ADHD IN SUBSTANCE USE DISORDERS
PREVALENCE AND PHARMACOTHERAPY

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To Kajsa, Emmi, Peter
Substance use disorders (SUD) and Attention deficit / hyperactivity disorder (ADHD) are persistent and prevailing disorders that conjointly are associated with negative life-events and mental distress. The overall aim of this thesis was to examine the rate of ADHD in substance using populations and to investigate the feasibility and efficacy of methylphenidate pharmacotherapy for treatment of co-existing ADHD and SUD.

The prevalence of ADHD was investigated in Studies I and II, which were cross-sectional investigations including two stages: screening and assessment. Study I included seven countries; France, Hungary, the Netherlands, Norway, Spain, Sweden, and Switzerland. Study II comprised incarcerated women in Swedish prisons. An initial screening was completed with WHO’s Adult ADHD Self-Rating Scale (ASRS). The assessment included Comers’ Adult ADHD interview for DSM-IV (CAADID) as a ‘gold standard’ for ADHD diagnosis. For differential diagnostics, the MINI Plus interview was used for mood disorders, antisocial personality disorder (ASP) and SUD, and SCID-II was used to assess borderline personality disorder (BPD). The results show that compared to the general population, the rate of ADHD is higher both in treatment-seeking substance users and in female prisoners (Study I and II).

Studies III and IV were randomized, double-blind, placebo-controlled trials with parallel groups design investigating the safety and efficacy of methylphenidate (MPH) for treatment of ADHD in amphetamine dependent patients. Study III was a 12-week trial investigating 18-72mg/day MPH in treatment-seeking outpatients (men and women) with change in ADHD symptoms as the primary outcome measure. Study IV was a 24-week trial investigating 18-180 mg/day MPH in men recruited from medium security prisons. The participants started treatment within two weeks before release from prison and continued treatment in an outpatient clinic. The primary outcome measure in Study IV was relapse to illicit drug use. Results from Study III show that both treatment groups significantly improved their ADHD symptoms, but there were no significant differences between the groups in either ADHD or substance use outcome measures. In study IV, compared to placebo treatment, MPH treatment resulted in significantly more negative urine samples, improvement in ADHD symptoms, and better retention in treatment.

Collectively, the findings from the epidemiological studies suggest that a significant number of individuals with SUD are also afflicted with ADHD. It is important that more attention is given to adult ADHD in addiction treatment centres and in criminal justice systems in order to address the clinical needs of this population. The results from the present clinical trials suggest that MPH given in structured settings may be safe to use in currently abstinent amphetamine dependent individuals with ADHD. A flexible dose range with a higher maximum dose improved ADHD symptoms, clinical condition and retention in treatment, and reduced the risk for relapse to illicit drug use in long-term drug dependent individuals.
LIST OF PUBLICATIONS


IV. Konstenius, M., Jayram-Lindström, N, Guterstam, J., Beck, O., Philips, B, Franck, J. Methylphenidate for Adults with ADHD Sub stance Dependence: A 24-week Randomized Placebo-controlled Trial (Manuscript)
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LIST OF ABBREVIATIONS

ADHD  Attention deficit hyperactivity disorder
ASI   Addiction Severity Index
ASPD  Antisocial personality disorder
ASRS  Adult ADHD Self-Report Scale
AUDIT Alcohol Use Disorders Identification Test
BAI   Beck’s Anxiety Inventory
BDI   Beck’s depression inventory
BPD   Borderline personality disorder
CAADID Conners’ Adult ADHD Diagnostic Interview for DSM-IV
CAARS:O Conners’ Adult ADHD Rating Scale: Observer
CAARS:SV Conners’ Adult ADHD Rating Scale: Screening version
CGI   Clinical Global Impression
CPT   Continuous performance test
DSM   the Diagnostic and Statistical Manual of Mental Disorders
DUDIT Drug Use Disorders Identification Test
ER    Extended release
IR    Immediate release
ITT   Intention to treat
LOCF  Last observation carried forward
MINI  Mini International Neuropsychiatric Interview
MPH   Methylphenidate
OROS  Osmotic-controlled Release Oral delivery System
OQ45  Outcome Questionnaire 45
SCID  Structured Clinical Interview for DSM-IV
SR    Slow release
SUD   Substance use disorders
TLFB  Time-line follow-back
WAIS  Wechsler Adult Intelligence Scale
1 BACKGROUND

1.1 SUBSTANCE USE DISORDERS

Substance abuse and dependence constitute a major health hazard worldwide with negative life consequences not only for the individual, but also for the health and well-being of those close to the user, and problems for the society. In fact, according to the World Health Organization (WHO) report Global health risks (WHO, 2009), alcohol use is one of the leading global risks (5%) for burden of disease as measured in disability-adjusted life years (DALYs) together with being underweight (6%), unsafe sex (5%) and unsafe water, sanitation and hygiene (4%). In high-income countries tobacco (inhaled) and alcohol are the top two causes for healthy life years lost and the use of illicit drugs is among the top ten risks (WHO, 2009). Still, these figures only count for a part of all the harm caused by abuse of psychoactive substances, consequences that include family distress, physical abuse, criminality, accidents, etc.

1.1.1 Classification

The WHO classification system the International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10) (WHO, 2010) distinguishes between harmful use of and dependence on psychoactive substances. Harmful use is defined as a pattern of substance use that causes damage to either physical (e.g. hepatitis) or mental health (e.g. depression). Dependence is defined as: ‘A cluster of behavioural, 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’.

