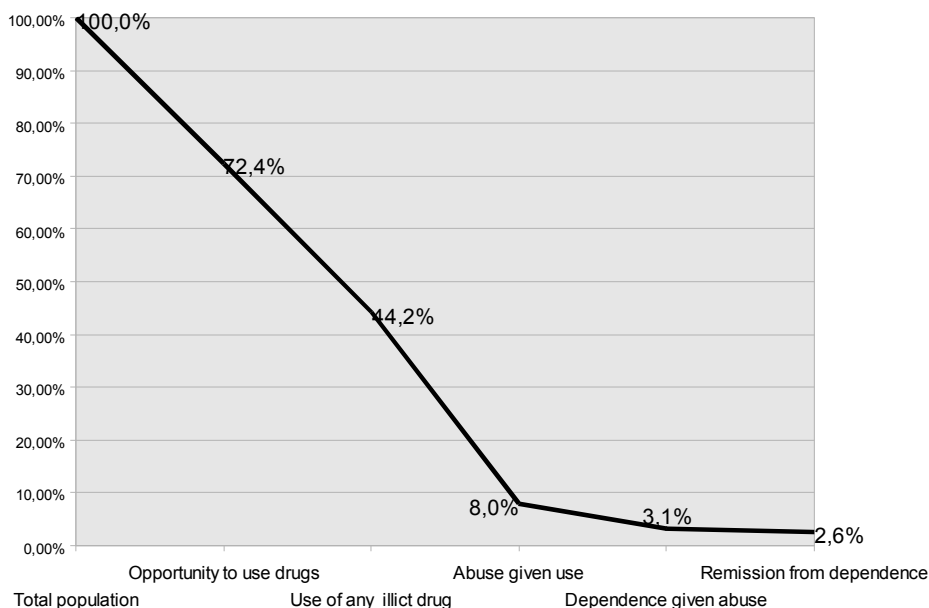


Fig. 4. Progression of substance use, proportions of transition (figures according to Swendsen *et al.* 2008).

2.10 Genetic and neurobiological factors influencing substance use

In conjunction with sociodemographic, environmental and comorbidity factors, genetic factors are essential in the development of substance use disorders (Corley *et al.* 2008). Vulnerability to developing persistent, progressive substance use and dependence is a heritable phenotype. Previous studies have reported heritability rates for tobacco (0.46), marijuana use (0.44), problem alcohol use (0.70) and problem marijuana use (0.64). It has been shown that a combination of genetic and environmental factors may contribute to a predisposition to substance dependence in general, rather than a substance-specific effect (Corley *et al.* 2008). The most well-established gene polymorphisms that have an association with risk for alcohol dependence are located in genes encoding alcohol metabolizing enzymes (alcohol dehydrogenase-1B and aldehyde dehydrogenase-2), gamma-aminobutyric acid receptor and opioid receptor mu-1 genes (Kimura & Higuchi 2011). Though several genes related to four major neural transmission systems of

the brain (serotonergic, dopaminergic, GABA-ergic and cholinergic) have been associated with substance dependence, there are inconsistencies among the results of previous studies (Corley *et al.* 2008).

It has been suggested that the understanding of motivational brain systems may provide important information about impulsivity and risk for substance use. Due to development of brain neural circuits that enable people to experience motivation and rewarding experiences, adolescence has been described as the “critical period of addiction vulnerability” (Chambers *et al.* 2003). Animal and human studies suggest the existence of a primary anterior motivation circuitry (involving the prefrontal cortex and ventral striatum) linked with more widely distributed secondary posterior motivation circuitry that provides multiplicity of sensory input. Hippocampus and amygdala provide contextual memory and affective information relevant to the motivational stimuli, while hypothalamic and septal nuclei provide information to primitive and instinctual motivated behaviors (Chambers *et al.* 2003).

Striatal dopamine release is considered the principal neuromodulatory event to motivate into action. A wide variety of motivational stimuli, including addictive substances such as nicotine, alcohol, cocaine, amphetamine, opiates and cannabis as well as natural rewards, such as sex, have been shown to increase dopamine concentration in the nucleus accumbens. As a person gets accustomed to the stimuli the role of nucleus accumbens dopamine release diminishes (Chambers *et al.* 2003). The most important inhibitory motivation systems are serotonin (5-HT) neurotransmitter system and the inhibitory system of the prefrontal cortex. Decreased 5-HT activity has been associated with impulsive behavior and impulsive responding in reward-related learning. Impaired impulse control has been reported in various psychiatric conditions (*i.e.*, antisocial personality disorder, affective disorders, schizophrenia and substance use disorders) that also present with abnormal measures of prefrontal cortex function (Chambers *et al.* 2003).

Chambers and colleagues suggested that adolescent neurodevelopment involves changes in brain function and organization, possibly leading to relatively greater influence of promotional substrates (central dopamine function) in the setting of immature inhibitory substrates (5-HT and precortical system) and therefore vulnerability to development of substance use disorders. Also noradrenergic, glutaminergic, and GABA-ergic systems have been suggested to be involved in development of drug addiction (Chambers *et al.* 2003, Ratsma *et al.*

2002). Frontal cortical development, taking place later in adolescence, which likely contributes to refinement of reasoning, goal and priority setting, impulse control and evaluating long- and short-term rewards has also been suggested to participate in adolescent vulnerability for addiction (Crews *et al.* 2007).

2.11 Psychotropic medication during adolescence

Only a few psychotropic medications have been approved and indicated for use among adolescents (Thomas *et al.* 2006), and due to lack of an evidence base for drug therapy in adolescents, the rationale for careful medication is derived from adult studies and assumptions of a similarity of these disorders in younger persons (Werry 2000).

The use of psychotropic medication has increased among adolescents since the 1980s (Thomas *et al.* 2006). The prevalences of psychotropic medication use in outpatient and inpatient samples have been reported to vary from 20%-25% and 40%-71%, respectively (Safer *et al.* 2003, Dean *et al.* 2006). Selective serotonin re-uptake inhibitors (SSRIs) have been found to be the most frequently used medication, mainly prescribed for depressive disorders (Dean *et al.* 2006). Autti-Rämö and colleagues (2009) described the use of antipsychotic medication among children and adolescents from 1997 to 2007 on the basis of the prescription register of the Social Insurance Institution of Finland. During that time frame, they found a three-fold increase in the number of adolescent patients using prescribed psychotropics. The use of antidepressants increased most rapidly and the prevalence of use was highest among women over 15 years old, while the use of antipsychotics had increased as well. The figures for anxiolytic and sedative use during adolescence have increased (Autti-Rämö *et al.* 2009).

Schepis & Krishnan-Sarin (2008) evaluated the characteristics of prescription misuse among a large general population of U.S. adolescents; 8.2% of the general population adolescents misused a medication while 3.0% demonstrated symptoms of a substance use disorder related to prescription medication misuse in the past year. They found furthermore that during the previous year the MDD (OR=2.9), alcohol (OR=7.3) and drug use were associated with misuse of prescription medication. The highest ORs were observed among cocaine and inhalant use (OR=10.7). Repeated prescription medication misuse in the previous year was associated with a three-fold risk for prescription medicine abuse or dependence symptoms (Schepis & Krishnan-Sarin 2008).

2.11.1 Antidepressive medication

Selective serotonin re-uptake inhibitors (SSRIs) have a robustly proven indication in the treatment of obsessive-compulsive disorder (OCD) among adolescents. Combining the data with clinical experience on adolescents and the results of adult studies, SSRIs play a valuable role in the treatment of adolescent depressive and anxiety disorders (Brent *et al.* 2008, Scheffer 2006, Ziervogel 2000), especially in combination with non-pharmaceutical therapy (Brent *et al.* 2008). Tricyclic antidepressants (TCAs) have not been shown to be particularly useful in clinical trials in children and adolescents (Scheffer 2006). The serotonin/noradrenalin re-uptake inhibitor (SNRI) venlafaxin and SSRIs have been proven equally effective in treatment of adolescent depression, yet SSRIs seem to relate to more rapid decline in depressive symptoms and suicidal ideation (Vitiello *et al.* 2011). The prevalence of the use of antidepressants among children and adolescents in Australia has been reported to be up to 14% in psychiatric outpatients and 44% in psychiatric inpatients (Dean *et al.* 2006). Among Finnish adolescents, the prevalence of antidepressive use is relatively uncommon; in general Finnish population, 0.5% of adolescents (0.6% of girls and 0.5% of boys) between the ages of 11 and 15 years received these medications. However, among the 21- to 26-year-old age group the respective prevalences rose to 8.2% among women and to 4.8% among men. Among Finns under 27 years of age, there has been an over three-fold increase in the use of antidepressive medication in the last decade (Autti-Rämö *et al.* 2009).

2.11.2 Antipsychotic medication

Atypical antipsychotic drugs (atypical neuroleptics) are indicated for use in the acute and maintenance treatment of psychotic disorders (Remschmidt *et al.* 2000). They have also been shown to be effective in the treatment and relapse prevention of manic and bipolar episodes. Other possible clinical indications for antipsychotic use are pervasive developmental disorder, Tourette's disorder, OCD and ADHD (Remschmidt *et al.* 2000). Atypical antipsychotics have been used in combination with other psychotropic medication to both aid sleep and reduce aggression (Safer *et al.* 2003). Because of their wider range of side effects, it is suggested that typical antipsychotics should be used sparingly and only in the most severe and incapacitating disorders, such as some psychotic conditions and

handicapping tic-disorders (Gillberg 2000). The prevalence of antipsychotic use among children and adolescents has been reported to be up to 3% in outpatient and 23% in inpatient settings (Dean *et al.* 2006). Among Finnish youths between 11 and 20 years, the prevalence of antipsychotic use was reported as 0.4% among girls and 0.5% among boys (Autti-Rämö *et al.* 2009).

2.11.3 Sedative and anxiolytic medication

Sedatives are used frequently in adults with anxiety disorders, but many young people experience disinhibition on benzodiazepines and therefore the use of this medication is limited among adolescents (Dean *et al.* 2006, Scheffer 2006). Clinicians are suggested to be cautious about prescribing anxiolytics to children and adolescents because of their depressant properties and the potential for dependency (Werry 2000). Adolescents' risk for prescription sedative/anxiolytic abuse and dependence has been reported to increase with increased levels of anxiety, depression and behavioral problems (Hall *et al.* 2010). It is unclear whether or not selective CNS depressants like benzodiazepines have a role in adolescent psychotropic treatment except in psychotic and manic states. General CNS depressants, such as barbiturates and alcohol, also make aggression more likely and their use is avoided in adolescents with conduct and behavioral disorders (Werry 2000).

Even though BDZs have been used in the past in children and adolescents with anxiety disorders, sleep-related disorders, psychosis and aggression, there is currently no firmly established indication for the use of BDZs in children or adolescents with psychiatric disorders (Witek *et al.* 2005). The prevalence of the use of sedatives among Australian children and adolescents has been reported to be up to 4% in outpatient and 14% in inpatient settings (Dean *et al.* 2006). Among the general population in Finland, the prevalence of the use of sedative/anxiolytic medication has been reported as 0.1% to 0.5% among adolescents aged between 11 and 20 years. It is evident that sedative/anxiolytic use increases with age. Among young adults aged between 21 and 26 years the prevalence is roughly 1% (Autti-Rämö *et al.* 2009).

2.11.4 Stimulant medication

Stimulants, mainly medicines containing methylphenidate (MPA) or amphetamine (AMPH), are well studied in adolescent samples with Attention Deficient Disorder (ADHD) and these studies have given indications for treatment in many countries (Dumortier *et al.* 2005, Nutt *et al.* 2007, Scheffer 2006). The prevalence of stimulant medication use among children and adolescents has been reported to be up to 8% in outpatient and 14% in inpatient settings (Dean *et al.* 2006), although higher figures, up to 49% among adolescents under 15 years, have been reported among young children diagnosed with ADHD (Safer *et al.* 2003). In Finland, stimulant medication use is relatively uncommon compared to the figures from the U.S.; roughly 1% of adolescent boys between 7 and 15 years receive psychopharmacological treatment for ADHD. Among girls the respective prevalence is one tenth, being 0.1%. Stimulant use decreases rapidly with age. Among the 21- to 26-year-old population, the prevalence of stimulant use is 0.1% among men (Autti-Rämö *et al.* 2009). In Finland, the use of stimulant medication is uncommon. In 1999, 274 Finnish patients received stimulant treatment (mainly MPA) for ADHD; the figure has since increased to 4,348 patients by 2005. In 2005 the prevalence of MPA treatment among 7- to 14-year-old Finnish children was less than 0.5%, equaling fewer than every tenth child with ADHD receiving stimulant treatment (Lundström *et al.* 2006).

2.12 Summary of the literature

Adolescents with substance use disorders have increased rates of other psychiatric disorders. Among substance-abusing youths, the presence of comorbidity is the rule rather than the exception. Substance use comorbidity is most prevalent among adolescents with behavioral disorders. Anxiety and depressive disorders have also been found to relate closely to substance dependence in adolescence, though gender also seems to play a role in the comorbidity of these disorders. Depressive, anxiety and behavioral disorders have been found to increase the risk for subsequent substance use disorders. The onset of anxiety and behavioral disorders has been found to precede the onset of substance use disorders among adolescents with both these disorders.

Peer drug use and influence have been associated with a high risk for adolescent substance use. Family characteristics also play an important role in the

development of adolescent substance use. Parental divorce, parental discord, lack of parental monitoring and family disruption have been identified as risk factors for adolescent drug use. Adolescents with SUD have closer attachment to their peers than to their parents. It has been suggested that sociodemographic risk factors have highly specific temporal associations with different stages of the substance use trajectory. For example, the influence of parental substance use is strongest at the age of school entry and the influence of peers is strongest during adolescence. The progression of substance use can be represented both in terms of the severity of SUD – from substance trial to substance dependence and in terms of the substances used – usually progressing from tobacco and cannabis use to the intravenous use of hard drugs.

The rationale for psychotropic medication use is largely derived from studies of adult populations. Antidepressive medications are used effectively in the treatment of anxiety and depressive disorders among adolescents. Antipsychotic medication is mainly used for acute and maintenance treatment of psychotic disorders and relapse prevention in manic and bipolar disorders. There are no proven indications for sedative medication use in psychiatric treatment of adolescents and they should be avoided in adolescents with behavioral disorders. Sedative medications are used as an adjuvant treatment among severely psychotic adolescents. Stimulant treatment is indicated for the treatment of ADHD among adolescents.

The demand for treatment of mental disorders among adolescents has risen during the last decades. At the same time substance use, particularly drug use, has increased while the age at which substance use commences has decreased. Previous data on the onset of substance disorders and substance use in relation to psychiatric comorbidity – reflecting possible causality – are insufficient and, in many cases, contradictory. There are few studies on gender differences of comorbidity of SUD in adolescent inpatients. The studies on the temporality of SUD and associated psychiatric comorbidity are scarce, especially among adolescent psychiatric inpatients. Though sociodemographic background of SUD is extensively studied among adults, there are few studies on adolescents that reflect the risk factors associated with the severity of SUD. Psychotropic medication history of inpatient adolescents is not comprehensively studied and even though psychotropic medication is abused, these medications are used among adolescents that are at risk for substance use disorders.

3 Aims of the study

The key aim of this study was to investigate the clinical background and gender differences in substance use disorders in adolescence. Psychiatric comorbidity and temporality in relation to substance use disorders in adolescents was also examined.

The specific aims were to study among adolescent psychiatric inpatients

1. What is the prevalence of different substance use disorders and what are the comorbidities of substance use disorders among psychiatric adolescent inpatients? (Original publications III and IV)
2. Are there gender differences in the prevalence and comorbidities of substance use disorders? (IV)
3. What is the temporality of onset of substance use disorders and its associated comorbidities? (I, III and IV)
4. What is the role of initiation of daily smoking in the development of substance use disorders? (III)
5. What are the sociodemographic risk factors for substance use disorders and intravenous drug dependence? (II)
6. Does the psychotropic medication history of adolescents with substance use disorders differ from that of other adolescent psychiatric inpatients and does it follow a scientifically proven rationale? (V)

4 Materials and methods

4.1 The Study-70 project

This work is a part of the STUDY-70 project, initiated to examine the association of various psychosocial risk factors with the outcomes of severe psychiatric and substance disorders among hospital-treated adolescents aged 12-17 years admitted for the first time to Unit 70 at Oulu University Hospital's Department of Psychiatry. The catchment area of Unit 70 covers the provinces of Oulu and Lapland. All adolescents within this catchment area who are in need of acute psychiatric hospitalization are initially treated at Unit 70. In the total study sample, 71% of adolescents came from the province of Oulu, 20% from the province of Lapland, and the remaining 9% were officially residents of other municipalities of Finland but residing in the catchment area. Of all the adolescents included in the study, 22% lived in a city with a population over 100,000.