The American Psychiatric Association’s classification system The Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM –IV) (APA, 2000) also differentiates damaging use as substance abuse and dependence under the heading of substance use disorders (SUD). For the detailed DSM-IV diagnostic criteria for SUD see Table 1. The definitions of these two diagnostic systems, ICD-10 and DSM-IV, are largely compatible. In the new fifth revised edition of the DSM (DSM-5), due to be published in May 2013, the distinction between abuse and dependence is most likely to disappear and be replaced by addiction. Instead, DSM-5 will use a dimensional approach defining the severity of the condition. Studies included in this thesis use the DSM-IV as the diagnostic system.

1 DALY is a concept used in epidemiology that can measure deaths at different ages and disability. One DALY corresponds to one lost year of “healthy” life, and the burden of disease can be understood as a measurement of the difference between current health status and a situation where everyone lives into old age, without disease and disability (WHO, 2012).
Table 1. DSM-IV diagnostic criteria for substance use disorders

<table>
<thead>
<tr>
<th>Dependence</th>
<th>Abuse</th>
</tr>
</thead>
<tbody>
<tr>
<td>A maladaptive pattern of substance use leading to clinically significant</td>
<td>A maladaptive pattern of substance use leading to clinically significant</td>
</tr>
<tr>
<td>impairment or distress, as manifested by three (or more) of the following,</td>
<td>impairment or distress is manifested by one or more of the following,</td>
</tr>
<tr>
<td>occurring any time in the same 12 month period:</td>
<td>occurring within a 12 month period:</td>
</tr>
<tr>
<td>1. Tolerance, as defined by either of the following:</td>
<td>1. Recurrent substance use resulting in a failure to fulfill major</td>
</tr>
<tr>
<td>a) A need for markedly increased amounts of the substance to achieve</td>
<td>role obligations at work, school, or home (e.g. repeated absences or</td>
</tr>
<tr>
<td>intoxication or the desired effect or</td>
<td>poor work performance related to substance use; substance-related</td>
</tr>
<tr>
<td>b) Markedly diminished effect with continued use of the same amount</td>
<td>absences, suspensions, or expulsions from school; neglect of children</td>
</tr>
<tr>
<td>of the substance.</td>
<td>or household).</td>
</tr>
<tr>
<td>2. Withdrawal, as manifested by either of the following:</td>
<td>2. Recurrent substance use in situations in which it is physically</td>
</tr>
<tr>
<td>(a) The characteristic withdrawal syndrome for the substance or</td>
<td>hazardous (e.g. driving an automobile or operating a machine when</td>
</tr>
<tr>
<td>(b) The same (or closely related) substance is taken to relieve or</td>
<td>impaired)</td>
</tr>
<tr>
<td>avoid withdrawal symptoms.</td>
<td></td>
</tr>
<tr>
<td>3. The substance is often taken in larger amounts or over a longer</td>
<td>3. Recurrent substance-related legal problems (e.g. arrests for</td>
</tr>
<tr>
<td>period than intended.</td>
<td>substance-related disorderly conduct)</td>
</tr>
<tr>
<td>4. There is a persistent desire or unsuccessful efforts to cut down or</td>
<td>4. Continued substance use despite persistent or recurrent social or</td>
</tr>
<tr>
<td>control substance use.</td>
<td>interpersonal problems caused or exacerbated by the effects of the</td>
</tr>
<tr>
<td>5. A great deal of time is spent in activities necessary to obtain the</td>
<td>substance (e.g. arguments with spouse about consequences of intoxication,</td>
</tr>
<tr>
<td>substance (such as visiting multiple doctors or driving long distances),</td>
<td>physical fights)</td>
</tr>
<tr>
<td>use the substance (for example, chain-smoking), or recover from its</td>
<td>Additionally, the symptoms for substance abuse have never met the</td>
</tr>
<tr>
<td>effects.</td>
<td>criteria for substance dependence.</td>
</tr>
<tr>
<td>6. Important social, occupational, or recreational activities are given</td>
<td></td>
</tr>
<tr>
<td>up or reduced because of substance use.</td>
<td></td>
</tr>
<tr>
<td>7. The substance use is continued despite knowledge of having a</td>
<td></td>
</tr>
<tr>
<td>persistent physical or psychological problem that is likely to have been</td>
<td></td>
</tr>
<tr>
<td>caused or exacerbated by the substance (for example, current cocaine</td>
<td></td>
</tr>
<tr>
<td>use despite recognition of cocaine-induced depression or continued</td>
<td></td>
</tr>
<tr>
<td>drinking despite recognition that an ulcer was made worse by alcohol</td>
<td></td>
</tr>
<tr>
<td>consumption).</td>
<td></td>
</tr>
</tbody>
</table>
1.1.2 Prevalence and correlates

The global prevalence of problematic alcohol use or alcohol dependence was estimated to be 1.2% by the 2004 WHO Global Status of Alcohol Report in population surveys. This means that approximately 76.3 million people worldwide are affected (Degenhardt and Hall, 2012). The total corresponding rate for problem users of amphetamines, opioids and cocaine was 0.3-0.9% or 15-39 million people together as estimated by the World Drug Report by the UN Office on Drugs and Crime (UNODC, 2010). There are large regional differences as to the patterns of drug use, but globally cannabis is by far the most commonly used illicit drug, followed by amphetamines, opioids, and cocaine. There are no global estimates on numbers of drug dependence, but systematic reviews of prevalence studies estimate that the adult rate of cannabis dependence range from 0.10-1.5%, amphetamine dependence from 0.10-0.73%, dependence on heroin and other opioids from 0.11-0.82% and cocaine dependence from 0.07-0.52% (Degenhardt and Hall, 2012).