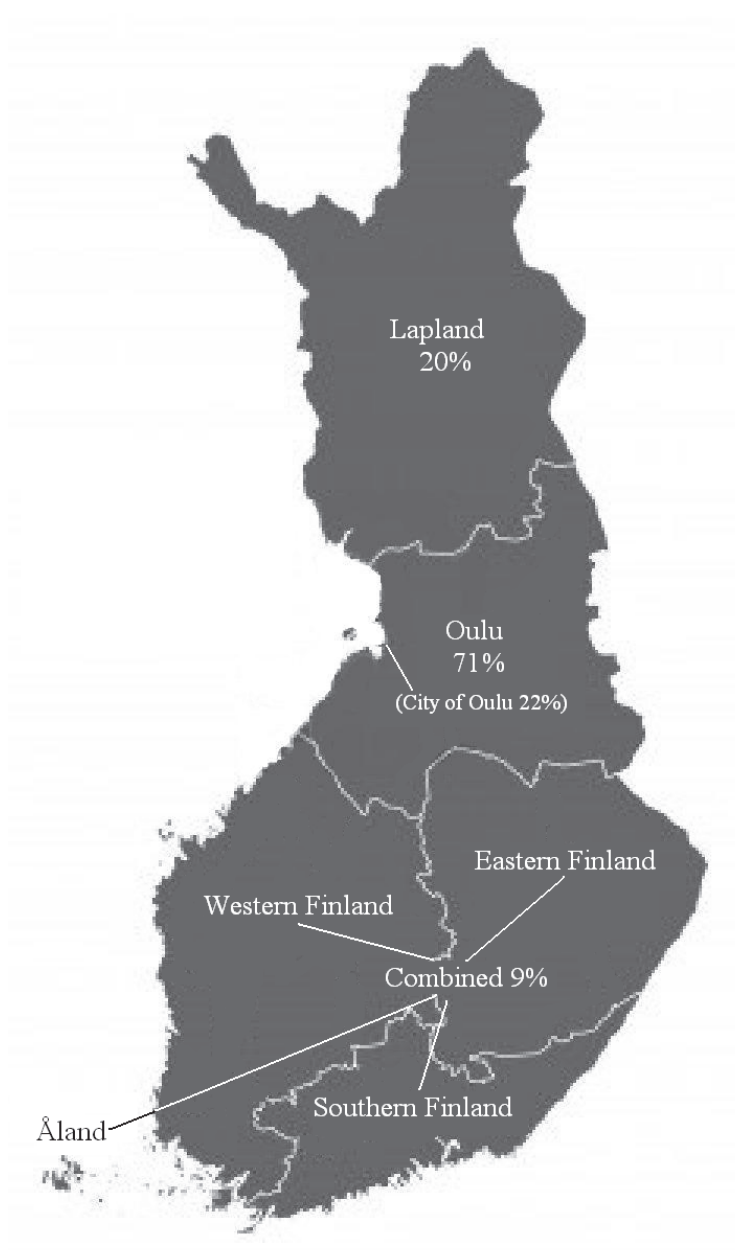


Fig. 5. Geographic distribution of the subjects of Study-70.

4.2 The study sample

The data covered psychiatric hospital admissions of adolescents aged 12-17 between April 2001 and March 2006. Of the total of 637 patients, 30 (4.7%) were excluded (mental retardation n=26, organic brain disorder n=3, age over 18 years n=1). Of the remaining 607 eligible adolescents, 77 refused to participate and 22 had a treatment period too short to complete the necessary interviews. Five hundred and eight (83.7%) provided written informed consent to participate. These 508 (208 boys, 300 girls) adolescents were interviewed during their treatment period and were enrolled in the study. The mean age of the participants was 15.5 years (SD 1.3 years), with the mean age of girls being 15.5 years (SD 1.3) and that of boys 15.4 years (SD 1.4). The mean (median) duration of treatment in Unit 70 was 13.2 days (8 days) for girls and 13.8 days (10 days) for boys. Figure 6 below presents the reasons for hospital admission among the adolescents of the study population.

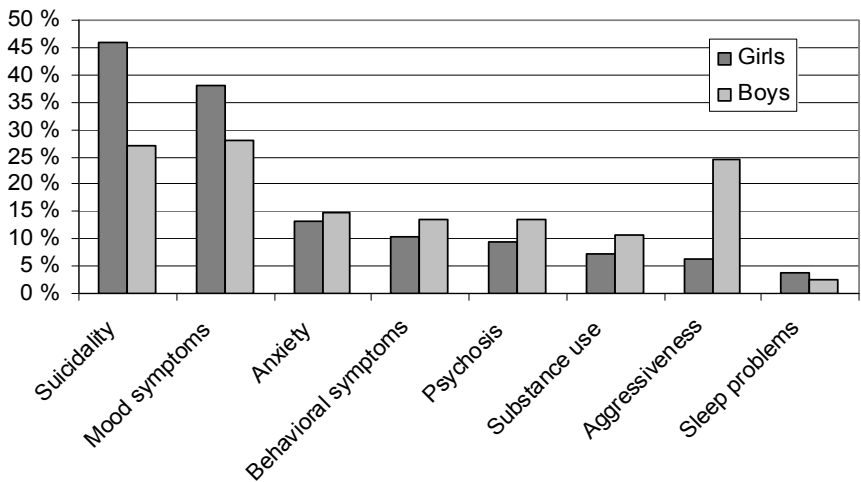


Fig 6. Reasons for hospital admission to Unit 70 among the study population.

The original publications (I-II) were completed in the middle of the data collection period. In publications III-V the full sample of 508 adolescents was used.

Table 5. Number of cases in original articles I-V.

Original publication	Number of cases	Girls	Boys
I	238	134	104
II	278	163	115
III	508 (full sample)	300	208
IV	508 (full sample)	300	208
V	508 (full sample)	300	208

4.3 Measures and procedures

4.3.1 Kiddie-Schedule for Affective Disorders and Schizophrenia – Present and lifetime

The semi-structured Schedule for Affective Disorder and Schizophrenia for School-Age Children, Present and Lifetime (K-SADS-PL) was used to obtain DSM-IV-based psychiatric diagnoses and onset ages on the accuracy of six months (Kaufman *et al.* 1997). The K-SADS-PL is a diagnostic interview routine designed to assess current and past psychopathological episodes in children and adolescents according to the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition Revised* (DSM-III-R, American Psychiatric Association 1987) and *Fourth Edition* (DSM-IV, American Psychiatric Association 1994). The test-retest reliability of diagnoses obtained from K-SADS-PL interviews has been described as good to excellent. The concurrent validity and inter-rater agreement have also been shown to be high (Ambrosini 2000, Kaufman *et al.* 1997).

4.3.2 European Addiction Severity Index (EuropASI)

During their stay at Unit 70, the adolescents were also interviewed by psychiatric nurses using the European Addiction Severity Index (EuropASI) (Kokkevi & Hartgers 1995). EuropASI is an objective, face-to-face structured interview which contains questions on the following life areas/problems: physical health, employment and financial support, illegal and criminal activity, family and social relationships, psychiatric symptoms, and alcohol and drug use. EuropASI has been proved to yield reliable and valid results on substance use when applied to substance-abusing populations (Kokkevi & Hartgers 1995).

4.3.3 Pompidou Questionnaire

On admission to Unit 70, the First Treatment Demand Protocol of the Pompidou Group of the Council of Europe (Pompidou Questionnaire) was completed for every patient. The Pompidou Questionnaire is used to collect data on individuals who contact drug treatment centers. The core data consist of a treatment contact description, socio-demographic information, drug use problems and risk behaviors. Reliability of the data on socio-demographic and drug use variables gathered on Pompidou Questionnaire has been reported to be approximately 90% (Kokkevi *et al.* 1997, Stauffacher & Kokkevi 1999).

4.3.4 CGAS (Adolescent's functional level)

An adolescent's functional level was assessed at both admission and discharge from the unit, by the physician treating her/him. Children's Global Assessment Scale (CGAS) was used for this purpose. CGAS is a numeric scale (1–100) based on clinician's evaluation and used by mental health professionals and doctors to rate the general functioning of children and adolescents under the age of 18. Ratings on a CGAS scale are independent of specific mental health diagnoses. CGAS 100 reflects the best and 1 the worst possible functional level. CGAS 80–71 reflects minor difficulties in home and school; CGAS 60–51 noticeable difficulties in many, but not all social and occupational areas, CGAS 40–31 major impairment in school, friends and home; and CGAS 20–11 need of considerable supervision to prevent hurting self or others. CGAS has been found to be reliable between raters and across time, and to demonstrate both discriminant and concurrent validity (Schaffer *et al.* 1983, Schorre & Vandvik 2004).

4.3.5 Procedures

During their hospitalization, adolescents were interviewed either by the physician treating them (8 individuals) or by trained medical students (4 individuals) under the supervision of the treating physician using the K-SADS-PI. All of the interviewers were introduced to using the K-SADS-PI by an experienced senior interviewer and made the first interviews with the senior interviewer present. Diagnostic interviews were mainly conducted with the adolescents. However, in cases of discrepancy between the information given by the adolescent and the

evaluation of the treating physician, the adolescent's parents/guardians (if they were available) were also interviewed. The final data recorded were based on the physician's evaluation of information obtained from diagnostic interviews with the patient and patient's parents/guardians. EuropASI and the Pompidou Questionnaire were completed by the psychiatric nurses at Unit 70 during patients' treatment period.

4.4 Outcome variables

4.4.1 Alcohol use disorders

Alcohol abuse

Diagnoses were based on diagnostic interview using K-SADS-PI. Alcohol abuse (DSM IV 305.00) was diagnosed if the adolescent presented with one or more of the following: continued use despite recurrent occupational (school) or social negative consequences caused or exacerbated by use; recurrent use in physically dangerous situations; recurrent legal-related problems; recurrent use when expected to fulfill major role obligations.

Alcohol dependence

Alcohol dependence (303.90) was diagnosed if the adolescent had three or more of the following symptoms, occurring at any time during the same 12-month period: 1) Drinks more than planned; 2) Continued use despite recurrent physical or psychological problems caused or exacerbated by use; 3) Important social, occupational, or recreational activities given up or reduced due to abuse; 4) Time consuming; 5) Tolerance (50% increase in substance required to achieve intoxication or desired effect); 6) Unsuccessful effort(s) to cut down or control alcohol consumption; 7) Withdrawal symptoms experienced or drinks to relieve withdrawal symptoms.

4.4.2 Drug use disorders

Drug use was divided in K-SADS according to substances: a) Cannabis (DSM-IV subcode .30), b) Stimulants (.90), c) Sedatives/Hypnotics/Anxiolytics (.10), d) Cocaine (.20), e) Opioids (.00), f) PCP (.90), g) Hallucinogens (.50), h) Solvents/Inhalants (.60), i) Other, (.70) j) Polysubstance (.80).

Drug abuse

An adolescent was diagnosed with drug abuse (DSM-IV 305.) if one or more of the following was present: continued use despite recurrent occupational (school) or social negative consequences caused or exacerbated by use; recurrent use in physically dangerous situations; recurrent legal-related problems; recurrent use when expected to fulfill major role obligations.

Drug dependence

Drug dependence (DSM-IV 304, including sedative dependence DSM-IV 304-10) was diagnosed if three or more of the following symptoms occurring at any time during the same 12-month period: 1) Uses more than planned; 2) Continued use despite recurrent physical or psychological problems caused or exacerbated by use; 3) Important social, occupational, or recreational activities given up or reduced due to abuse; 4) Time consuming; 5) Tolerance (50% increase in substance required to achieve intoxication or desired effect); 6) Unsuccessful effort(s) to cut down or control drug consumption; 7) Withdrawal symptoms experienced or drugs used to relieve withdrawal symptoms.

Intravenous drug dependence

Diagnosis of intravenous drug dependence (IDD) was made if an adolescent was diagnosed with drug dependence according to DSM-IV and presented with continuous intravenous drug use. The limit for intravenous drug use was set to at least six total injections according to EuropASI.

4.4.3 Daily smoking

Information on daily tobacco smoking was obtained from K-SADS-PL. The threshold for daily smoking was one or more cigarettes per day. The initiation age of daily smoking was reported within an accuracy of six months.

4.5 Independent variables and risk factors

4.5.1 Age of an adolescent

The age of an adolescent was recorded as continuous variable and was reported within an accuracy of 1 year. The age of an adolescent was obtained from K-SADS-PL.

4.5.2 Depressive disorders

The diagnostic group of Depressive Disorders (DEP) included: Major depressive disorder [DSM-IV-code 296.2], Recurrent major depressive disorder [296.3], Dysthymic disorder [300.4], Depressive disorder NOS [311].

4.5.3 Behavioral disorders

The diagnostic group of Behavioral Disorders (BD) included: Conduct disorder (312.8), Disruptive behavior disorder NOS (312.9), Oppositional defiant disorder (313.81), Attention deficit/hyperactivity disorder (314).

4.5.4 Anxiety disorders

The diagnostic group of Anxiety disorders (ANX) included the subgroups of Phobic Disorders (PHO) (including; Agoraphobia [DSM-IV 300.21], Social Phobia [300.23] and Specific phobias [300.29] used in I and IV) and Other anxiety disorders (including; Anxiety disorder NOS [300.00], Panic disorder with [300.21] and without agoraphobia [300.01], Generalized anxiety disorder [300.02], Obsessive-Compulsive disorder [300.3], Acute stress disorder [308.3] and Post-traumatic stress disorder [309.81]).

4.5.5 Psychotic disorders

The diagnostic group of psychotic disorders (PSY) included Schizoaffective disorder (DSM-IV 295.70), Undifferentiated Schizophrenia (296.0), Delusional disorder (297.1), Shared psychotic disorder (297.3), Brief psychotic disorder (298.8) Psychotic disorder NOS (298.9), Dissociative Fugue (301.13), Schizotypal disorder (301.22)

4.5.6 Other psychiatric disorders

The diagnostic group of other psychiatric disorders in this sample included Anorexia nervosa (DSM-IV 307.1), Bulimia nervosa (307.51), Enuresis (307.6), Encopresis (307.7), TIC disorder (307.2), Bipolar NOS (296.80), Bipolar I (296.0-7) and Bipolar II (296.89).

4.5.7 Risk factors for intravenous drug dependence and other SUD

Family risk factors

The family risk factors assessed in the original publication II were gathered from EuropASI and Kiddie-SADS-PI and categorized into adolescent and parental risk factors. Adolescent risk factors included gender, age at first hospitalization at Unit 70, biological father and biological mother (present vs. absent in the adolescent's life), sibling status (firstborn vs. not firstborn), presence of another individual with substance problems in the residence (present vs. absent) and adolescent's own monthly income in euros (€), main source of income (normal salary, unemployment benefit, social aid, a benefit related to social security, friends, illegal activities, prostitution, parents/relatives, other sources of income). Parental information included mother's occupational status (full time vs. other), interparental violence (yes vs. no), parental substance use (yes vs. no), experienced fathers SUD (yes vs. no), experienced mothers SUD (yes vs. no), parental mental disorders (yes vs. no), and inter-parental violence (yes vs. no).

School-related factors

School-related factors, gathered from EuropASI and Kiddie-SADS-PI, included school performance; measured grade point average of the completed comprehensive school or the last completed class in comprehensive school (on a scale from 4 to 10), having failed a grade (yes vs. no), learning disability (yes vs. no), truancy before the age of 13 years (yes vs. no) and transfer to special class (students who have not been able to participate in normal education due to disruptive behavior or learning difficulties), (yes vs. no).

Tobacco smoking and previous substance experiences

Variables concerning previous substance use included regular cigarette smoking (yes vs. no) and initiation age of regular smoking (at least once a day), previous alcohol, cannabis and other substance use (yes vs. no), age at first tobacco trial, age at first alcohol trial and age at first cannabis trial. Data regarding previous substance use and first experiment ages were gathered from the EuropASI and the Pompidou Questionnaire.

4.5.8 Other characteristics of the study population

The variables used for presenting the characteristics concerning treatment; duration of treatment (in days), hospitalization from another unit (yes vs. no), in involuntary treatment (yes vs. no), previous psychiatric hospitalizations (number), place of residence (city>100,000 inhabitants, town 100,000 – 10,000 habitants, rural area<10,000 habitants), type of dwelling (two-parent family, one-parent family, child welfare placement, other family type), under custody (yes vs. no) and criminal history; been arrested (yes vs. no), times arrested (continuous variable), convicted of a crime (yes vs. no), awaiting a trial (yes vs. no) were gathered from EuropASI.

4.6 Statistical Methods

In all of the original studies I-V the differences between groups in categorical variables were analyzed with Pearson's Chi-Square or Fisher's exact test as appropriate. Group differences between sums and means in two groups in

continuous variables were investigated with Student's *t*-test or Mann-Whitney *U*-test. All statistical tests were two-sided and the limit for statistical significance was set at 0.05. P-values lower than 0.05 and Odds and Hazard ratios with 95% confidence intervals excluding 1 were considered statistically significant. Statistical analyses were carried out with SPSS (PASW) for Windows (versions 13.0 (Original publications I, II and III), 14.0 (IV) and 17.0 (V), SPSS Inc. 2004, 2005 and 2008, respectively) and with SAS (version 9.1 for windows SAS, 2007). In addition; in (I) the association between phobic disorders and dependence was assessed with logistic regression model and Kaplan-Meier's method was used to study the temporality. In (II) the differences in continuous variables were also investigated with analysis of variance (ANOVA) and the Kruskal-Wallis one way analysis of variance (H) as appropriate. In (III) the Cox proportional hazard model was used to compare the initiation of daily smoking in the presence and absence of psychiatric morbidity. In (IV) the homogeneity of Odds ratios for association between substance dependence and each psychiatric disorder between genders was assessed with the Breslow-Day test.

4.7 Ethical considerations and personal involvement

The research plan for the STUDY-70 project, which the present research is part of, was reviewed by the Ethics Committee of the Faculty of Medicine, University of Oulu, on 11th April 2001. In addition, the topic of this doctoral thesis was approved by the Postgraduate Research Committee of the Faculty of Medicine at the University of Oulu.

The subjects were given a complete description of the research plan and were also advised that declining to participate in the research would not have any affect on their treatment. A signed informed consent was obtained from the adolescents and at least one parent or guardian before enrollment.

The author of this thesis has been participating in the STUDY-70 project as a researcher since the initiation of the project in the beginning of 2001. The author started in the project by developing the database for the STUDY-70-project. The database included the sheets for K-SADS-PI, EuropASI, The Pompidou questionnaire and the Fagerström Nicotine Dependence questionnaire. The author completed the K-Sads-PI diagnostic interview for roughly one sixth of the study population and also completed EuropASI, the Pompidou Questionnaire and Fagerström Nicotine Dependence questionnaire to a small proportion of

adolescents whose interviews were initiated in Unit 70, but completed in other psychiatric units. The author entered at least two thirds of the data into computer for statistical analyses. The author has made a major contribution in all of the original papers. The author planned the study design and research questions for studies (I)-(V) in consultation with co-authors. The author made the preliminary statistical computer analysis on (I)-(V) and the final statistical analysis in (II)-(V) in co-operation with a statistician. He wrote the first draft of manuscripts (I), (II), (IV) and (V) and was the first author in all of the manuscripts. He was the corresponding author in (I)-(III) and responsible for the final form of each paper as submitted.

5 Results

5.1 The Study population

Table 6 (below) presents the characteristics of all the girls and boys in the total study sample in comparison to those girls and boys who were diagnosed with alcohol or drug dependence.

Table 6. Demographic, treatment-related and social characteristics of all the girls/boys in the study sample, in comparison to these characteristics in alcohol and drug dependent girls/boys.

Characteristics	All adolescents		Adolescents with substance dependence			
			Girls		Boys	
	Girls n=300	Boys n=208	Alcohol dependence n=50 (17%)	Drug dependence n=22(7.3%)	Alcohol dependence n=42 (20%)	Drug dependence n=31 (15%)
Mean age, years (SD) ^a	15.5 (1.3)	15.4 (1.4)	16.2 (0.8)*	16.4 (0.7)*	16.3 (1.0)*	16.2 (1.0)*
Treatment						
Duration of treatment, days mean (median) ^a	12.2 (8)	11.8 (9)	13.1 (10)	16.5 (6)	10.9 (10)	13.8 (11)
In involuntary treatment	42%	50%	44%	50%	36%*	29%*
Hospitalized from another institution	21%	23%	30%	68%*	43%*	48%*
Previous psychiatric hospitalizations, mean (SD) ^a	0.5 (1.0)	0.8 (1.2)	0.7 (1.3)	1.3 (1.8)*	1.0 (1.3)	1.1 (1.8)
Place of residence						
City (>100,000 inhabitants)	21%	23%	22%	23%	36%	32%
Town (10,000-100,000)	24%	30%	42%*	32%	26%	29%
Rural area (<10,000)	55%	47%	36%*	46%	38%	39%
Type of dwelling						
Two-parent family (%)	51%	38%	28%*	22%*	27%*	23%*
One-parent family (%)	18%	22%	20%*	9%*	12%*	13%*
Child welfare placement (%)	17%	29%	24%*	41%*	37%*	50%*
Other family type (%) ^b	14%	11%	28%*	27%*	24%*	13%*

Characteristics	All adolescents		Adolescents with substance dependence			
			Girls		Boys	
	Girls n=300	Boys n=208	Alcohol dependence n=50 (17%)	Drug dependence n=22(7.3%)	Alcohol dependence n=42 (20%)	Drug dependence n=31 (15%)
Under custody (%)	20%	29%	28%	59%*	43%*	52%*
Substance use model						
Experienced Father SUD	26%	22%	36%	32%	21%	26%
Experienced Mother SUD	17%	11%	30%*	38%	10%	7%
Living with other SU	16%	12%	26%*	40%*	18%	33%*
School background						
Repeated grades	10%	23%	14%	27%*	36%	29%
Special education	55%	68%	66%	68%	81%	77%
Truancy	29%	46%	38%	50%*	60%*	68%*
Criminal history						
Been arrested	7.3%	20%	54%*	55%*	71%*	81%*
Times arrested, (median) ^a	0.6 (0)	2.4 (0)	1.7 (1)**	3.0 (3)**	7.0 (3) *	8.8 (5) *
Convicted of a crime	4%	17%	14%*	23%*	38%*	39%*
Awaiting for a trial	5.7%	13%	12%*	23%*	38%*	48%*

a= Independent samples T-test *p<0.05, comparison between SUD and the whole population

5.1.1 Diagnostic distribution (III)

Of the 508 patients enrolled in this study, 208 (40.9%) were boys and 300 (59.1%) girls. On admission to the hospital, the mean age was 15.4 (SD 1.4) years for the boys and 15.5 (SD 1.3) years for the girls (*i.e.*, no significant gender difference).

Of the 508 subjects enrolled in the study, 206 (40.6%) were suffering from alcohol use disorders, 89 (17.5%) from drug use disorders, 165 (32.5%) from anxiety disorders, 67 (13.1%) from phobic disorders, 309 (60.8%) from depressive disorders, 253 (49.8%) from behavioral disorders and 73 (14.4%) from psychotic disorders. The combined prevalence of mania and other bipolar disorders was 15 (3.0%). A total of 333 (65.6%) fulfilled the criteria for at least two diagnostic groups. The distribution of the diagnoses differed significantly between the sexes in diagnostic groups of drug use disorders (23.6% of boys vs. 13.3% of girls, $\chi^2=8.89$, $df=1$, $p=0.003$), anxiety disorders (24.5% of boys vs. 38.0% of girls, $\chi^2=10.18$, $df=1$, $p=0.001$), depressive disorders (45.7% of boys vs. 71.3% of girls, $\chi^2=33.94$, $df=1$, $p<0.001$), and conduct or oppositional defiant disorder (62.0% of boys vs. 41.3% of girls, $\chi^2=21.03$, $df=1$, $p<0.001$). Figures 7 and 8 show the diagnostic distribution and the prevalence of comorbidity in the study sample.

In boys, significant associations were observed between diagnostic groups of conduct and oppositional defiant disorders with alcohol use disorders ($\chi^2=9.57$, $df=1$, $p=0.002$), drug use disorders ($\chi^2=12.76$, $df=1$, $p<0.001$), and depressive disorders ($\chi^2=3.94$, $df=1$, $p=0.047$), depressive disorders with anxiety disorders ($\chi^2=12.00$, $df=1$, $p=0.001$), and alcohol use disorders with drug use disorders ($\chi^2=47.36$, $df=1$, $p<0.001$). Among girls, alcohol use disorders ($\chi^2=36.95$, $df=1$, $p<0.001$) and drug use disorders ($\chi^2=24.90$, $df=1$, $p<0.001$) were significantly associated with conduct and oppositional defiant disorders. Association between anxiety and drug use disorders ($\chi^2=4.12$, $df=1$, $p=0.042$) and drug and alcohol use disorders ($\chi^2=27.04$, $df=1$, $p<0.001$) was also found among girls.

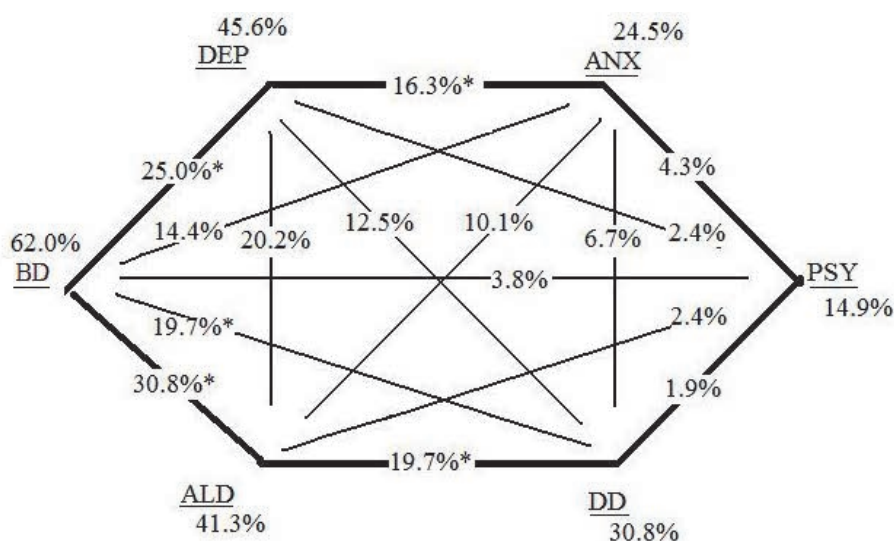


Fig. 7. The diagnostic distribution and comorbidity between diagnostic groups of adolescent boys, n=208 (Original paper 3, figure 1).

BD=Behavioral disorders, DEP=Depressive disorders, ANX=Anxiety disorders, PSY=Psychotic disorders. DD=Drug dependence, ALD=Alcohol dependence. Lines between the two disorders present the overall prevalence of respective comorbidity in the sample of 208 boys. * for statistically significant univariate association χ^2 $p < 0.05$.

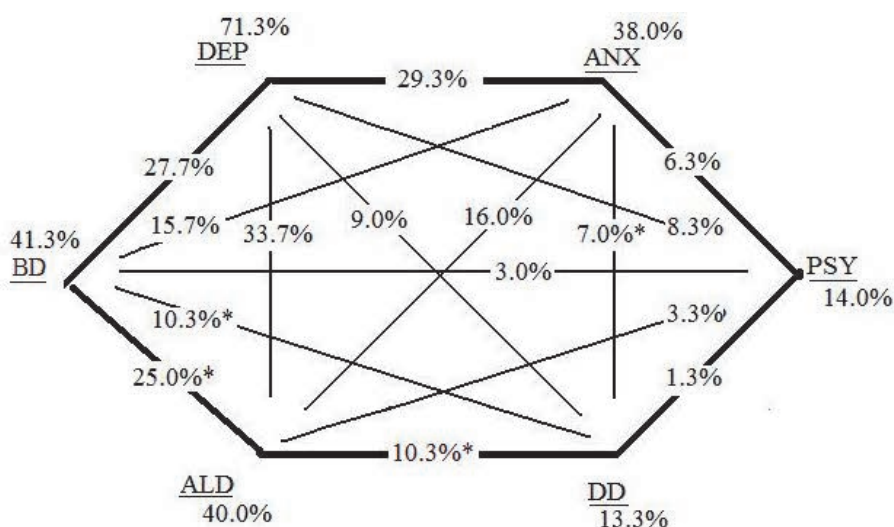


Fig. 8. The diagnostic distribution and comorbidity between diagnostic groups of adolescent girls, n=300 (Original paper 3, figure 2).

BD=Behavioral disorders, DEP=Depressive disorders, ANX=Anxiety disorders, PSY=Psychotic disorders. DD=Drug dependence, ALD=Alcohol dependence. Lines between the two disorders present the overall prevalence of respective comorbidity in the sample of 300 girls * for statistically significant univariate association χ^2 $p < 0.05$.

5.2 Prevalence of substance use disorders

Substance use disorders were found to be common among inpatient adolescents. Of all the 508 adolescents, 223 (44%) were diagnosed with lifetime substance use disorders. 58 out of 208 (28%) boys and 86 out of 300 (29%) girls had been diagnosed with lifetime alcohol abuse. In addition, 42 (20%) of the boys and 50 of the girls (17%) were alcohol dependent. The combined lifetime prevalence of alcohol use disorders (abuse and/or dependence) was 40% among girls and 41% among boys.

The lifetime prevalence of drug abuse was 9% among girls (28 out of 300) and 14% for boys (28 out of 208). The lifetime prevalence of drug dependence was 7% (22) for girls and 15% (31) for boys ($\chi^2=7.53$, $df=2$, $p=0.006$). The combined lifetime prevalence of drug use disorders was 13% among girls and 24% among boys ($\chi^2=8.89$, $df=2$, $p=0.003$).

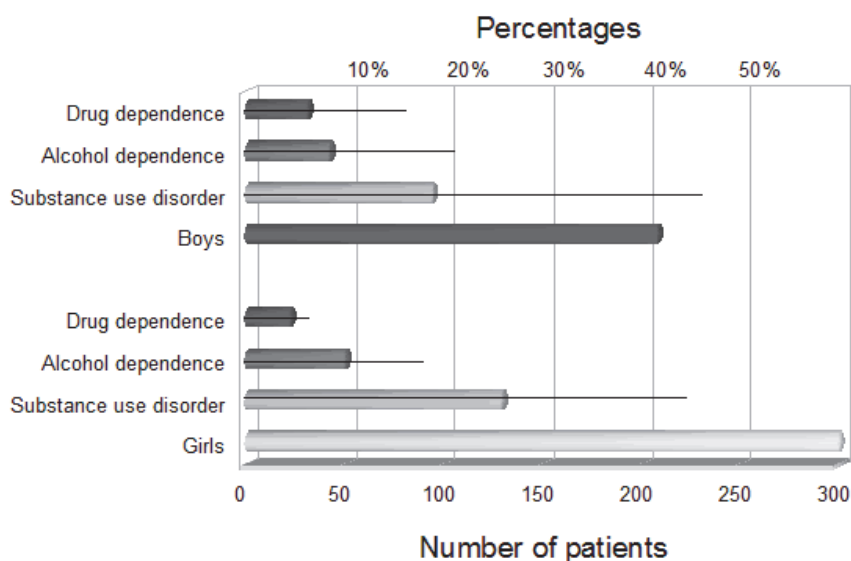


Fig. 9. Prevalence of lifetime substance use disorders.

The number of patients is represented with cylinders with the scale (n=0-300) visualized below. Respective percentages among genders represented with lines, the scale (0-50%) is above the figure.

5.3 Psychiatric comorbidity of substance use disorders

5.3.1 Comorbidity of alcohol dependence (IV)

As illustrated below in Figure 10, the diagnostic group of behavioral disorders was significantly associated with an increased likelihood of alcohol dependence among girls (OR 7.13, 95%CI 3.36-15.13, $p<0.001$). Among adolescent boys, alcohol dependence was associated with depressive (OR 3.07, 95%CI 1.09-7.00, $p=0.033$) and behavioral disorders (OR 4.62, 95%CI 1.94-14.63, $p=0.001$). Among both genders, phobic disorders showed a trend towards significant association with alcohol dependence. Higher age, used as a covariate, was associated with increased likelihood of alcohol dependence both among girls (OR 2.34, 95%CI 1.63-3.37, $p<0.001$) and boys (OR 2.71, 95%CI 1.79-4.10, $p<0.001$).

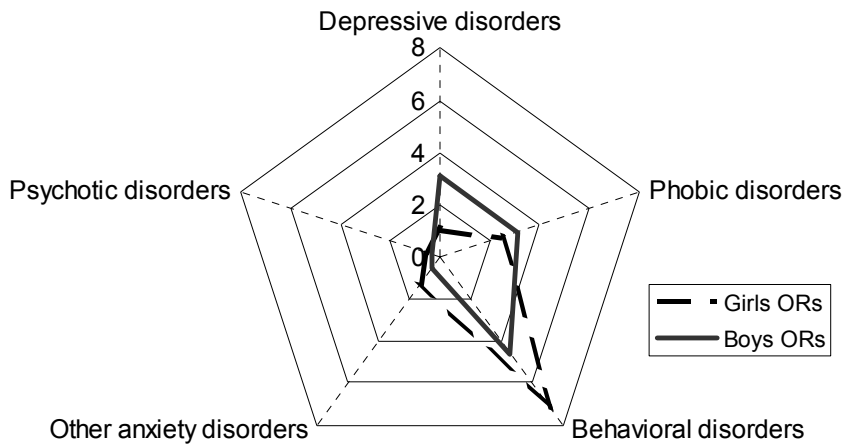


Fig. 10. Gender difference in comorbidity of alcohol dependence.

ORs from a logistic regression model (method=enter) predicting alcohol dependence with age and psychiatric disorders of adolescents. ORs > 1.0 indicate higher likelihood of alcohol dependence. Placement and shape of the two pentagons reflect the diversion and magnitude of comorbidity. Areas that are covered by just one pentagon reflect the gender difference in comorbidity of alcohol dependence.

5.3.2 Comorbidity of drug dependence (IV)

Increased risk for drug dependence among girls was evident in those diagnosed with phobic disorders (OR 5.43, 95%CI 1.41-20.81, $p=0.014$) and behavioral disorders (OR 18.40, 95%CI 4.73-71.56, $p<0.001$), see Figure 11 below. Among boys, drug dependence was associated with depressive disorders (OR 3.76, 95%CI 1.41-9.99, $p=0.008$) and conduct disorders (OR 9.06, 95%CI 2.58-31.73, $p<0.001$). Higher age, used as a covariate, was associated with an increased likelihood of drug dependence among both girls (OR 3.23, 95%CI 1.73-6.07, $p<0.001$) and boys (OR 2.19, 95%CI 1.45-3.30, $p<0.001$).