In Sweden, the estimated 12-month prevalence of alcohol use disorders is 2.27% for females and 6.32% for males (UNODC, 2010), amounting to approximately 330,000 adults who are alcohol dependent and 780,000 who abuse alcohol. Based on register data from the Swedish National Board of Health and Welfare and the Swedish Prison and Probation Service, respectively, the number of problem drug users in Sweden is estimated to 29,500. However, in population surveys, 127,000 people confirm regular use of illicit drugs or prescription medicine without doctor’s prescription suggesting that many drug users never come in contact with the health services for their addiction (Statens folkhälsoinstitut, 2010).

Substance abuse and dependence are frequently associated with other mental disorders such as mood disorders, anxiety, behavioural disorders and other SUD both in population surveys (Compton et al., 2007, Hasin et al., 2007, Kessler et al., 2006, Swendsen et al., 2010) and in treatment-seeking populations (McGovern et al., 2006). Results from a large survey from the USA, the National Epidemiological Survey on Alcohol and Related Conditions (NESARC), show that alcohol use disorders are related to e.g., depression, bipolar disorders, anxiety disorders as well as adverse socio-economic variables such as unemployment, homelessness, poor physical health, educational or work-related underachievement, and low-socioeconomic status (Hasin et al., 2007). Drug dependence is strongly associated with other SUD, mood disorders, generalised anxiety and antisocial personality disorder (ASPD), even after controlling for socio-economic factors and other psychiatric disorders (Compton et al., 2007). Motivation to seek treatment for substance use is more related to psychiatric symptoms than substance use per se (O'Brien et al., 2004).

Rates of psychiatric disorders in adolescents and young adults with SUD vary from 61% to 88% (Couwenbergh et al., 2006). The authors also found externalising disorders such as Conduct Disorder (CD) most consistently linked to SUD in treatment seeking adolescents. Girls had higher rates of comorbid internalising disorders. Especially high rates of comorbid CD were found in juvenile offenders suggesting that
young people with SUD and comorbid disorders are at high risk of getting involved in criminal activities.

The direction of these associations between SUD and mental illness is not fully understood and may work in several ways. Psychoactive substances may cause mental illness such as depression, or mental illness may precede the SUD and facilitate the transition from substance use to abuse and dependence (Swendsen et al., 2010).

1.1.3 Neurobiology
Drug addiction is a chronically relapsing disorder associated with changes in brain mechanisms. Transition from substance use to dependence is a result of complex interactions between environmental factors (e.g., availability of the drug, cultural norms), individual vulnerability (e.g., genetic, psychological) and the effect of the drug on brain physiology. Results from preclinical and brain imaging studies have provided important insight regarding the mechanisms of this process (Le Moal and Koob, 2007, Volkow et al., 2003b).

An important brain pathway involved in addiction is the mesolimbic reward system, arising from the ventral tegmental area (VTA), projecting to the nucleus accumbens (NAcc) and the frontal cortex. The reward system has an important function for the survival of the species and is activated by natural pleasures such as food, sex, and social affiliation. A number of signal substances are involved in the reward process, e.g., dopamine (DA), γ-aminobutyric acid (GABA), endogenous opioids, serotonin, acetylcholine, endocannabinoids and glutamate. DA is important for salient stimuli and has a central role in the regulation of reward and motivation (Koob and Bloom, 1988, Ross and Peselow, 2009, Volkow et al., 2004).

One of the shared effects of drugs of abuse is a rapid increase in DA levels in the NAcc paralleled by an intensively pleasurable sensation, or ‘high’. The increase in DA transmission is generated either directly by stimulating dopamine release in the NAcc and inhibiting the dopamine transporter (by e.g., amphetamine, cocaine) or influencing VTA directly or through neurons regulating DA cells (nicotine, opioids, cannabis). The level of increase in DA transmission has been associated with subjective experience of drug effects. In addition, low levels of D2 receptors have been associated with insensitivity to natural rewards in chronic use and to vulnerability for addiction and, quite recently, to relapse in methamphetamine users (Wang et al., 2009, Volkow et al., 2003a).

After a period of repeated use, the drug effect loses its saliency; instead, DA release is conditioned to related stimuli predicting reward. Such a cue could be e.g., a place where the drug is taken or a social situation related to drug use, and may elicit an intense desire (craving) for the drug. The positive, reinforcing effect of the drug gradually fades (tolerance) and the continued drug use becomes motivated by negative reinforcing effects (avoiding negative sensations, such as withdrawal symptoms). Activation of the brain stress system also appears to be linked to withdrawal symptoms and relapse (Koob and Volkow, 2010). Acute withdrawal states are related to some general neurobiological effects; decreased DA D2 receptor levels, decreased levels of
dopamine, serotonin, GABA and glutamate in the NAcc or/and amygdala and increased levels of dynorphin in the NAcc and noradrenalin in amygdala. In addition, results from imaging studies show decreases in D2 receptors and in dopamine release even after the acute withdrawal is over and may explain the symptoms of anhedonia and amotivation that patients experience at this stage (Koob and Volkow, 2010, Nylander, 2011, Ross and Peselow, 2009). Chronic drug use results in decreased DA activity associated with the deregulation of frontal brain regions, resulting in weakened executive functions. There is a switch from prefrontal to striatal control of drug seeking and drug taking behaviour. Impulsive behaviour in rats is associated with low DA D2/3 receptors and predicts the shift to compulsive drug-seeking behaviour (Everitt et al., 2008).

Transition from substance use to addiction is a result of successive neuroadaptations of circuits involving 1) reward and motivation, 2) memory, conditioning and habituation, 3) executive function and inhibitory control, 4) interoception and self-awareness, and 5) stress reactivity (Koob and Volkow, 2010).

Evidence from adoption, family, and twin studies show moderate to high heritability in SUD (Bevilacqua and Goldman, 2009). The initiation of substance use in early adolescence is to a higher extent determined by environmental factors, and the genetic impact becomes more important in early and middle adulthood. However, there is no single gene that causes addiction, but multiple genes of modest, cumulative and interactive effect. Both environment and genes interact in the initiation of drug use, and in the transition from substance use to dependence (Agrawal and Lynskey, 2008).

1.1.1 Treatment
The goal in treatment of substance dependence should always be defined by the patient, but it typically involves either total abstinence or prevention of relapse to uncontrolled use. This can be achieved by using psychosocial treatment methods or pharmacotherapy, or a combination of both.

1.1.1.1 Psychosocial treatment of substance use disorders
An overview of psychosocial treatments modalities for SUD is outside the scope for this thesis. Treatments with the strongest empirical support for alcohol use disorders include motivational enhancement therapy (MET) and various behavioural and brief interventions. Meta-analyses suggest typical effect sizes in the low-to-moderate range (Martin and Rehm, 2012).

1.1.1.2 Pharmacotherapy of substance use disorders
Insights into the neuroadaptations underlying substance dependence have led to promising developments of medications that reduce the risk of relapse. Three medications for alcohol dependence are currently approved by the Swedish Medical Products Agency (and most EU countries): acamprosate, naltrexone, and disulfiram. Acamprosate modulates NMDA-receptor function and, although its mechanism of action is not entirely understood, blunts some of the rewarding effects of alcohol (Rosner et al., 2010). Naltrexone is an opioid receptor antagonist that
effectively blocks the effects of endogenously released opioids. It has been shown to reduce the risk for relapse to heavy drinking and decrease the amount of alcohol consumed (O’Brien et al., 1996, O’Malley et al., 1992, Volpicelli et al., 1992). Disulfiram is an inhibitor of acetaldehyde, an enzyme involved in alcohol metabolism. When alcohol is consumed, acetaldehyde is accumulated which leads to unpleasant physical reactions (Hald et al., 1948). Several published and on-going clinical trials are evaluating the efficacy of novel medications for relapse prevention (e.g., nalmefene) (Mann et al., 2013).

For opiate dependence, methadone (an opioid agonist), buprenorphine (a partial opioid agonist), and a combination of buprenorphine and naloxone are approved for maintenance therapy in Sweden.

Regarding amphetamine dependence see section 1.1.2 below.

To summarise, addiction is a disease of the brain caused by complex interaction of individual and environmental factors. Its central features are withdrawal, tolerance, craving and loss of control (compulsive use). Each stage has neurobiological underpinnings, some specific for the drug of abuse and some more general adaptations of brain mechanisms. Pharmacotherapies have shown efficacy in and are approved for treatment of alcohol and opioid dependence.

1.1.2 Amphetamine use disorders

The last two studies included in this thesis evaluate pharmacotherapy in amphetamine dependent individuals with ADHD. Hence, more focus is given to amphetamine dependence compared to other SUD. This chapter gives a short overview of prevalence, pattern of use, and treatment of amphetamine dependence.

In Europe, approximately 2 million people (0.6%) had used amphetamine during the last year, with the highest prevalence in Estonia, the United Kingdom, Bulgaria, Latvia, Finland and Sweden (EMCDDA, 2012). Amphetamine is usually taken orally or snorted, but in Sweden, Finland, Norway, Latvia and the Czech Republic, the majority (63-80%) of treatment-seeking primary amphetamine users reported injecting the drug. In Sweden, amphetamine as a primary drug is particularly frequent among incarcerated criminal offenders, noticeably more common than heroin; 24% of offenders reported amphetamine as their primary drug compared to 13% for polydrug, 13% for alcohol, 11% for cannabis, and 7% for heroin. The proportion of women among amphetamine users in the criminal justice system was 15% (Hakansson et al., 2009).

Amphetamine is a synthetic central stimulant that induces a potent increase in extracellular DA by both promoting the release of DA and inhibiting its reuptake (Seiden et al., 1993) and, to some extent, also affects noradrenalin and serotonin transmissions. The illicit amphetamine sulphate most commonly used in Sweden is racemic to its molecular content, i.e. it contains both d- (dextro) and l- (levo) isomers of which d-isomers have a much more pronounced effect on the CNS. Dextroamphetamine in low doses is medically used to treat e.g., ADHD and narcolepsy. The use of methamphetamine, a derivate of amphetamine, is common in
the USA and Asia, and is increasing in Europe (EMCDDA, 2012). In 2001, methamphetamine constituted 10-15% of amphetamine-positive drug tests in the Swedish forensic toxicology database (TOXBASE), and this figure increased to 20-25% in 2010 (Jones and Holmgren, 2013).

Amphetamine abuse is often characterised by a ‘binge and crash’ pattern. A period of intensive use, sometimes without sleep for days, is followed by a period of increased sleeping and eating, along with a cluster of depression-related symptoms, anxiety and craving-related symptoms (McGregor et al., 2005). Chronic amphetamine abuse can lead to adverse cardiovascular effects, paranoid behaviour, violence, impulsivity, and schizophrenia-like symptoms (Holmgren and Lindquist, 1975).