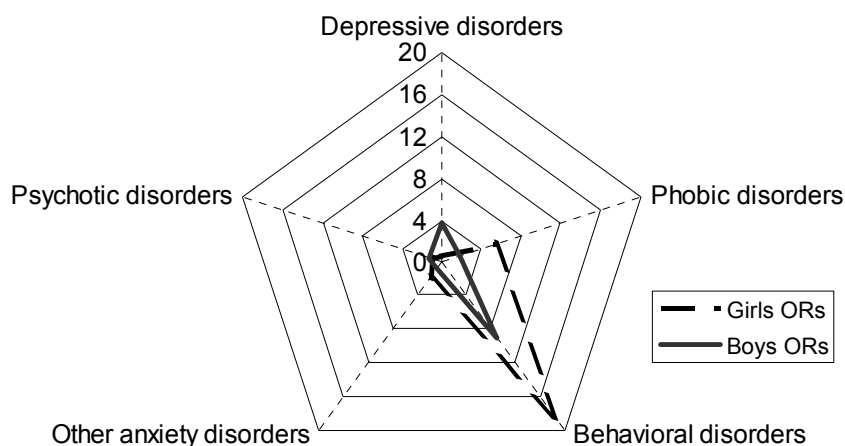


Fig. 11. Gender difference in comorbidity of drug dependence.

ORs from a logistic regression model (method=enter) predicting the drug dependence with age and psychiatric disorders of the adolescents. ORs > 1.0 indicate higher likelihood of drug dependence. Placement and shape of the two pentagons reflect the diversion and magnitude of comorbidity. Areas that are covered by just one pentagon reflect the gender difference in comorbidity of drug dependence.

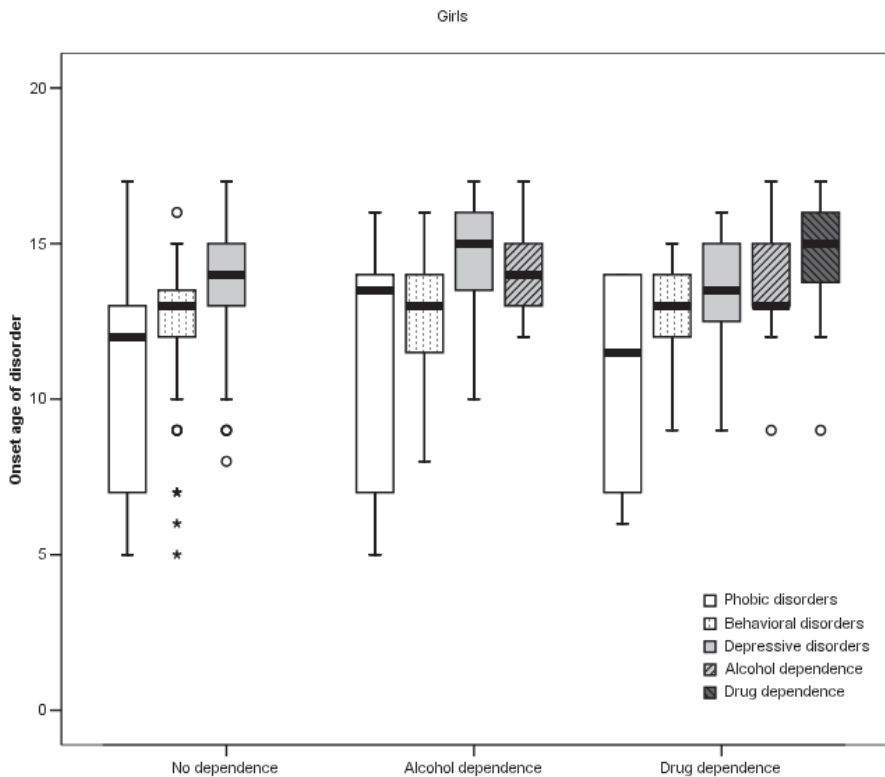
There was a statistically significant gender difference in the comorbidity of depressive disorders and drug dependence (Girls, OR 0.6, 95%CI 0.2-2.0 vs. Boys, OR 3.8, 95%CI 1.4-10.0, Breslow-Day test, $p=0.028$). Among the drug dependent adolescents, 52% of the girls and 58% of the boys had previous or concurrent comorbid alcohol dependence.

5.4 Temporality of alcohol and drug dependence and psychiatric disorders (I,IV)

The mean age of onset for alcohol dependence was 14.0 years (SD 1.5) for girls and 13.8 years (SD 1.6) for boys. Among girls, the mean age of onset for drug dependence was 14.6 years (SD 1.9) and among boys 13.9 years (SD 1.6).

Figures 12 (for girls) and 13 (for boys) present the onset age of psychiatric disorders as well as that of alcohol and drug dependence in each subgroup of substance use disorders. In both alcohol dependent boys and girls, onset of phobic

and behavioral disorders preceded the onset of alcohol dependence – *i.e.*, phobic and behavioral disorders were primary to alcohol and drug dependence, while depressive disorders began at later age than alcohol dependence – *i.e.*, depression is secondary. In drug dependence, the onset age of phobic, behavioral and depressive disorders occurred before the onset of drug dependence in both



genders.

Fig. 12. Temporality of alcohol and drug dependence among girls (Original paper 4, figure 1).

Age at onset of phobic, behavioral and depressive disorders and dependencies in three subgroups of alcohol/drug dependence among adolescent girls. * extreme value; ° outlier value.

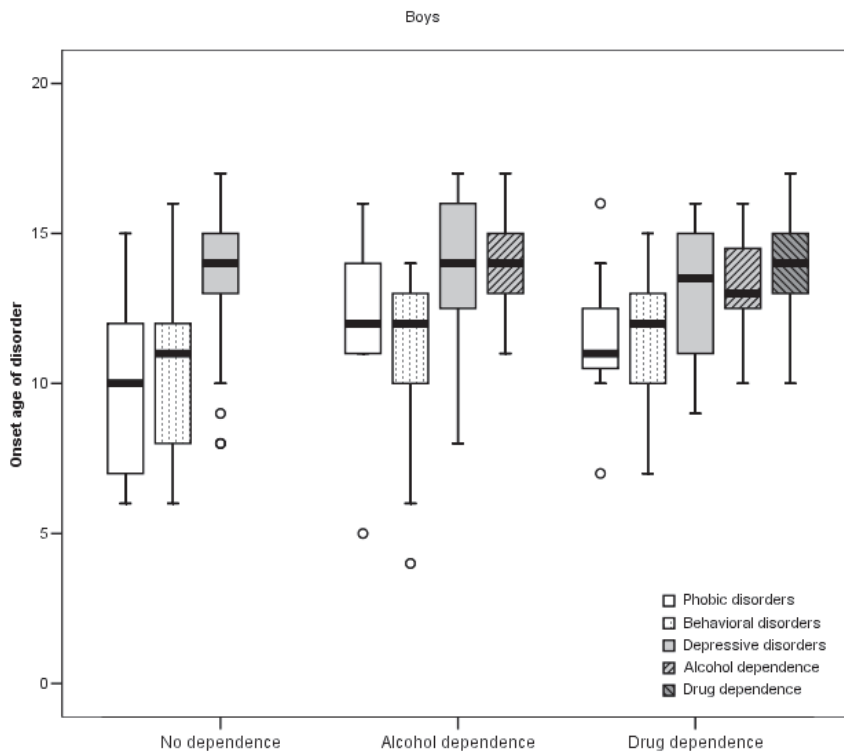


Fig. 13. Temporality of alcohol and drug dependence among boys (Original paper 4, figure 2).

Age at onset of phobic, behavioral and depressive disorders and dependencies in three subgroups of alcohol/drug dependence among adolescent boys. ° outlier value

Temporality of phobic disorders and substance use disorders was examined in Study I. The study sample consisted of 238 adolescents, 134 girls and 104 boys. The number of cases involved was lower as the study was conducted in the middle of a 5-year prospective data collection process (Table 5).

In 90.5% of the adolescents with both phobic disorder and substance dependence, the onset of a phobic disorder preceded substance dependence or began at the same time. The mean onset age of phobias was 11.4 years (11.5 [SD 3.3] for boys and 11.2 [SD 4.3] for girls. The subsequent onset of substance dependence occurred at the age of 14.4 years (13.7 [SD 1.4] in boys and 15.4 [SD 0.9] in girls; gender difference: $t=-3.08$, $df=19$, $p=0.006$). Over one half (57.9%)

of the adolescents with phobic disorders and substance dependence had developed substance dependence within three years of the onset of phobia.

5.5 Daily smoking and the development of substance dependence (III)

5.5.1 Prevalence of daily smoking

The majority of the subjects (369, 72.6%) smoked regularly (at least one cigarette per day). The proportion of smokers did not differ significantly between boys (158, 76.0%) and girls (211, 70.3%). The proportion of subjects who smoked daily was very high in each diagnostic category. The highest prevalence of daily smoking was observed among patients diagnosed with substance-related disorders and with behavioral disorders. The lowest prevalence of smoking was found among subjects with psychotic disorders. Among the subjects with depressive disorders, a significantly higher proportion of boys were daily smokers as compared to girls ($\chi^2=5.98$, $df=1$, $p=0.014$).

5.5.2 Onset Age of Daily Smoking

The mean onset age of daily smoking in the study population was 12.8 (SD 1.7) years. The boys in the present sample had started smoking regularly at an earlier age (12.4 years, SD 1.8) than girls (13.0, SD 1.6) (Student's t-test, $t=-3.873$, $df=369$, $p<0.001$). The mean onset age of daily smoking was earlier among boys with depressive disorders than among girls with depressive disorders ($t=-3.271$, $df=223$, $p=0.001$). A similar gender difference was also noted in the onset of daily smoking among the adolescents diagnosed with anxiety disorders ($t=-2.881$, $df=121$, $p=0.005$) and behavioral disorders ($t=-2.083$, $df=220$, $p=0.038$).

5.5.3 Initiation of daily smoking

The Cox proportional Hazard model was used to assess the relationship between the initiation of daily smoking and psychiatric disorders. After adjusting for other psychiatric diagnoses and the age of an adolescent, girls with alcohol use (Hazard Ratio [HR]=2.7, $p<0.001$) and drug use disorders (HR=1.8, $p<0.001$) and boys

with alcohol (HR=1.7, $p=0.008$) and drug use disorders (HR= 1.7, $p=0.012$) started daily smoking earlier compared to adolescents without these disorders. Earlier initiation of daily smoking was also observed among adolescents diagnosed with behavioral disorders (Girls: HR= 1.8, $p<0.001$, Boys: HR=1.7 $p=0.003$).

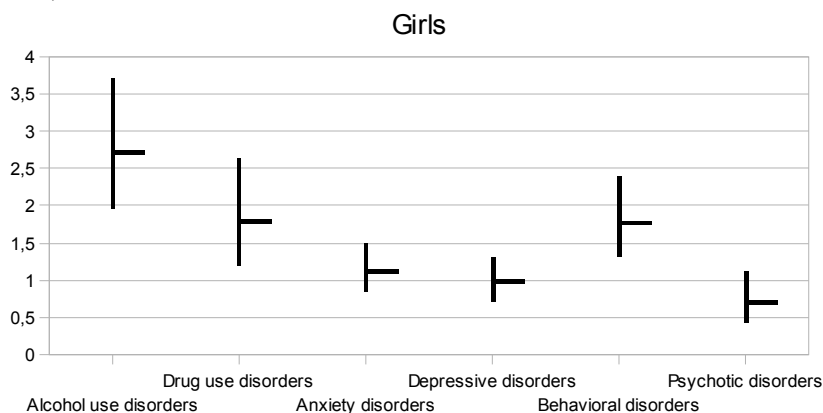


Fig. 14. The risks for earlier initiation of daily smoking according to psychiatric morbidity among girls.

Adjusted for other diagnostic categories and the age of the adolescents. Horizontal lines express the HRs, vertical lines express the confidence intervals of HRs.

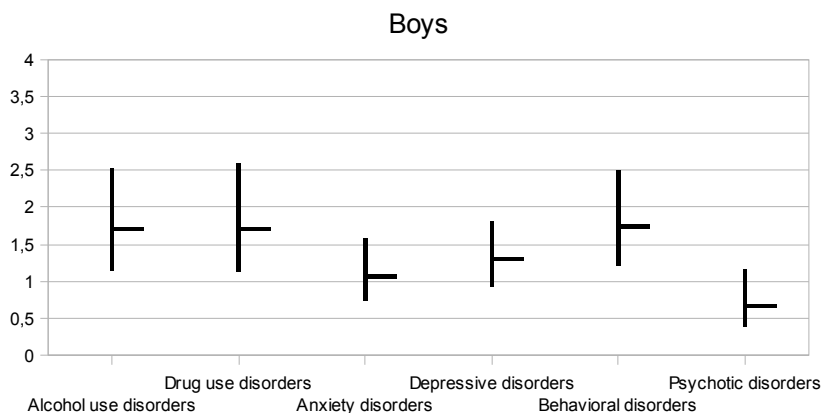


Fig. 15. The risks for earlier initiation of daily smoking according to psychiatric morbidity among boys.

Adjusted for other diagnostic categories and the age of the adolescents. Horizontal lines express the HRs, vertical lines express the confidence intervals of HRs.

5.5.4 Temporality of daily smoking and psychiatric disorders

The difference in the onset ages of daily smoking and psychiatric diagnoses was also evaluated with Cox proportional hazard model. A difference less than 0 (zero) suggests that daily smoking is secondary to a disorder, while a difference greater than 0 suggests that daily smoking is primary to a psychiatric disorder (see Figure 16 below). Among boys, the mean differences between the onset age of daily smoking and onset of psychiatric disorders were as follows (+ sign indicates that the disorder started after the onset of smoking and – indicates that it preceded it); alcohol use disorders: +1.4 years (SD 1.8, $p < 0.001$), drug use disorders: +2.0 years (SD 1.9, $p < 0.001$), anxiety disorders: -1.2 years (SD 3.8, $p = 0.090$), depressive disorders: +1.1 years (SD 2.6, $p = 0.001$), behavioral disorders: -1.1 years (SD 2.8, $p < 0.001$) and psychotic disorders: +2.6 years (SD 1.8, $p < 0.001$). Among girls, the corresponding differences were: alcohol use disorders: +1.0 years (SD 1.5 years, $p < 0.001$), drug use disorders: +2.0 years (SD 1.9 years, $p < 0.001$), anxiety disorders: -0.3 years (SD 3.4 years, $p = 0.434$), depressive disorders: +0.9 years (SD 2.1 years, $p < 0.001$), behavioral disorders: -0.1 years (SD 2.0 years, $p = 0.669$) and psychotic disorders: +0.9 years (SD 2.5 years, $p = 0.132$). The differences between the onset ages of daily smoking and behavioral disorders ($t = 3.271$, $df = 194$, $p = 0.001$) and daily smoking and psychotic disorders ($t = -2.150$, $df = 32$, $p = 0.039$) were greater among boys than girls.

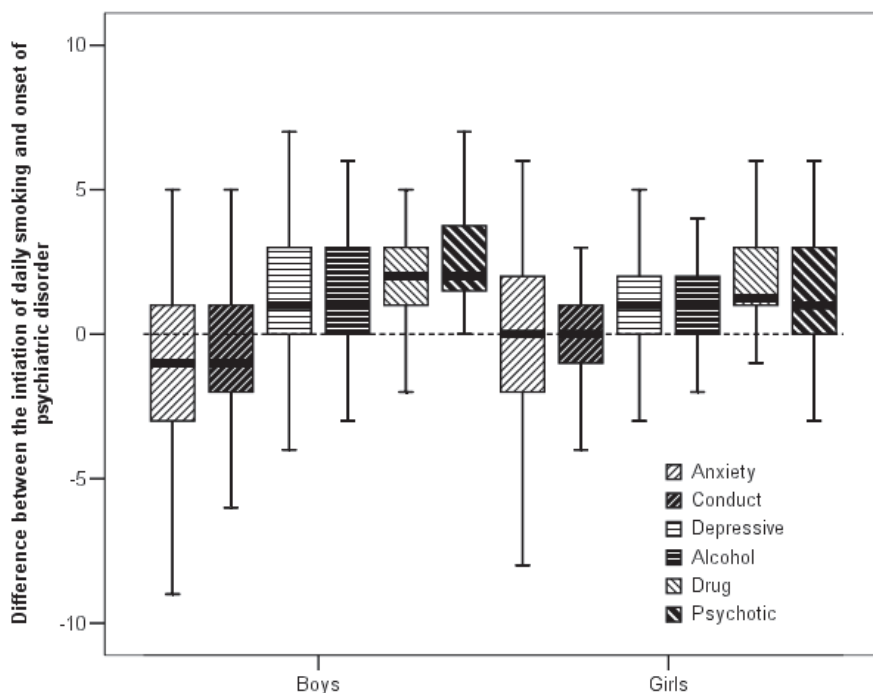


Fig. 16. Difference between the initiation of daily smoking and onset of psychiatric disorder (Original paper 3, Figure 3).

5.6 Intravenous drug dependence (II)

5.6.1 Prevalence of intravenous drug dependence

Intravenous drug dependence (IDD) was evaluated in the sample of 342 adolescents. Ten percent (n=28) were diagnosed as drug dependent and having used drugs intravenously (more than five times). The most common drugs used intravenously were amphetamine (75% of the IDD), opiates – other than heroin (54%), heroin (32%) and sedatives/anxiolytes (28%) (Figure 17).