1.1.2.1 Pharmacotherapy of amphetamine dependence

Up to date, there is no approved pharmacotherapy for amphetamine dependence although several pharmacotherapies have been tested, with little success. However, in a placebo controlled trial by Jayaram-Lindström et al. (Jayaram-Lindstrom et al., 2008), naltrexone significantly reduced the risk of relapse to amphetamine use. These results are supported by results from a trial of naltrexone implants in poly drug dependent individuals, in which naltrexone significantly reduced amphetamine and heroin intake compared to placebo (Tiihonen et al., 2012).

With respect to evaluating the efficacy of psychostimulant pharmacotherapy for amphetamine dependence, a clinical trial in 49 of dexamphetamine patients with methamphetamine dependence, showed better retention in treatment, but without significant reduction of amphetamine use compared to placebo (Longo et al., 2010).

Tiihonen and co-workers (Tiihonen et al., 2007) investigated the effect of methylphenidate (MPH), with a daily dose of 54 mg, in a three-armed trial comparing bupropion, aripiprazole, and MPH in patients with amphetamine dependence and found reduced amphetamine use in a subgroup of amphetamine abusers, but these results could not be replicated in a recent larger trial evaluating the same dosage (Miles et al., 2013). Other agents such as aripiprazole, GABA agents (gabapentin, baclofen, vigabatrin), SSRIs, ondansetron and mirtazapine have failed to show efficacy. In methamphetamine dependent patients, trials involving bupropion and modafinil did not show significant effect, but demonstrated a possible benefit in a subgroup of methamphetamine dependent patients (Karila et al., 2010).

1.1.2.2 Psychosocial treatment of amphetamine dependence

The general treatment target in substance dependence is the prevention of relapse. This can be achieved by using psychosocial treatment methods or pharmacotherapy, or a combination of both. Only a few randomised controlled trials (RCTs) regarding psychosocial treatment programs for stimulant dependence have been found efficacious. Cognitive behaviour therapy (CBT) (Baker et al., 2001), Brief intervention using behavioural techniques (Baker et al., 2005), and Acceptance and commitment therapy (ACT) (Smout et al., 2010) have shown efficacy for retaining abstinence in amphetamine users. In cocaine dependent patients, Motivational interviewing techniques/MET (Stein et al., 2009), Community reinforcement approach (CRA)
(Higgins et al., 1994, Higgins et al., 2000) and 12-step program (Crits-Christoph et al., 1999) have shown positive results. Psychological interventions in stimulant dependence are moderately effective in achieving drug abstinence. Contingency management interventions can help to improve retention in treatment (Voci and Montoya, 2009).

In conclusion, amphetamine use disorders yearly affect 2 million people in Europe. The treatment of this condition poses challenges and while some progress has been made in the past decade only a few treatments have demonstrated efficacy.

### 1.2 ATTENTION DEFICIT HYPERACTIVITY DISORDER

#### 1.2.1 Diagnostic criteria
The two diagnostic systems DSM-IV and ICD-10 both define this childhood disorder as characterised by inattention, hyperactivity and impulsivity with partly overlapping diagnostic criteria. However, in ICD-10 (WHO, 2010), hyperkinetic disorder could be considered as a more restricted and severe subtype of the DSM-IV combined-type ADHD (Nutt et al., 2007). The DSM-IV ADHD diagnosis is divided into three subtypes; predominantly inattentive subtype, predominantly hyperactive/impulsive subtype and a combined subtype characterised by impairing symptoms of both inattention and hyperactivity/impulsivity. To fulfil the DSM-IV ADHD criteria (Table 2), six out of nine impairing and age inappropriate symptoms of either inattention and/or hyperactivity/impulsivity have to be present in at least two different settings (e.g., at home, at school). Some of the impairing symptoms must have started before the age of seven and the symptoms should not be better explained by another mental disorder (e.g., a mood disorder or psychosis) (APA, 1994).

DSM-IV-TR includes ADHD ‘in partial remission’ that can be applied to individuals with some persistent symptoms and continued clinical impairment, but who no longer fulfil the full criteria. DSM-IV-TR has also included the diagnosis ADHD NOS (not otherwise specified) with a more lenient age-of-onset criterion (7 years old or after), and a pattern of sluggish cognitive tempo and hypoactivity without meeting the full criteria (APA, 2000).
Table 2. DSM-IV Diagnostic criteria for Attention Deficit/Hyperactivity Disorder