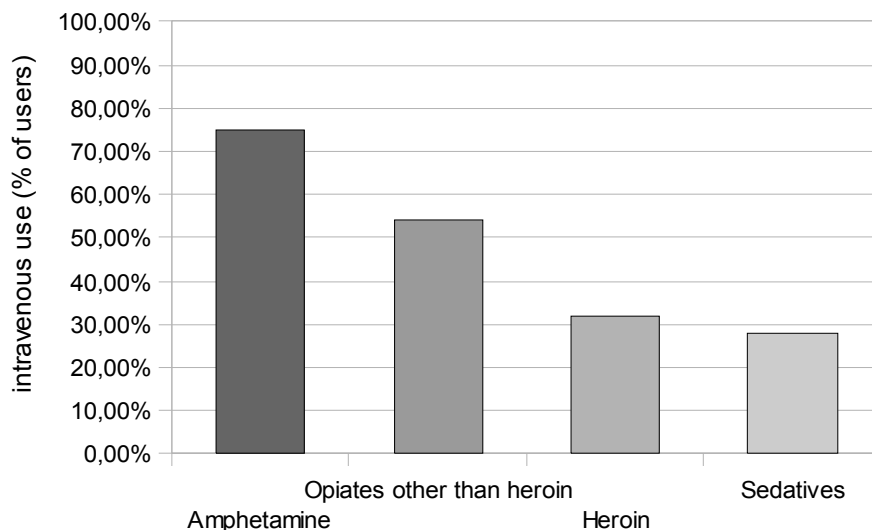


Fig. 17. Distribution of intravenously used substances among adolescent psychiatric inpatients diagnosed with intravenous drug dependence.

5.6.2 Social risk factors for intravenous drug dependence

5.6.3 Family risk factors

The family risk factors for IDD are shown in Table 7 (below). Adolescents with IDD were older than both adolescents with other SUD and those without SUD when admitted to the study unit (ANOVA: $F=18.273$, $df=2$, $p<0.001$), and a lesser proportion of adolescents with IDD lived with their biological father ($\chi^2=14.94$, $df=2$, $p=0.001$) or biological mother ($\chi^2=21.73$, $df=2$, $p<0.001$) when compared to other adolescents. There was also a significant difference between the groups in the monthly income of the adolescents ($H=17.11$, $df=2$, $p<0.001$). Adolescents with SUD had higher monthly incomes than adolescents without substance use. The most common sources of income of the IDD adolescents were social aid (36%) and illegal activities (18%). The corresponding sources of income among adolescents without substance diagnose and adolescents with substance diagnose

but no intravenous use, were parents (71% non-SUD and 54% SUD) and social aid (19% non-SUD and 25% SUD adolescents).

5.6.4 School Background

The differences in school background between the groups are shown in Table 7 (below). The results show that a greater proportion of the IDD adolescents had unauthorized absence from school before 13 years of age ($\chi^2=21.65$, $df=2$, $p<0.001$), and more of them had been transferred to special classes ($\chi^2=14.34$, $df=2$, $p=0.001$) than of both adolescents with other SUD and of those adolescents without SUD.

5.6.5 Social risk factors and the severity of substance use disorder

All of the adolescents in the study population reported a high prevalence of each studied risk factor. The proportion of adolescents with social risk factors increased from the non-SUD to the SUD group and was the highest among adolescents with IDD.

5.6.6 Smoking, substance use and intravenous drug dependence

All of the IDD adolescents smoked daily, and the difference compared to other adolescents was statistically significant ($\chi^2=50.31$, $df=2$, $p<0.001$). All of the IDD adolescents had started smoking before their first intravenous trial. The mean difference between the initiation of regular smoking and first intravenous use was 3.0 years (SD 1.6), 2.2 (SD 1.2) years and 3.7 (SD 1.6) years for all IDD adolescents, girls and boys, respectively (gender difference ANOVA: $F=7.412$, $df=1$, $p=0.011$). Prior to their intravenous use, IDD adolescents had wider substance use experience of alcohol ($\chi^2=33.04$, $df=2$, $p<0.001$), cannabis ($\chi^2=110.97$, $df=2$, $p<0.001$) and other substances ($\chi^2=50.64$, $df=2$, $p<0.001$) than the other adolescents. The prevalence of regular smoking, alcohol use, cannabis use and other substance use grew gradually along substance use severity from non-SUD to other-SUD to IDD subgroups.

Table 7. Adolescent and family risk factors, school background and previous substance use in adolescent substance users.

	Intravenous drug dependence (IDD)	Other substance use disorders	No substance use disor. (=reference)	p-value
Adolescent risk factors				
Gender, male	53.6% (n=15)	41.2% (n=47)	39.0% (n=53)	0.360
Age at admission to Unit 70 ^a	16.5 (SD=.74)	15.8 (SD=1.13)	15.2 (SD=1.35)	<0.001
Firstborn child	50.0% (n=14)	36.8% (n=42)	32.4% (n=44)	0.202
Monthly income €, median (IQR) ^b	42 € (25, 100)	60 € (33, 160)	33 € (16, 83)	<i>H</i> <0.001
Family background				
Another substance user in apart.	47.8% (n=11)	28.8% (n=30)	24.2% (n=30)	0.072
Biological father absent	89.3% (n=25)	54.0% (n=73)	51.5% (n=70)	0.001
Biological mother absent	71.4% (n=20)	48.2% (n=55)	28.7% (n=39)	<0.001
Mother's full-time employment	74.1% (n=20)	51.4% (n=54)	48.4% (n=60)	0.052
Interparental violence	28.6% (n=8)	29.8% (n=34)	27.2% (n=37)	0.901
Parental substance use	32.1% (n=9)	20.2% (n=23)	22.1% (n=30)	0.393
Parental mental disorders	17.9% (n=5)	16.7% (n=19)	22.1% (n=30)	0.512
Parental physical abuse	39.3% (n=11)	28.9% (n=33)	26.5% (n=36)	0.394
School background				
Learning disability	35.7% (n=10)	39.5% (n=45)	30.9% (n=42)	0.363
Truancy	67.9% (n=19)	43.0% (n=49)	25% (n=43)	<0.001
Transfer to special class	50.0% (n=14)	24.6% (n=28)	16.9% (n=23)	0.001
Failed a grade	25.0% (n=7)	21.1% (n=24)	14.7% (n=20)	0.274
grade point average ^c (scale 4 to 10) ^a	7.09 (SD=1.02)	7.03 (SD=0.87)	7.52 (SD=0.96)	0.378

	Intravenous drug dependence (IDD)	Other substance use disorders	No substance use disor. (=reference)	p-value
Previous substance use				
Regular smoking	100% (n=28)	96.5% (n=110)	63.7% (n=86)	<0.001
Age at regular smoking ^a	11.8 (SD=2.10)	12.8 (SD=1.48)	13.0 (SD=2.02)	0.115
Alcohol use	100% (n=28)	98.2% (n=112)	75.7% (n=103)	<0.001
Cannabis use	100% (n=28)	53.5% (n=61)	8.1% (n=11)	<0.001
Other substance use ^d	96.4% (n=27)	43.9% (n=50)	25.0% (n=34)	<0.001

a=Analysis of variance

b=Kruskal-Wallis-Test

c=grade point average of completed comprehensive school or the last completed class in comprehensive school

d=other substances such as sedatives, stimulants, opioids, hallucinogens, solvents, ecstasy

5.6.7 Temporal progression to intravenous use

The time period from first substance trials (tobacco, alcohol, cannabis) to intravenous use is seen in Figure 18. IDD adolescents experimented with alcohol ($H=16.28$, $df=2$, $p<0.001$) and cannabis for the first time ($H=13.11$, $df=2$, $p=0.001$) at a younger age than other adolescents. Among adolescents with IDD, the respective ages for boys and girls were 9.3 (SD 2.8) and 10.4 (SD 2.2) years at first tobacco trials, 11.0 (SD 2.0) years and 12.7 (SD 1.9) years at initiation of daily smoking, 10.9 (SD 1.6) years and 12.2 (SD 1.4) years at first alcohol trials, 12.8 (SD 1.6) years and 13.4 (SD 1.9) years at first cannabis trials and 14.7 (SD 1.4) years and 14.8 (SD 1.5) years at the initiation of intravenous drug use. IDD boys started smoking regularly (ANOVA: $F=5.070$, $df=1$, $p=0.033$) and first experimented with alcohol (ANOVA: $F=5.145$, $df=1$, $p=0.032$) statistically significantly earlier than IDD girls.

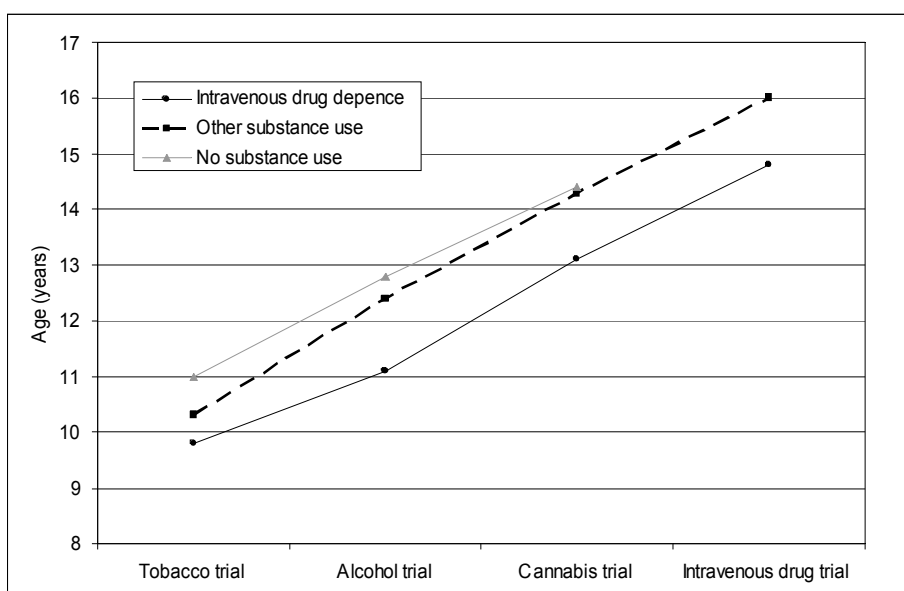


Fig. 18. The time period from first substance trials to intravenous use in adolescents (Original paper 2, Figure 1).

The differences between initiation age of intravenous drug use in relation to family and school risk factors were also analyzed. The results showed that adolescents who were living without their biological father (Mann-Whitney U-test: $p=0.043$) or mother ($p=0.020$), whose mothers were employed full-time ($p=0.036$) or who had been transferred to special class ($p=0.035$) initiated intravenous use at a statistically significantly younger age than the other IDD adolescents. Parental substance abuse was also associated with a younger age at the initiation of intravenous drug use; the difference, however, was not statistically significant. Significant correlations were found between the initiation age of IDU and the initiation of regular smoking ($r=0.696$, $p<0.001$) and also between the initiation age of IDU and ages at first alcohol ($r=0.548$, $p=0.001$) and cannabis trials ($r=0.718$, $p<0.001$).

5.7 Psychotropic medication history and SUD (V)

Psychotropic medication history was evaluated for all the 508 adolescents. Of the boys, 23.5% (n=47) and of the girls, 30.5% (n=89) had been using prescribed psychotropic medication before admission to Unit 70. The lifetime prevalences for psychotropic medication use are shown, by active ingredients, in Figure 19. Figures 20 and 21 show previous psychotropic medication use by gender, divided into three categories based on the active ingredients (antidepressants, antipsychotics and sedatives). Very few adolescents (n=8) had received other medication, of which methylphenidate (n=3) was the most common. Girls had used antidepressants and sedatives statistically significantly more commonly than boys.

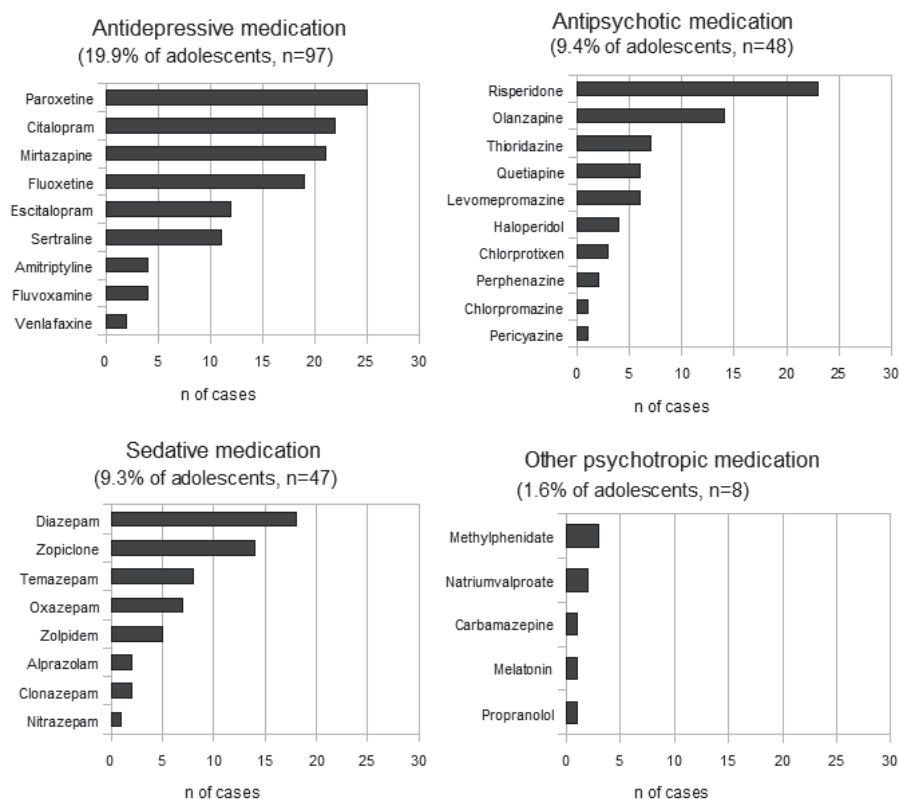


Fig. 19. Psychotropic medication of adolescents before admission to inpatient care (Original paper 5, Figure 1).

As seen in Table 8, adolescents with psychotic disorders and drug use disorders and girls with anxiety disorders had statistically more commonly used medication before admission as compared to those adolescents without these disorders. Among adolescents with diagnosed psychotic and alcohol use and among girls with drug use disorders had slightly lower CGAS scores compared to those adolescents without these disorders. In general, adolescents' functional levels at admission were similar among the diagnostic groups (CGAS 40+/-5).

Table 8. Previous psychotropic medication and the functional level at admission to inpatient care according to psychiatric disorders (n=508).

Lifetime psychiatric disorders	Pre-hospitalization psychotropic medication among adolescents with the given disorder	CGAS at admission (disorder yes vs. no)
Depressive		
-Boys (n= 95)	28.9% (22)	42.9 vs. 42.8
-Girls (n=214)	28.7% (51)	42.9 vs. 40.2*
Behavioral		
-Boys (n=130)	25.4% (29)	44.4 vs. 40.5*
-Girls (n=124)	29.1% (30)	42.5 vs. 41.6
Anxiety		
-Boys (n=51)	21.6% (8)	41.5 vs. 43.1
-Girls (n=114)	42.4% (36)*	41.2 vs. 42.2
Psychotic		
-Boys (n=31)	40.0% (12)*	38.3 vs. 43.6*
-Girls (n=42)	51.3% (20)*	36.9 vs. 42.7*
Alcohol use		
-Boys (n=86)	20.5% (17)	38.6 vs. 44.5*
-Girls (n=120)	32.5% (37)	39.0 vs. 43.2*
Drug use		
-Boys (n=49)	36.2% (17)*	40.8 vs. 43.6
-Girls (n=40)	52.5% (21)	39.7 vs. 43.9*

* Student's t-test, p-value <0.05. Comparison between adolescents with and without the given disorder (left paragraph)

5.7.1 Antidepressive medication

The most commonly used antidepressants were paroxetine (25.8% of adolescents with antidepressive medication), citalopram (22.7%), mirtazapine (21.6%) and fluoxetine 19.6%).

Multivariate logistic regression analysis (Figure 20 – for girls and Figure 21 – for boys) was used to present the association between previous use of psychotropic medication and psychiatric disorders after adjusting with covariates. Boys with depressive disorders had been using anti-depressive medication before admission (21%, OR=5.90, 95%CI 2.1-16.7, $p=0.001$). The prevalence was roughly the same (25%, OR=1.63, 95%CI 0.8-3.2, $p=0.153$) among girls, but was not elevated compared to figures for the other diagnostic groups of inpatient adolescents. A relationship between behavioral disorders and antidepressants was also found among boys; however, this finding was not statistically significant

(14.0%, OR=2.88, 95%CI 1.0-8.5, $p=0.056$). Alcohol use disorders were reversely associated with previous antidepressant use among boys (8.1%, OR=0.15, 95%CI 0.0-0.6, $p=0.004$). Among girls, elevated rates of previous antidepressant use were associated with drug use disorders (42.5%, OR=2.73, 95%CI 1.2-6.2, $p=0.017$). Although anxiety disorders were also associated with antidepressive medication among girls (29.8%, $p=0.037$), the association was not statistically significant in the logistic regression model (OR=1.34, 95%CI 0.8-2.4, $p=0.322$). Figures 20 and 21 demonstrate the likelihood for different psychotropic medication by diagnostic groups.