<table>
<thead>
<tr>
<th>Criterion A: At least six of symptoms of 1 AND/ OR 2 have persisted for at least 6 months to a degree that is maladaptive and inconsistent with the developmental level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(1) Inattention</strong></td>
</tr>
<tr>
<td>a) often fails to give close attention to details or makes careless mistakes</td>
</tr>
<tr>
<td>b) often has difficulty sustaining attention in tasks or play activities</td>
</tr>
<tr>
<td>c) often does not seem to listen when spoken to directly</td>
</tr>
<tr>
<td>d) often does not follow through on instructions and fails to finish school work, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)</td>
</tr>
<tr>
<td>e) often has difficulty organizing tasks and activities</td>
</tr>
<tr>
<td>f) often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort</td>
</tr>
<tr>
<td>g) often loses things necessary for tasks or activities</td>
</tr>
<tr>
<td>h) is often easily distracted by extraneous stimuli</td>
</tr>
<tr>
<td>i) is often forgetful in daily activities</td>
</tr>
<tr>
<td><strong>(2) Hyperactivity</strong></td>
</tr>
<tr>
<td>a) often fidgets with hands or feet or squirms in seat</td>
</tr>
<tr>
<td>b) often leaves seat in classroom or in other situations in which remaining seated is expected</td>
</tr>
<tr>
<td>c) often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)</td>
</tr>
<tr>
<td>d) often has difficulty playing or engaging in leisure activities quietly</td>
</tr>
<tr>
<td>e) is often &quot;on the go&quot; or often acts as if &quot;driven by a motor&quot;</td>
</tr>
<tr>
<td>f) often talks excessively</td>
</tr>
<tr>
<td><strong>Impulsivity</strong></td>
</tr>
<tr>
<td>g) often blurts out answers before questions have been completed</td>
</tr>
<tr>
<td>h) often has difficulty awaiting turn</td>
</tr>
<tr>
<td>i) often interrupts or intrudes on others</td>
</tr>
<tr>
<td><strong>B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years.</strong></td>
</tr>
<tr>
<td><strong>C. Some impairment from the symptoms is present in two or more settings (e.g., at school [or work] and at home).</strong></td>
</tr>
<tr>
<td><strong>D. There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning.</strong></td>
</tr>
<tr>
<td><strong>E. The symptoms do not occur exclusively during the course of another or/ and are not better accounted for by another mental disorder such as a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder (e.g., Mood Disorder, Anxiety Disorder, Dissociative Disorders, or a Personality Disorder).</strong></td>
</tr>
</tbody>
</table>
In the coming DSM-5, an age of onset prior to 12 is most likely to replace age of onset prior to 7 as currently specified in the DSM-IV. Moreover, the number of symptoms for ages over 17 years is reduced to five out of nine symptoms instead of six out of nine (http://www.psych.org/practice/dsm/dsm5).

One of the challenges in diagnosing ADHD in adults is that the clinical presentation of ADHD in adulthood is different compared to childhood ADHD. The symptoms of inattention, hyperactivity and impulsivity may have more subtle expressions in adult life. Aspects like age, gender and cognitive ability must be taken into account (Kooij et al., 2010).

### 1.2.2 Prevalence and correlates

Numerous studies around the world have investigated the rate of ADHD in children, adolescents and adults. Results vary between studies for several reasons such as the method used to assess ADHD symptoms, e.g., if studies use symptom ratings only or include impairment criteria. Moreover, studies based on general population surveys and community samples typically generate lower estimates compared to clinically referred samples.

In a meta-analysis of 103 studies in children, Polanczyk et al. (Polanczyk et al., 2007) reported a pooled ADHD prevalence of 5.0-5.6%. Similar results (5.9-7.1%) were reported by (Willcutt, 2012) in a more recent meta-analytic review of studies using DSM-IV criteria. No country differences were found in these two meta-analyses after controlling for the diagnostic procedure (Polanczyk et al., 2007, Willcutt, 2012).

During the past two decades, based on longitudinal data, there is a growing consensus of the persistent nature of ADHD. A meta-analysis of prospective studies suggests that childhood ADHD persists into adulthood in two-thirds of cases (Faraone et al., 2006). The symptoms of hyperactivity decline more than symptoms of inattention that seem to stay quite stable (Larsson et al., 2006, Wilens and Spencer, 2010). The estimated prevalence of adult ADHD in National Comorbidity Survey Replication (NCS-R) was 4.4% (8.1% for lifetime ADHD) (Kessler et al., 2006). Two recent meta-analyses reported ADHD prevalence of 2.5% and 5.9% respectively (Simon et al., 2009, Willcutt, 2012).

ADHD was previously viewed as a predominantly male disorder and the focus was on hyperactive boys. In the past decade or so, there has been increased awareness of ADHD and the nature of the problems it causes also in girls and women. The diagnostic criteria have been criticised for being tailored to the expression of symptoms in boys resulting in clinicians missing the disorder in girls. Early studies reported a high male-female ratio in ADHD, ranging from 2:1 to 9:1 (APA, 2000). In the meta-analysis by Wilcutt (Willcutt, 2012), the overall male-female ratio in adults was 1.6:1 with little difference between the subtypes. The expression of ADHD appears to vary through development. The largest male-female ratio was found in those 13-18 years old with ADHD combined subtype (5.6:1) and lowest in 3-5 year olds with ADHD primarily...
inattention subtype (1:1) (Willcutt, 2012). The large gender differences reported in early samples of clinically referred children suggest that boys due to externalising behaviour are more likely to be referred to treatment compared to girls who have more internalising problems (Biederman et al., 2002).

It has been repeatedly reported that childhood ADHD is associated with negative outcomes across lifespan. Individuals with ADHD are more likely to experience educational and occupational under-achievement, lose jobs, get divorced, and have more accidents and poorer health (Barkley et al., 1991, Biederman et al., 2008, Murphy and Barkley, 1996). Results from the NESARC study (Bernardi et al., 2012) suggest that ADHD is associated with impulsive behaviours, greater numbers of traumas, and lower quality of life, perceived social support and social functioning, even after adjusting for additional co-morbidity. Death by suicide has been found more commonly in individuals with ADHD compared to those without ADHD (Barbaresi et al., 2013). Co-existence with psychiatric disorders is common; individuals with ADHD have higher rates of lifetime substance use, mood disorders, anxiety disorders, and antisocial personality disorder. ADHD is also related to having multiple psychiatric disorders (Bernardi et al., 2012, Fayyad et al., 2007, Kessler et al., 2006, Rasmussen and Gillberg, 2000, Shekim et al., 1990). In a case control study, girls with ADHD had a greater life-time hazard ratios for various comorbid psychiatric disorders; antisocial disorders (7.2), mood disorders (6.8), anxiety disorders (2.1), developmental disorders (3), addictive disorders (2.7), and eating disorders (3.5) compared to controls (Biederman et al., 2010b). Hinshaw et al (Hinshaw et al., 2012) followed 380 girls with childhood diagnosis of ADHD and found that they had continued impairment with more self-injuring behaviour and suicide attempts compared to controls. In spite of the chronic and disabling nature of the disorder, community-based surveys indicate that only a small proportion of adults with ADHD receive treatment (Bernardi et al., 2012, Fayyad et al., 2007, Kessler et al., 2006, Kooij et al., 2010).