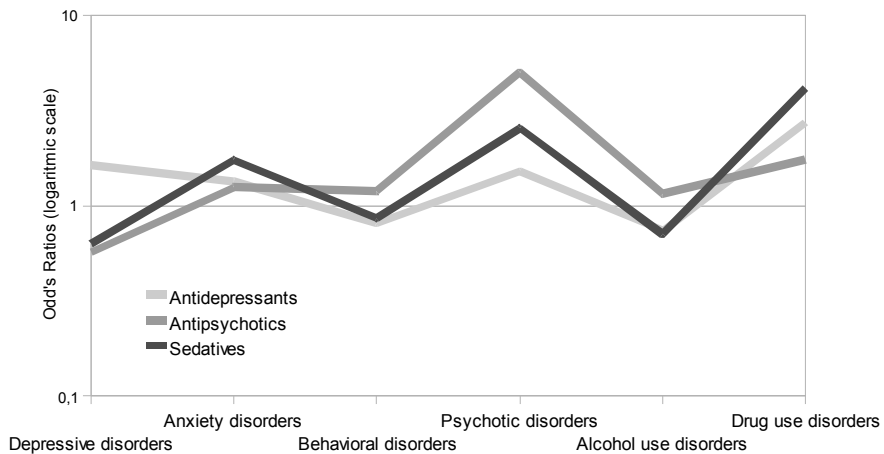


Fig. 20. Psychotropic medication before admission by lifetime diagnoses among girls. Multivariate regression analysis.

ORs from binary logistic regression analysis after adjusting for age and other psychiatric diagnostic groups.

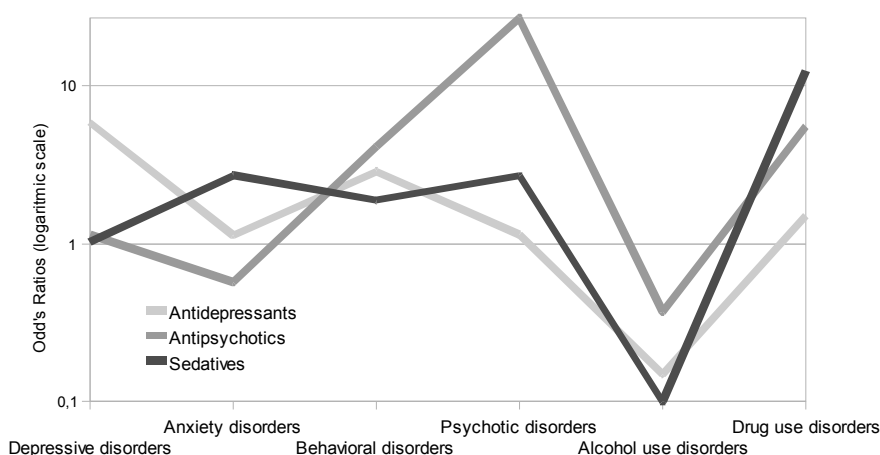


Fig. 21. Psychotropic medication before admission by lifetime diagnoses among boys. Multivariate regression analysis.

ORs from binary logistic regression analysis after adjusting for age and other psychiatric diagnostic groups.

5.7.2 Antipsychotic medication

The most commonly used antipsychotic medication was risperidone (48% of adolescents with anti-psychotic medication) followed by olanzapine (29%). Previous use of antipsychotics was associated with psychotic disorders among both genders. Thirty-nine per cent of boys (OR=26.9, 95%CI 6.4-113.6, $p < 0.001$) and 24% of girls (OR=5.0, 95%CI 1.9-13.0, $p=0.001$) with psychotic disorder had used antipsychotic medication before admission. The logistic regression model also revealed that among boys, previous antipsychotic use was statistically significantly associated with both behavioral (OR=4.1, 95%CI 1.0-16.3, $p=0.045$) and drug use disorders (OR=5.6, 95%CI 1.3-24.5, $p=0.024$).

5.7.3 Sedative and anxiolytic medication

The most commonly used sedative medication was diazepam (38% of adolescents with sedative medication) and zopiclone (30%). Univariate analysis revealed that previous use of sedatives was significantly associated with drug use disorders among boys (12% of boys with drug use disorders had used prescribed sedative medication) and girls (28%), and among girls with anxiety (17%) and psychotic

disorders (24%). Multivariate analysis showed that a history of sedative medication use was notable among boys (OR=12.4, 95%CI 1.8-86.8, $p=0.011$) and girls (OR=4.1, 95%CI 1.5-11.3, $p=0.006$) with diagnosed drug use disorders and also among girls with psychotic disorders (OR=2.6, 95%CI 1.1-6.2 $p=0.039$). Among boys with alcohol use disorders, previous use of sedatives was less common than among boys without alcohol use disorders in our sample (2.9%, OR=0.10, 95%CI 0.0-0.7, $p=0.021$). Previously prescribed benzodiazepine (BZD) medication was associated with a 2.9-fold increased rate of sedative dependence. Of sedative dependent adolescents, 21% had a history of prescribed sedative medication. The results of multivariate regression analysis are seen in Figures 20 and 21. The prevalences of psychotropic medication use before admission are seen in Figure 22. The use of medications other than sedatives, antidepressants or antipsychotics was very rare in the sample (2.4% of boys, $n=5$ and 1.0% of girls, $n=3$).

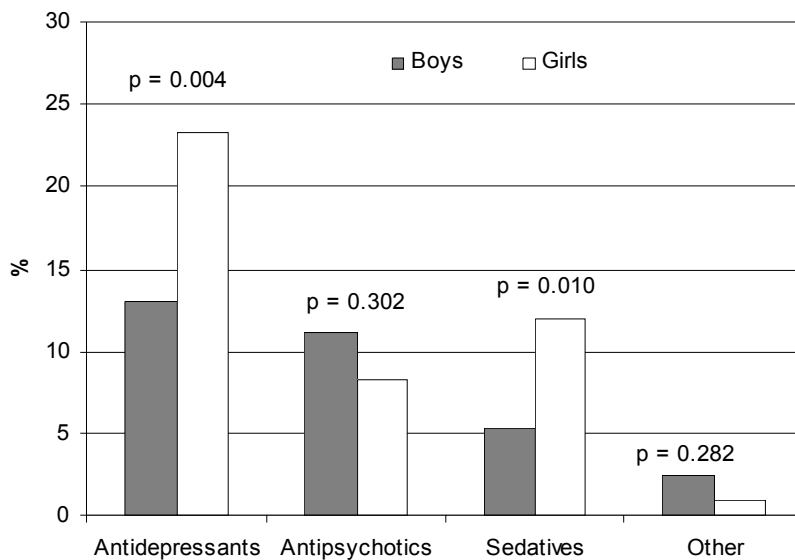


Fig. 22. Use of psychotropic medication before admission to hospital.

Prevalences of lifetime psychotropic medication use among adolescents (300 girls and 208 boys) before admission to Unit 70.

6 Discussion

6.1 Main Findings

Substance use disorders were commonly diagnosed among adolescent inpatients of the study population. The main findings of this study were that, among young adolescent inpatients, behavioral and phobic disorders were significantly associated with alcohol and drug dependence. The onset of behavioral and anxiety disorders preceded the onset of comorbid substance dependence. Depressive disorders were also associated with an increased risk for alcohol and drug dependence among boys. Drug dependent boys were found to suffer from depression more frequently than drug dependent girls. Behavioral disorders were associated with earlier initiation of daily smoking. Earlier initiation of daily smoking was associated with alcohol and drug use disorders and development of intravenous drug dependence later in adolescence.

A background of a broken home, school problems and initiation of regular smoking at a young age was very common among adolescents with substance use disorders as well as among adolescents with intravenous drug dependence (IDD). Age at first trial of alcohol and cannabis was significantly lower among adolescents with IDD compared to other adolescents with or without substance use disorders. A broken home, mother's full-time employment and transfer to special education were associated with a lower onset age for IDD.

The use of prescribed psychotropic medication among adolescents prior to admission to the inpatient unit generally complied with current indications and recommendations for antidepressive and antipsychotic medications. Previous benzodiazepine (BZD) use did not follow the guidelines outlined in evidence-based medical literature. Extensive use of prescribed sedative medication before admission was present among adolescents with diagnosed drug use disorders. The results are further discussed in detail below.

6.2 Prevalence of substance use disorders

Substance use disorders were common among both boys and girls. The lifetime prevalence of alcohol use disorders was roughly 40% among both genders, and 17% of girls and 20% of boys were alcohol dependent. Niethammer and Frank (2007) presented similar prevalence figures for alcohol use disorders in German

inpatient adolescent population, 33% for boys and 25% for girls. The prevalence of diagnosed alcohol use disorders has scarcely been studied in Finnish inpatient and general adolescent populations. The prevalence of adolescents who drink alcohol weekly has been reported to be 19% for boys and 16% for girls (Rimpelä *et al.* 2007). The prevalence of high alcohol consumption has been reported to be lower, 2.5% among girls and 9.5% among boys, in German general adolescent population (Ravens-Sieberger *et al.* 2008). In the U.S. general adolescent population lifetime prevalence of alcohol use disorders has been reported to be 6.4% (Merikangas *et al.* 2010).

The prevalence of drug use disorders in the present study was 13% among girls and 24% among boys. Of girls 7% and of boys 15% were diagnosed with lifetime drug dependence. Among German inpatient adolescents, cannabis use disorders were most common and the prevalence of drug abuse was reported to be 9% and of drug dependence 17% (Niethammer & Frank 2007) - figures similar to those in the present study, even though these disorders have been suggested to be rather uncommon among German general adolescent population - 1.2% of adolescents reported repeated drug use with impairment (Ravens-Sieberger *et al.* 2008). The prevalence of substance use disorders, of which cannabis use was evaluated to cover 80%, has been reported to be 25% among treatment population adolescents in the U.S. (Wu *et al.* 2011) and 9% in the U.S. general adolescent population (Merikangas *et al.* 2010).

Among the study sample, substance use disorders were the reason for hospitalization in less than 10% of the adolescents; in that respect, the prevalences presented are surprisingly high. K-SADS-PI, EuropASI and The Pompidou Questionnaire used in the present study use a systematic approach to substance use and one reason for the discrepancy between the admission reasons and the final prevalences could be accurate and sensitive diagnostics. Another reason which could also explain the elevated proportion of alcohol use disorders in comparison to other treatment populations (Wu *et al.* 2011, Niethammer & Frank 2007) lies in the Finnish culture and attitudes towards alcohol use. Even though buying alcohol is illegal for adolescents in Finland, the attitudes towards alcohol are less strict than those towards other illegal substances. Acquiring alcohol is relatively easy to an adolescent with normal social skills, at least compared to illegal substances. This could also reflect the findings in Finnish general adolescent population: elevated binge drinking and less prevalent illicit drug use as compared to other European adolescents (Hibell *et al.* 2007).

6.3 Comorbidity and temporality of substance use disorders

6.3.1 Comorbidity and temporality with depressive disorders

The majority of girls (71%) in the present study sample were diagnosed with depressive disorders. Of depressed girls, roughly 4 out of 10 were diagnosed with comorbid alcohol use disorder and 1 out of 10 with comorbid drug use disorder. In spite of the high comorbidity rates among girls, the multivariate regression did not reveal an increased risk for substance use disorders according to depressive disorders among girls.

Roughly half of the boys of the study population were diagnosed with depressive disorders; of these boys, 1 out of 5 were also diagnosed with alcohol use disorder and 1 out of 8 with drug use disorder. Depressive disorders were associated with both three-fold risk for alcohol dependence and four-fold risk for drug dependence among boys. The comorbidity of depressive and substance use disorders among adolescents has previously been well documented in both general (Chi *et al.* 2006, Warner *et al.* 2001, Kandel *et al.* 1999) and clinical (Chan *et al.* 2008, Hodgins *et al.* 2007, Roberts *et al.* 2007, Sakai *et al.* 2004) population samples, and the findings of this study are in line with the majority of previous literature among boys. Even though the comorbidity of substance use disorders and depressive disorders was considerably high among girls, putative significant associations between these disorders were not found in the study sample. The findings on gender difference in comorbidity of substance use disorders are discussed below.

Among alcohol dependent adolescents of this study, the onset of depressive disorders usually followed the onset of alcohol dependence. Controversially, the observed onset of depressive disorders among drug dependent adolescents occurred at younger age than the onset of drug dependence, suggesting that the presence of a depressive disorder significantly increases the risk for later onset of drug dependence, particularly among adolescent boys. The timing of onset of comorbid substance use and depressive disorders is indefinite in the previous literature; depressive disorders have been equally found to be primary and secondary to substance use disorders (Compton *et al.* 2000). It has been suggested that gender relates to the temporality of depression and substance use disorders; among women depression has been found to be primary, and among men secondary, to the onset of SUD (Zilberman *et al.* 2003). This gender difference was not evident in the present study. As the onset of depressive disorders among

substance dependent adolescents in the present study seemed to occur between the onset of alcohol and drug dependence, and alcohol dependence was found primary to both depressive disorders and drug dependence, depressive disorders can also play a role in the progression of substance use from alcohol use to harder drugs.

On the other hand, drug-induced changes in neurotransmitter systems alter the function of the dopamine-dependent reward circuitry and behavioral and motivational systems in the brain. This causes depressive symptoms such as dysthymia, anhedonia, irritability, and motivational and emotional changes during drug withdrawal (Langås *et al.* 2011). As motivational and rewarding feedback is still developing in adolescence, adolescents are especially vulnerable to addiction (Chambers *et al.* 2003), and presumably to substance-induced depression.

All in all, the observed comorbidity and temporality of substance use disorders and depressive disorders in the present study seem more complex than with other psychiatric disorders in adolescence.

6.3.2 Comorbidity and temporality with behavioral disorders

Behavioral disorders were common among both genders in the study sample. Of the SUD comorbidities, behavioral disorders were the most pronouncedly associated with both alcohol and drug abuse and dependence. Boys with behavioral disorders had a 5-fold risk for alcohol dependence and a 9-fold risk for drug dependence. Girls with behavioral disorders had an even stronger association with SUD, the risk for alcohol dependence being 7-fold and the risk for drug dependence 18-fold. The comorbidity of behavioral disorders and substance use disorders has previously been well documented among adolescents in general (Copeland *et al.* 2009, Roberts *et al.* 2007, Costello *et al.* 1999) and treatment populations (Wu *et al.* 2011, Chen *et al.* 2008, Ribeiro *et al.* 2008, Vreugdenhil *et al.* 2003), and equally high ORs have been reported among adolescents (Roberts *et al.* 2007, Vreugdenhil *et al.* 2003).

The onset age of behavioral disorders preceded the onset of daily smoking, alcohol and drug dependence among both genders. Previously it has been concluded that there is significant comorbidity between behavioral disorders and substance use disorders, and that the temporal progression of these disorders is usually seen as the onset of substance disorder following the onset of behavioral disorder (Copeland *et al.* 2009, Deas 2006, King *et al.* 2004, Haesys *et al.* 2002,

Costello *et al.* 1999). The findings on comorbidity and temporality of behavioral and substance use disorders of the present study support the previous literature (Haesly *et al.* 2002, King *et al.* 2004, Costello *et al.* 1999, Deas 2006). The results of this thesis support the existence of an association, rather than providing any evidence of causality, between behavioral and substance use disorders. However, in light of significantly elevated rates of comorbidity and clear results regarding the temporality of onset, it is possible to conclude that behavioral disorders greatly increase the risk for subsequent substance use, abuse and dependence and are, if not the most important, then clearly among the most important comorbidities of substance use disorders in adolescence.

The prevalence of ADHD in our study sample was relatively low compared to figures for the U.S. general adolescent population and clinical adolescent population samples (Merikangas *et al.* 2010). Brook and colleagues (1998) suggested that the connection between ADHD and substance use disorders is probably mediated through the influence of comorbid conduct disorder. ADHD was not analyzed separately in the present study.

6.3.3 Comorbidity and temporality with anxiety disorders

Anxiety disorders were significantly more common among girls (38%) than boys (25%). Although the comorbidity of anxiety disorders and substance use disorders was not uncommon in the study sample, anxiety disorders, as analyzed without phobic disorders, were not significantly associated with alcohol or drug dependence.

The comorbidity of anxiety and substance use disorders among adolescents has been documented in previous studies (Wu *et al.* 2011, Chan *et al.* 2008, Deas 2006, Cornelius *et al.* 2003) and the results on comorbidity in this study concur with the findings noted in the previous literature. Couvenbergh and colleagues (2006) reported a prevalence of 7% for anxiety disorders among the SUD treatment population, a figure that is rather similar to the prevalences found in the Study 70 sample. However, recent studies on treatment population samples have reported higher comorbidity (Essau 2011, Langenbach *et al.* 2010, Chen *et al.* 2008). Armstrong and Costello (2002) reviewed population-based adolescent studies and reported that, in the majority of studies, anxiety disorders neither increased nor decreased the risk for substance use disorders. Controversially, Roberts and colleagues (2007) found a three-fold increase in alcohol dependence

and a two-fold increase in drug dependence in the presence of anxiety disorders among adolescents in the general population of the U.S.

In the present study, anxiety disorders were found to be mainly primary to comorbid alcohol and drug dependence. Anxiety symptoms have been found to precede the onset of substance use in adolescents by approximately 2 years (Deas 2006). Although the previous literature states that anxiety symptoms are generally more likely to precede substance use disorders (Fröjd *et al.* 2011, Costello *et al.* 1999, Deas 2006), it appears that anxiety disorders are not a homogenous group in that respect (Merikangas *et al.* 1998, Marquez *et al.* 2003), and the differing comorbidity results of the present study could be explained by separate analyses of phobic disorders.