Collectively, studies show that ADHD is a prevalent and persisting disorder associated with psychiatric comorbidity and negative life-events in adulthood.

1.2.2.1 ADHD in criminal offenders

There is a well-established link between ADHD and various types of antisocial behaviour (Moffitt, 1990). Longitudinal data suggests that childhood ADHD is associated with a higher risk of criminality by early adulthood (Klein et al., 2012, Mannuzza et al., 1998). In a large survey investigating psychiatric disorders in youths (aged 10-19) in a juvenile detention centre, Teplin et al. (Teplin et al., 2002) estimated that the prevalence of ADHD was 17% in males and 21% in females. Similar results were reported by Fazel et al. (Fazel et al., 2008) in a meta-analysis of 25 surveys in juvenile offenders. The aggregated ADHD prevalence was 11.7% in males and 18.5% in females and were associated with high rates of psychiatric problems. It might seem surprising with higher rates of ADHD in female juvenile offenders given the male-female ratio of ADHD, however, female offenders generally demonstrate higher rates of psychiatric problems than males (Cauffman, 2007).
Studies on ADHD in adult criminal offenders have not been as numerous as in juvenile delinquency and only a few have reported on ADHD in female forensic and prison populations, although the literature is growing. Prevalence estimates of adult ADHD in male criminal offenders range from 10% to 45% (Eyestone and Howell, 1994, Ginsberg et al., 2010, Gunter et al., 2008, Rasmussen et al., 2001, Rosler et al., 2004, Young et al., 2011). In a German study of 129 young incarcerated men (Rosler et al., 2004) ADHD was diagnosed in 45% and ADHD in partial remission in 26.4%. A study by Ginsberg et al. (Ginsberg et al., 2010) estimated ADHD to be present among 40% of a sample of 194 adult male longer-term prison inmates in Sweden. Gunter et al. (Gunter et al., 2008), using MINI Plus interview, estimated a life-time ADHD prevalence to 22% in male (n=264) and female (n=56) offenders entering Iowa (in the USA) correctional services (offenders on any kind of special supervision such as violent offenders and maximum security detainees were discarded from the study). Psychiatric disorders were more prevalent in offenders with ADHD. Significantly more inmates with ADHD had a current suicide risk, and higher rates of other psychiatric symptoms such as mood disorders, anxiety disorders, borderline personality disorder (BPD), ASPD and childhood conduct disorder (Westmoreland et al., 2010).

ADHD is associated with repeat offending and disruptive behaviour in male offenders. The Scottish prison project (Young et al., 2009) found a significant effect of ADHD symptomatology on critical incidents, both verbal and physical aggression, and severity of these incidents in a male prison population. ADHD was associated with younger age of first conviction and number of convictions. Childhood ADHD was the most powerful predictor of violent offending (Young et al., 2011). Higher rates of reactive violence rather than proactive violence has been reported in aggressive offenders with ADHD compared to those without ADHD (Retz and Rosler, 2010). Proactive (i.e. premeditated) violence was more common in the non-ADHD group.

In incarcerated women, the rate of childhood ADHD was estimated to 45.8% using the Utah criteria, which include symptoms of emotional dysregulation in addition to symptoms of inattention, hyperactivity and impulsivity (Wender et al., 2001). In a recent German study of 110 adult female offenders (mean age 34 years) the prevalence of ADHD was estimated to 10% (Rosler et al., 2009b) ranging from 17.9% in young women before the age of 25, 10% for ages 26-45 and 0% in women over 45 years old. ADHD in partial remission was found in 14.5% of the cases. Women with ADHD, compared to non-ADHD women, had spent more time incarcerated and were younger at the time for their conviction. The debut age for the first conviction was also influenced by a lifetime diagnosis of SUD. Moreover, the women with persistent ADHD reported more problems with their social surroundings. They had significantly more eating disorders (of any kind), SUD (especially amphetamine use), and BPD. No differences in mood or anxiety disorders were found between the groups.

Rate of adult ADHD (Edvinsson et al., 2010) was estimated the to 30% in a sub-population (n = 65) of incarcerated women in Sweden. Women with ADHD reported higher levels of difficulties and suffering associated with ADHD symptoms; lower
GAF scores, more reading and spelling difficulties, and higher frequencies of conduct disorder (CD), and current ASPD, as compared with non-ADHD women.

In a Canadian sample of 192 incarcerated women, Hennessey et al. (Hennessey et al., 2010) found that 45.8% met the Utah criteria for childhood ADHD using the Wender Utah rating scale (WURS). Women with childhood ADHD were significantly less likely to have completed high school, to report having been homeless in the past year and were more likely to have been incarcerated for more than 90 days in their lifetime. Cigarette smoking, marijuana use, and cocaine use were significantly more prevalent among women with a positive ADHD history.