This study presents further evidence to suggest that phobic disorders are extensively associated with substance use. The multivariate regression analyses revealed that phobic disorders were associated with a five-fold increase in drug dependence among girls. There was also a trend towards an association with alcohol dependence among both genders. This finding, however, was not statistically significant. Among all adolescents, phobic disorders were associated with substance dependence with a five-fold risk, and over one half of the adolescents with phobic disorders had developed substance dependence within three years after the onset of phobia. The onset age of phobic disorders was significantly lower than the onset age of alcohol and drug dependence among adolescents of both genders with these comorbid disorders. As with behavioral disorders, it seems that phobic disorders are an initiative comorbid factor in the progression of substance disorders.

Similar results regarding the comorbidity of phobic disorders and substance use disorders have also been reported in previous literature (Hodgins *et al.* 2007, Robbins *et al.* 2002, Nelson *et al.* 2000). Although the appearance of phobic disorders prior to comorbid substance dependence has been demonstrated previously in adult samples (Compton *et al.* 2000, Merikangas *et al.* 1998), the time interval between the two disorders has rarely been studied. Even though phobic disorders were highly comorbid with and preceded the onset of SUD in the Study 70, Fröjd and colleagues (2011) suggested, based on their study in Finnish adolescent population, that social phobia is likely to protect adolescents from substance use problems. The differences in the findings of these two Finnish studies can be explained by the differences in the samples and the severity of substance use. The prevalences of alcohol and drug dependence among

adolescent inpatients of the present study were 10-fold as compared to general population prevalences of frequent drunkenness (3%) and cannabis use (3%), whereas the prevalence of phobic disorders and anxiety as a reason for admission to Unit 70 was roughly the same as the prevalence of social phobia (9%) in general population (Fröjd *et al.* 2011). Among general adolescent population, social phobia was found to be associated with lower risk for frequent alcohol use, but not with lower risk for frequent drunkenness or with cannabis use (Fröjd *et al.* 2011), whereas among inpatients in the present study phobic disorders were associated with increased risk for alcohol and drug dependence, more severe forms of substance use. Furthermore, behavioral disorders, a major distribution to comorbidity of substance use disorders, were not assessed in the study of Fröjd and colleagues (2011). On the basis of these studies it could be suggested that Finnish adolescents with phobic disorders are less likely to initiate substance use, but might be vulnerable to developing substance use disorders.

6.3.4 Comorbidity and temporality with other disorders

Psychotic disorders

The prevalence of psychotic disorders in the study sample was approximately 15% among boys and girls. The overall comorbidity of psychotic disorders was noticeably lower than with other psychiatric diagnoses; especially substance comorbidity was rare among these adolescents. Multivariate regression analyses suggested rather protective ORs, since adolescents in other psychiatric diagnoses groups had considerably higher rates of substance use disorders. Despite alcohol and drug abuse being relatively rare among psychotic adolescents in the study 70 sample, roughly half of the boys and girls with psychotic disorders smoked regularly. The onset of psychotic disorders was found to follow the initiation of daily smoking within 3 years among boys and 1 year among girls.

Psychotic disorders have been found, to some extent, to associate with substance use in adolescence in the previous literature (Hodgins *et al.* 2007). However, it seems that psychotic disorders in adolescence are secondary to substance use, and the use of cannabis and amphetamine contributes to risk of psychosis (Barkus & Murray 2010). The comorbidity of psychotic disorders and drug use was assessed among Hungarian substance users, and the most important findings suggested that clinically relevant psychotic states were quite rare

(Matuzka & Gerevich 2009). In addition, Wu and colleagues (2011) studied medical records of adolescent patients and found comorbidity of psychotic disorders and substance use disorders to be rare; the prevalence of comorbidity was reported to be only 4% with adjusted OR=0.3. In this study, the low level of comorbidity of substance use disorders with psychotic disorders is in part explained by the relatively slow development of substance use severity among psychotic disorders compared to that observed among other psychiatric disorders and the temporality of psychotic disorders and daily smoking. Assuming that daily smoking is the first stage in substance dependence, adolescents with psychotic disorders may not have developed substance abuse or dependence by the time of admission to a psychiatric hospital.

It is worth noting that adolescents with psychotic disorders presented with statistically significantly lower functional levels at hospitalization. Psychotic adolescents may not have resources to earn funds or contacts to obtain substances. By the age of 18, buying alcohol is no longer illegal and acquiring alcohol is less problematic. Social isolation, as a prodromal symptom of psychotic disorder, limits contact with other adolescents and reduces the opportunity for peer influence in substance use. Also, the strong genetic aspect of psychotic disorders (Gejman *et al.* 2010) might be one reason for the relatively low prevalence of substance use disorders among patients with psychosis in the study sample. Psychotic disorders, behavioral disorders and substance use disorders are associated with genetic factors; substance use disorders are also strongly associated with family background and substance use culture (Gelhorn *et al.* 2005, Swadi 1999). In other words, psychoses also appear in families that do not have social, substance, or psychiatric problems or lack parental supervision.

Bipolar disorders

Although bipolar disorders have been strongly linked with substance use disorders in the previous literature (Deas 2006), a strong association was not found in this study. In fact the prevalence of bipolar disorders was low, being 3.0% in the clinical study sample, as compared to the recent lifetime general adolescent population prevalence of 2.9% (Merikangas *et al.* 2010). However, the lifetime prevalence of Bipolar I disorder in Finnish general population of adults has been reported to be considerably lower, only 0.24% (Perälä *et al.* 2007). The prevalence of bipolar disorders observed in the current study sample is reasonable

and explains, in part, the lack of association with substance use disorders. Even though the comorbidity of bipolar disorders and substance dependence was assessed in the initial statistical analyses of study I, there were no comorbid cases, leaving the ORs incalculable. It is possible that, in some cases, where the early symptoms of bipolar disorders are depression, the adolescents affected are incorrectly diagnosed as having depressive disorders in the analysis of this study. The temporality of bipolar and substance use disorders could not be evaluated due to the small number of individuals in the sample with both of these disorders. The prevalence of bipolar disorders has been reported to increase steadily during adolescence (Merikangas *et al.* 2010). In the light of the results of Study 70, it can be assumed that the comorbidity of bipolar disorders and substance use disorders generally develops later, after adolescence.

6.3.5 Gender differences in comorbidity of substance use disorders

A main finding of this study, that drug dependent boys were significantly more likely to have comorbid depression than girls, is in line with a previous study by Costello and colleagues (1999) which discovered increased rates of depression among substance-dependent boys, but not girls. Hodgins and colleagues (2007) found MDD to be statistically significantly associated with SUD among both genders in Swedish adolescent substance misusers. Among Finnish adolescent outpatients with depressive disorders, current comorbidity with substance use disorders was independent of age (Karlsson *et al.* 2006). On the contrary to the findings of the present study, Latimer and co-workers (2002) found that depression was associated with female gender among adolescent substance users. The psychiatric comorbidity of substance use disorders, particularly of depression, is more often primary in women, while in men the comorbidity is more often secondary to the substance use disorders (Zilberman *et al.* 2003). These findings can explain the different findings observed in the Study 70 study sample. Firstly: girls start drinking at a later age than boys and develop comorbid substance use disorders later, or secondly: comorbid depression symptoms develop later among girls than among boys and were thus not yet observed among adolescent girls of the Study 70 population. It has also been reported that women with comorbid depression and alcoholism present for treatment with less severe symptoms of alcoholism than women who have never had depression (Zilberman *et al.* 2003).

However, it has also been noted that 41% of adolescent women seek treatment for depression, while only 15% seek help for substance use disorders

(Merikangas et al. 2011) This suggests that the symptoms driving these patients to seek treatment are of depressive rather than substance origin and could affect the selection of the Study 70 sample. The majority of the girls in Unit 70 were hospitalized due to mood symptoms and suicidality, rather than substance use (Figure 6), and depressive disorders were statistically significantly more common among girls, in which respect the Study 70 population differs greatly from the adolescent SUD populations presented above (Hodgins et al. 2007, Latimer et al. 2002) that have shown different results on gender difference of comorbidity. On the other hand, the depressed boys in the Study 70 might have increased their substance use to alleviate depression, leading to hospitalization because of alcohol/drug use or further problems caused by increased use.

6.4 Tobacco trial and initiation of daily smoking

In the present study, three fourths of the subjects smoked regularly. Basically all of the adolescents with substance use disorders (SUD) smoked daily. Tobacco trial was found to precede alcohol trial among adolescents without and without SUD, and the initiation of daily smoking was found to precede the onset of alcohol and drug use disorders. The mean time difference from the initiation of daily smoking to onset of alcohol use disorders was one to one and a half years and to onset of drug use disorder two years.

The health behaviors of adolescents in the Finnish general population have been monitored by comparable methods biennially since 1977 via national postal surveys. The latest survey was conducted in the spring of 2007, to which a total of 5,840 adolescents responded (61%). Tobacco trial and the prevalence of regular daily smokers have decreased over the last years in all adolescents. In 2007, approximately 60% of 16-year-old adolescents in the general population had tried tobacco while 19% of adolescents (14-18 years) in the general population were daily smokers (Rimpelä *et al.* 2007). An obvious reason for the higher prevalence of daily smoking in the study sample is the higher prevalence of psychiatric morbidity as compared to general population. The same comorbidity and social risk factors that account for other substance use disorders are also in the background of nicotine dependence. Adolescent psychiatric patients may also use nicotine to alleviate symptoms of other disorders.

Earlier initiation of daily smoking was associated with behavioral as well as alcohol and drug use disorders among girls and boys. These findings on an

association between smoking and disruptive behavior (Dierker *et al.* 2001, Brown *et al.* 1996) and early initiation of smoking and substance use disorders (Upadhyaya *et al.* 2002) are in line with previous literature. In the present study behavioral disorders tended to precede the initiation of daily smoking among boys and were associated with earlier initiation of daily smoking among both sexes. The fast development from tobacco use to drug dependence in the adolescents of the study sample reflects the substance vulnerability of these severely ill adolescents. It remains to be seen how many of the adolescents in the study group will progress to more serious substance use later on in adolescence and young adulthood.

6.5 Progression of substance use

In the present study, the adolescents with intravenous drug dependence (IDD) had started regular smoking approximately three years before intravenous use, had their first alcohol trials in primary school before the age of 13 years, cannabis trials at 13 years and first intravenous use at 15 years. Compared to adolescents without SUD and less severe SUD, all of these were significantly younger. Early onset of substance use – alcohol and particularly cannabis use – is frequently present in adolescents who subsequently progress to intravenous drug use (Stenbacka *et al.* 1993), and the correlation of early onset of substance use and fast progression among IDD adolescents observed in the present study is in line with previous literature (Fuller *et al.* 2001).

In general, when compared to adults, adolescents have been found to go through shorter durations of illicit drug use before progressing to intravenous administration (Fuller *et al.* 2001). The average age from initiation of alcohol and cannabis use to first intravenous administration has been found to vary from 2 to 5 years (Dinwiddie *et al.* 1992b, Fuller *et al.* 2001) which is in line with the results of this study. Initiation of cannabis use before the age of 15 years has been found to increase the risk for Intravenous Drug Use (IDU) 2.7-fold (Dinwiddie *et al.* 1992a). Cannabis use has been found to increase the risk for stimulant use, which has also been found to increase the risk for intravenous use (Swadi 1999). The usual pathway to intravenous drug use starts with tobacco, followed by alcohol, cannabis and possibly stimulants and finally intravenous use of hard drugs. The results of the studies in this thesis support the hypothesis of gateways from less hazardous substances to more dangerous ones (Degenhardt *et al.* 2009, Chen *et al.* 2002). On the basis of the results of the present study, the most

alerting symptoms of this trajectory should be notably earlier trial and regular use of tobacco, alcohol and cannabis – most of these already in primary school.

6.6 Social risk factors for substance use disorders

An adolescent's family status was found to be significantly associated with substance use disorders in this study. Among adolescents with intravenous drug use, the biological father was absent from home in 90% of cases and the biological mother in 70%. A disproportionate share of all the adolescents admitted to Unit 70 reported that their father and/or their mother did not live with the family, but the adolescents with intravenous drug dependence nevertheless differed in this regard from both adolescents with other SUD and those without SUD. Biological father was absent from the home for 90% of the adolescents with IDD, and the mother was absent for 70% of IDD adolescents. Reported inter-parental violence, physical abuse, parental mental disorders and parental substance use were, however, equally common in IDD, SUD and non-SUD adolescents of the sample. This underlines the disturbed social background of adolescent psychiatric inpatients at large.

In Finland, full-time employment of both parents of families with children is normative, save during the first 3 years of the child's life when family benefits compensate for the lost income and allow one of the parents' staying at home. It is rather suggestive of psychosocial problems such as poor physical or mental health or difficulties in finding employment if the parents of a minor well beyond early childhood are not participating in the labor market. Given this, the finding that mother's full-time employment was associated with earlier initiation of IDD drug use, and almost statistically significantly associated with IDD, seems contradictory and needs to be interpreted with caution. These findings were unadjusted and possibly fail to explore whether other risk factors actually explained the association. The high prevalence of father's absence in combination with mother's full-time job could lead to decreased parental supervision which has been identified as a risk factor for adolescent substance use in the previous literature (Botwin & Griffin 2010, Swadi 1999).

It is also noticeable that in the catchment area served by Unit 70, a specific form of fundamental Christianity is much more common than elsewhere in Finland. Adolescents from fundamental families are most unlikely to use substances, and they also will have mother who stays at home with the children.

Kylmänen and colleagues (2010) reported previously that in the Study 70 sample, the prevalence of psychoses – disorders not comorbid with SUD in the present study – were increased among adolescents from families with six or more children, common to those in fundamental Christian families. Thus, in adolescent psychiatric patients in this area, the mother not being in the labor market is likely to be associated with other disorders than SUD, which may bias the findings regarding risk factors of SUD.

Half of the adolescents with intravenous drug dependence in this study were sharing accommodation with another substance user, and one third of adolescents with intravenous drug dependence had experienced parental substance use. The high proportion of parental substance use and the steep growth in substance use observed among intravenous drug dependence in this study is supported by the previous finding that parental substance use accelerates substance use progression of adolescents (Griffin & Botvin 2010). Previous studies suggest that the initiation of adolescent intravenous use is usually assisted by a significant other person; females are more likely to be injected by their partner or lover, while males are injected by their friends or acquaintances. Few are injected by parents or other relatives, including siblings, and even fewer are injected by unknown dealers (Crofts *et al.* 1996, Stenbacka *et al.* 1993). The absence of parental supervision and lack of supportive relationship with parents can make adolescents turn to their peers and undesirable networks that support substance use (Botwin & Griffin 2010). Half of the intravenous drug-dependent adolescents in the present study were living with another substance user; as fewer than one in three adolescents with IDD were living with either of their parents, it is quite possible that their drug use was initiated with this other person who was apparently emotionally closer to the adolescent than their parents. Although 18% of adolescents with substance use disorders reported parental mental disorders, parental mental disorders were no more common among adolescents with SUD than among adolescents with other psychiatric morbidity in the Study 70 sample.

The school background of adolescents with intravenous drug dependence differed from other psychiatric inpatients in the study sample. Two thirds of the adolescents with intravenous drug dependence had a history of truancy in elementary school and half of the adolescents had been transferred to special classes. However, the level of school achievement of adolescents with substance use disorders was not significantly lower, nor was the prevalence of learning disabilities higher, when compared to adolescents without substance use disorders. This finding might be biased by the exclusion of mentally handicapped

adolescents from the study population. Poor academic achievement has previously been associated with adolescent substance use disorders (Beman 1995). Fuller and colleagues (2002) found that school drop-out rates among adolescents with intravenous drug use were 2.3-fold as compared to adolescents without intravenous use. The potential association between learning disabilities, grade point average, failing a grade or transfer to special class and intravenous drug dependence had not been studied previously. In the present study, one out of four adolescents with intravenous drug use and one out of five adolescents with other substance use had failed a grade. Among Finnish general population the prevalence of repeating a grade has been reported to be significantly lower, being 2.8% among PISA (Program for international student assessment) participants in Finland – a prevalence well below the average of 13% in OECD countries (Sulkunen *et al.* 2010). Although repeating a grade was not especially associated with SUD among adolescent inpatients, the ten-fold prevalences among IDD adolescents as compared to general population and the significant findings on truancy and transferring to special class suggest that the school achievement of adolescents with substance use disorders is severely impaired even before the diagnosis of substance use disorder. The results of this thesis suggest that poor school achievement among substance users is rather a product of decreased functional level than of mental incapacity.

In this study, the earlier initiation of intravenous drug use among adolescents with intravenous drug dependence was associated with those adolescents who were living without their biological father or mother, whose mothers were employed full-time, or adolescents who had been transferred to special class. Parental substance use was also found to lower the initiation age of intravenous drug use, but the clinical finding did not reach statistical significance – a reason for this lies within the study population: as the prevalence of parental substance use was high among all adolescents of the study, SUDs were not associated with parental substance use over other psychiatric morbidity.

Sherman and colleagues (2005) studied the correlates for the initiation of intravenous drug use among the adolescent/young adult population (ages 15 to 30 years). They found that a younger age at first trial of alcohol and marijuana, parental drug use and having witnessed others injecting were associated with the initiation of intravenous drug use. Early drug use patterns and drug exposure are closely associated with initiation of intravenous drug use (Sherman *et al.* 2005).

In this study, the age at first alcohol, cannabis and intravenous drug trials was significantly lower among adolescents with intravenous drug dependence when compared to both adolescents without substance use and adolescents with other substance use disorders; indeed, the ages of initiation in the latter groups differed only marginally from each other. Goldsamt and colleagues (2010) reported that in half of the cases the reported reason for initiation of intravenous use is development of tolerance to the substance injected. Faster development of tolerance is one possible reason for both earlier initiation ages and the more rapid development of drug use disorders observed among adolescents in this study.

6.7 Psychotropic medication history

6.7.1 Antidepressive medication

Depressive disorders were clearly associated with previous use of antidepressants among both boys and girls. Roughly one fifth of the adolescents with depressive disorders had received antidepressive medication before hospitalization. The prevalence for the use of SSRIs has previously been reported as 13.5% in outpatient settings. The main indications for prescriptions of SSRIs are mood and anxiety disorders (Dean *et al.* 2006). The use of antidepressive medication before admission to Unit 70 generally followed the recommendations outlined in previous literature on adult population (Scheffer 2006, Ziervogel 2000).

6.7.2 Antipsychotic medication

As expected, pre-hospitalization antipsychotic medication was mainly prescribed to adolescents with psychotic disorders. Two fifths of the boys with psychotic symptoms and one fourth of the girls with psychotic symptoms had received antipsychotic medication prior to their first hospitalization at Unit 70. The boys' behavioral disorders were also associated with antipsychotic use. The prevalence of antipsychotic use in outpatients has been reported as 3.2% and, as Dean and colleagues (2006) concluded, the most common indications for antipsychotic medication in adolescents are psychotic and behavioral disorders. Surprisingly, in the present study, antipsychotic use was also associated with drug use disorders among boys, although psychotic disorders were not generally associated with substance use disorders. One in six boys with drug use disorders had received

antipsychotic medication before hospitalization. One explanation for antipsychotic use could be that quetiapine has shown promising results in the treatment of alcohol, amphetamine and cocaine use disorders, even without comorbid psychiatric disorders (Hanley & Kenna 2008). Another possible explanation for antipsychotic use among adolescents with substance use disorders is that the sedative/anxiolytic effect of atypical antipsychotic medication (Safer *et al.* 2003) – for example as seen with a low dose of quetiapine or risperidone – might be utilized in the treatment of sleep disorders, particularly as these medication present lower risk for abuse than benzodiazepines. Zhornitzky and colleagues recently reviewed the use of antipsychotic medication in the treatment of substance use disorders among patients with and without psychotic disorders. It was suggested that among patients with psychotic disorders, atypical antipsychotic agents (in particular clozapine) may decrease substance use among individuals with alcohol and drug (mostly cannabis) use disorders. Studies among patients without psychotic disorders suggested that atypical antipsychotic agents may be beneficial for the treatment of alcohol dependence, at least in some subpopulations of alcoholics. Zhornitzky and colleagues also noted that these agents are not effective in treating stimulant dependence and may in some cases even aggravate the condition (Zhornitzky *et al.* 2010).

The use of antipsychotic medication before admission to Unit 70 followed the guidelines presented in previous literature (Remschmidt *et al.* 2000) and their “off-label” use could be explained by the sedative effects of these medications (Safer *et al.* 2003).

6.7.3 Sedative/anxiolytic medication

In this study, previous use of prescribed benzodiazepines was associated with drug use disorders; 1 out of 8 boys with drug use disorders and more than 1 out of 4 girls with drug use disorders had received benzodiazepines before admission. The likelihood of previous benzodiazepine use was twelve-fold among boys with drug use disorders and four-fold among girls with drug use disorders. The prevalence of sedative use in Europe’s adult population has been reported to be 4.3% (Ohayon & Lader 2002). Approximately 4% of adolescents in outpatient treatment and 14% of adolescents in inpatient treatment receive sedative medication (Dean *et al.* 2006). The high prevalence of sleep disorders among drug users (Johnson & Breslau 2001) might, in part, explain the increased rates of

previous sedative use in drug-abusing adolescents noted in this study. A more likely explanation is that drug-abusing adolescents are more amenable to benzodiazepines. Although O'Brien (2005) concluded that only a few cases arise following the legitimate use of benzodiazepines, the result of this study suggest that previous use of benzodiazepine medication is associated with a three-fold increase in risk for sedative abuse or dependence.

Clark and colleagues (2004) reported that, contrary to published guidelines, rates of benzodiazepine use are higher among patients with severe mental illness and concomitant substance use disorders than among individuals with severe mental illness alone, and recommended a reassessment of prescribing guidelines among adults. Among drug users, benzodiazepines are usually a secondary drug of abuse and are mainly used to augment the high received from another drug or to negate the adverse effect of other drugs. In the present study sample, 21% of adolescents with sedative dependence had previously received prescribed benzodiazepine medication. However, in 79% of the cases, abused sedatives were acquired by other routes (prescribed benzodiazepines are often sold to fund the use of other substances). This study's findings regarding the use of sedative medication among young adolescents before admission to inpatient care differ significantly from the guidelines recommended in the previous literature. Benzodiazepines do not have a scientifically proven indication among adolescents (Witek *et al.* 2005) and, although prescription sedative use disorders have been scarcely studied among adolescents, it has been suggested that adolescents with behavioral and psychiatric dysfunction are at increased risk for prescription sedative abuse and dependence (Hall *et al.* 2010). This study's discovery of an association between the early use by adolescents of sedative medication and the subsequent development of substance use disorders, including sedative dependence, is perhaps a reflection of the complexity and challenges present in the treatment of substance dependence, rather than evidence of inappropriate prescribing or ignorance of the evidence-based indications for these medications.

6.8 Methodological considerations

6.8.1 Strengths of the study

The population studied here represents an epidemiologically unselected sample of young adolescents in need of acute psychiatric care and hospitalization in a closed ward. The catchment area covers all such adolescents in the district of Northern Finland during the time the data were gathered (between April 2001 and March 2006). The data therefore consist of psychiatric adolescent patients hospitalized during that period. This allows a sufficiently large database for the representative analysis of comorbidity and background variables assessed in this thesis. The adolescent psychiatric practices and criteria for hospitalization in Finland remained unchanged during the gathering of the data. The final series of inpatients is an unselected sample of those admitted to Unit 70 and the participation rate was as high as 84%.

The results of the studies in this thesis are based on well-established semi-structured diagnostic interviews (Ambrosini 2000, Kaufman *et al.* 1997). All the interviews were carried out by medical professionals during the inpatient treatment period. The patients were evaluated throughout their treatment at Unit 70. All interviewers had been trained in the use of K-SADS-PL, EuropASI and The Pompidou Questionnaire data sheet.

The data were recorded very close to the onset of the psychiatric disorders and provide a good opportunity to examine the temporal relationships between substance use disorders and other psychiatric disorders. It has been demonstrated that self-reports of the age at first substance use experiences are sufficiently reliable for most current epidemiological and clinical applications (Johnson & Mott 2001, Brown *et al.* 1992).

6.8.2 Limitations of the study

There are a number of limitations that need to be acknowledged with regard to interpretation of the findings of this study. Due to the cross-sectional nature of the study, the potential causal relationships involved in the associations between substance use disorders and their comorbidities cannot be assessed without caution, even though the time sequences involved were properly documented. The information with regard to the ages at onset of psychiatric disorders was gathered

retrospectively and was largely based on patients' and their parents'/guardians' reports. The semi-structured K-SADS-PL rating scale was used in the process of obtaining the psychiatric diagnoses and onset ages, and recall bias should be of minor importance when investigating the previous ages at onset in cases that occurred close to the onset of disorders. Although the validity and inter-rater agreement of K-SADS-PL have been shown to be high (Ambrosini 2000, Kaufman *et al.* 1997) the lack of inter-rater reliability of the K-SADS-PL interviews on the present study is to be considered a limitation.

The study population consisted exclusively of adolescents with severe psychiatric impairment leading to hospitalization in an inpatient ward and, therefore, limits the possibilities of applying the findings to the general population. The service utilization of different psychiatric disorders differs greatly and might affect the composition of the study population. Studies of service utilization in the general Finnish population are presently lacking. Recent results in the U.S. suggest that only one third of adolescents seek or receive services for their psychiatric conditions and contact to treatment varies among diagnoses (Merikangas *et al.* 2011). Only a minority of these patients are admitted to psychiatric adolescent inpatient care.

The study population was gathered from the relatively large area of Northern Finland and the majority of the adolescents in the study come from the districts of Oulu and Lapland. This geographically large area includes only one city with population over 100,000. This can affect both the differences in availability of substances and differing treatment utilization. Luopa and colleagues (2008) reported of regional differences in drug experiments among Finnish adolescents; drug experiments were most common in Southern Finland, with up to 16% of 16- to 17-year-old adolescents in Helsinki. The prevalence of drug experiments in the districts of Oulu and Lapland was 8%, below the average of 10% in the whole country (Luopa *et al.* 2008). On the other hand, among American adolescents, urban dwelling was not associated with increased rates of alcohol or drug use disorders (Compton *et al.* 2007, Hasin *et al.* 2007).

Some of the adolescents in the study sample had been placed under custody and relocated to Northern Finland. One of the grounds for custody of an adolescent in the Finnish law is that the adolescent's substance use seriously endangers his/hers health or development (Lastensuojelulaki 2007). The prevalence of substance use disorders among adolescents that have been relocated into correctional school has been reported high (Lehto-Salo *et al.* 2009). In the present study over one half of drug-dependent adolescents were taken into

custody and hospitalized from another institution before treatment at Unit 70. It is plausible that the majority of adolescents from southern districts of Finland increase the prevalence of alcohol and drug use disorders and associated comorbidity in the present study. At the same time, these adolescents affect a variety of socio-demographic factors evaluated in the study.

Large family size has been reported to be overrepresented among underage adolescents admitted for psychiatric hospitalization in Northern Finland; in the Study sample 17% of adolescents had 5 or more siblings (Kylmänen *et al.* 2010). The most prominent reason for exceptionally large family sizes in the region is a specific form of fundamental Christianity that puts tight constraints on adolescent behaviors. This may bias the findings regarding the associations between demographic and social risk factors for SUD in the Study 70 sample as compared to adolescent psychiatric inpatient samples elsewhere in Finland.

In Finland, treatment of adolescent substance use disorders is organized by two separate service systems: adolescent psychiatric treatment and social welfare systems (Pylkkänen *et al.* 2003). The first can be considered to treat mainly adolescents with comorbid psychiatric disorders and the latter to focus particularly on substance use disorders. However, in the light of previous studies on SUD treatment populations (Chan *et al.* 2008, Chinot *et al.* 2006, Kelly *et al.* 2004) selected rather similarly as Finnish adolescents in treatment units under social welfare system, the comorbidity of other psychiatric disorders can be assumed to be high also among adolescents treated under social welfare systems.

Information regarding the adolescents who refused or were excluded is confidential under the Medical Research Act of Finland. In addition, although the response rate in the present study was high, analyses concerning non-participation were not performed. It is unclear what kind of psychiatric morbidities and socio-demographic backgrounds were lost from the study population. Supposedly lower functional level of an adolescent could lead to refusal. Such patients could suffer from severe psychotic symptoms or difficult withdrawal symptoms. The prevalence and comorbidity figures in this study can be applied cautiously to other treatment populations, but perhaps only as a guide to trends within the general population. The present data represent both the adolescent inpatients and the most serious cases in the general population of Northern Finland.

Risk factors of substance use disorders and intravenous drug dependence (II) were not analyzed with multivariate regression models and might thus represent associations with variables that are better explained by other risk factors.

Inter-rater reliability tests were not conducted during data gathering for the Study 70 sample, but all psychiatric diagnoses were made under the supervision of the physician treating the patient. Articles I and II were published while the study data were still being gathered and due to restrictions regarding the data size, genders were not evaluated separately. However, the diagnostic distributions of the partial data seem to reflect those of the full 508 patient dataset.

7 Conclusions

1. Adolescents' alcohol and drug dependence are frequently accompanied by psychiatric comorbidity. The most common comorbidities are behavioral, depressive and phobic disorders.
2. Boys with drug dependence are significantly more likely to suffer from depressive disorders than girls with drug dependence.
3. Temporality of substance dependence and psychiatric comorbidity plays an important role in development of dependence and putative causality. Whereas phobic and behavioral disorders are more likely to appear prior to the onset of alcohol and drug dependence, the onset of depressive disorders tends to occur after the initiation of alcohol and drug use.
4. Phobic disorders may influence the development of secondary substance dependence within a few years from the onset of phobia.
5. Earlier initiation of daily smoking is clearly associated with increased risk for alcohol and drug dependence in adolescence. Behavioral disorders are associated with both earlier initiation of daily smoking and decreased age of initiation of smoking.
6. The main social background factors associated with intravenous drug dependence and decreased age of initiation of intravenous use in adolescence are parental absence and troubled school background, beginning already in primary school. Adolescents with intravenous drug dependence start drug experiments significantly younger than other substance-dependent and non-substance-dependent adolescents, often even before the age of 10 years.
7. History of medically prescribed benzodiazepine use is significantly more common among adolescents with drug abuse and dependence and prescribed benzodiazepine medication is associated with an increased risk of sedative dependence.

7.1 Clinical implications

Based on the findings and conclusions of this thesis, I'd like to say the following to adolescents with substance use disorders: "Even if you don't feel like seeking treatment for your substance use, please try to accept help for the other psychiatric comorbidities that you, without a doubt, are at risk of developing. Don't let the burden of your comorbidities become too high. If there comes a day when you want to get rid of the substances the other comorbidity won't be

standing in the way.” To parents of adolescents I’d like to say: “Please be present in your child’s life, think about how your own attitudes on the subject may affect his or her future substance use, view early experimentation with cigarettes and alcohol as a potentially serious warning sign and become aware and interested in his or her friends”. To teachers of adolescents I’d like to say “Please notice that impaired school performance might be a manifestation of an adolescent’s substance problems, please consult your school’s nurse or relevant medical professionals if you have any suspicions or concerns”. To clinicians treating adolescents in General Practice I’d like to say: “Even when time is short try to evaluate an adolescent’s underlying condition. Also, please be cautious in prescribing benzodiazepines in an outpatient setting, this ‘quick fix’ will lead to problems later on”. To clinicians treating inpatient adolescents I’d like to say: “Be aware and look out for the less obvious forms of comorbidity in substance use. Consider using diagnostic interviews as a tool when you encounter adolescents for the first time. The treatment of comorbidity will be easier if you have the diagnostic information from the beginning.”

7.2 Research Implications

Based on earlier studies that support the findings of this thesis and the findings in this study, the results on the comorbidity of behavioral disorders and substance use disorders are robust. However, the results on the comorbidity of anxiety disorders, depressive disorders and substance use disorders are ambiguous, and it seems that gender plays an important role in the comorbidity of these disorders. Studies of the same magnitude in European samples are yet to be conducted, and such studies would possibly provide valuable information on the subject in slightly different cultural and health care settings. Due to obvious economic realities, it is difficult to gather large sets of representative and valid data for the general population. Closer co-operation between European/Northern countries could also be considered in achieving such goals. Further studies on the onset and causality of these comorbid disorders are also required.

More studies on sociodemographic risks at different ages and different substance use stages are recommended. On the basis of the findings on the temporal progression of substance use, it should be very interesting to identify those children and adolescents who start experimenting with cigarettes and alcohol at a young age and are thus more likely to develop serious substance use

disorders in late adolescence or early adulthood. Also, focusing biochemical studies on adolescents with early substance use initiation could give us more information on the neurochemistry, and hopefully, treatment of these disorders.

At the initiation of the Study 70, adolescents and their parents were also asked for permission to use the data on their subsequent hospital discharge records, criminal records and death certificate. As this data grows over time, the results on increased mortality and criminality among these adolescents should also be assessed. Further studies on the disbenefits of sedative medication use among adolescents are required and, hopefully, the results of these studies will lead to more careful and considered benzodiazepine prescription policies for adolescents.

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List of original Publications

This thesis is based on the following publications, which are referred to in the text by the Roman numerals I-V

- I Ilomäki R, Hakko H, Timonen M, Lappalainen J, Mäkiyö T & Räsänen P (2004) Temporal relationship between the age of onset of phobic disorders and development of substance dependence in adolescent psychiatric patients. *Drug and Alcohol Dependence* (6): 327–330.
- II Ilomäki R, Kaartinen K-L, Viilo K, Mäkiyö T, Räsänen P & Study-70 workgroup (2005) Intravenous drug dependence in adolescence – what lies in the background? *Journal of Substance use* 10(5): 315–326.
- III Ilomäki R, Hakko H, Riala K, Räsänen P, Lappalainen J, Mäkiyö T, Timonen M & Study 70 workgroup (2008) Temporal association of onset of daily smoking with adolescent substance use and psychiatric morbidity. *European Psychiatry* 23(2): 85–91.
- IV Ilomäki R, Södervall J, Viilo K, Hakko H, Räsänen P & Study-70 workgroup (2008) Drug dependent boys are more depressed compared to girls: a comorbidity study of substance dependence and mental disorders. *European Addiction Research* 14(3): 161–168.
- V Ilomäki R, Ilomäki E, Hakko H, & Räsänen P (2011) Psychotropic medication history of inpatient adolescents – is there a rationale for benzodiazepine prescription? *Addictive Behaviors* 36 (1–2): 161–165.

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- I 171. Ilomäki, Essi (2012) Conduct disorder among girls: violent behaviour, suicidality and comorbidity : A study of adolescent inpatients in Northern Finland

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