In a large epidemiological study of 3439 men and 523 women, mean age 33.6 years (SD = 9.5), Cahill et al. (Cahill et al., 2012) found higher rates of ADHD in incarcerated women compared to incarcerated men (15.1% vs. 9.8%) using self-report (Coolidge correctional inventory). A majority (48%) had the hyperactive/impulsive subtype, 36% inattentive subtype and 16% combined subtype.

To sum up, ADHD in criminal offenders is associated with repeat offenses, critical incidents while incarcerated, mental health problems, substance use, and socio-economic problems. The estimates of ADHD in adult offenders vary, but importantly, compared to general population, ADHD is substantially elevated in both female and male offenders.

1.2.3 Neurobiology
A plethora of studies have investigated the neurobiological and genetic underpinnings of ADHD. Several theoretical models of underlying core deficits in ADHD have been proposed e.g., cognitive energetic model (Sergeant, 2000, Sergeant and Scholten, 1983), executive functioning (Pennington and Ozonoff, 1996), and dual pathway model of executive functions and reward deficiency (Sonuga-Barke, 2003). One of the most influential theories was formulated by Barkley (Barkley, 1997) who proposed that executive function deficits seen in children with ADHD are secondary to failure in inhibition. This section presents some of the findings from neurocognitive and brain imaging studies regarding the neural mechanisms associated with ADHD.

1.2.3.1 Neuropsychological findings
Two meta-analytic reviews (Nigg, 2005, Willcutt et al., 2005) concluded that, compared to controls, the most consistent differences across studies on cognitive deficits in individuals with ADHD were response inhibition, vigilance, spatial working memory, signal detection (arousal), set shifting and some measures of planning. Interestingly, the deficits in inhibitory control seem to be more specific and more pronounced in adults with ADHD than in children with ADHD (Lijffijt M, 2005).

1.2.3.2 Structural imaging
A reduced total brain volume, reduced volume of both gray and white matter, reduced volume of prefrontal cortex (PFC), especially the right PFC, and cerebellum abnormalities (Castellanos et al., 2002, Durston et al., 2004) are some of the key
findings from structural imaging studies in children with ADHD. With improving imaging techniques the research has moved from investigating a few brain areas of interest, which were identified based on theories of psychopathology in ADHD, to a broader approach (Cortese and Castellanos, 2012). A recent meta-analysis of structural imaging studies using voxel-based morphometric methods found a significant global reduction in gray matter in those with ADHD. The most prominent and replicable structural abnormalities were in the basal ganglia (Nakao et al., 2011). Controlling for age and pharmacological treatment revealed an association between increasing age and stimulant treatment with more normal basal ganglia volumes. This suggests that the abnormalities, to some extent, can be viewed as developmental delays that are normalised by late adolescence or early adulthood and that medication facilitates this development (Nakao et al., 2011). In a 33-year follow-up of boys with a childhood diagnosis of ADHD, a reduction in brain gray matter was found in areas involved in attention, emotion regulation and motivation (Proal et al., 2011). These results were independent of current diagnosis and the authors suggest that remission in ADHD is linked to compensatory maturation of prefrontal, cerebellar and thalamic circuitry.

1.2.3.3 Functional imaging
Initially, functional brain imaging studies investigated subjects during activity, typically performing a neuropsychological test that activates brain areas of interest. Such studies were often based on theories of core deficits in ADHD, comparing individuals with ADHD to controls or medicated to non-medicated. Involvement of fronto-striatal-cerebellar networks has repeatedly been implicated in the neurobiology of ADHD by both structural (Castellanos et al., 2002) and functional imaging studies e.g., (Bush et al., 1999, Vaidya et al., 1998) which would indicate involvement of catecholamine neurotransmission (NA, DA). Arnsten (Arnsten, 2009) has highlighted the role of the PFC in the pathophysiology of ADHD. PFC regulates information received from sensory cortices (bottom-up attention) and regulates attention based on relevance (i.e. top-down attention). PFC is important for sustaining attention over delay and shifting attention based to task demands and also regulates behaviour and emotion. Catecholamines are vital to PFC function and either too little or too much NA or DA impairs PFC functions (Arnsten, 2009).

In a review by Trip and Wickens (Tripp and Wickens, 2009) the authors discuss two endophenotypes of ADHD: executive function and motivation. Endophenotypes have been proposed to outline measurable components, e.g., neuropsychological, neurophysiological, and neuroanatomical, between genetics and behaviourally defined diagnostic categories, providing more amenable targets for experimental analysis (Castellanos et al., 2002). Trip and Wickens (Tripp and Wickens, 2009) argue that executive function deficits, although frequently present in children with ADHD, are not necessary for diagnosis of ADHD. Instead, altered reinforcement mechanisms may explain several symptoms in ADHD. This is supported by results from experimental studies showing that children with ADHD prefer immediate over delayed reward.
Recently, interesting results from resting-state imaging studies are emerging (Swanson et al., 2011) suggesting a more diffuse connectivity between functional networks in individuals with ADHD.

Instead of focusing mainly on the influence of prefrontal brain regions in ADHD, Castellanos and Proal (Castellanos and Proal, 2012) have proposed an involvement of several large-scale brain systems, based on findings from brain imaging studies. This would help to explain the heterogeneity of ADHD symptoms. The suggested brain systems include: 1) the fronto-parietal network, also referred to as an executive control circuit involved in goal directed behaviour, 2) the dorsal and ventral attentional networks, which form the key components of the attention regulatory system; especially the dorsal attentional network is implicated in ADHD, 3) the visual network, which is important in sustained attention and interacts with the dorsal attentional network, 4) the motor network; ADHD children often exhibit motoric hyperactivity, and 5) the default network, the activity of which is diminished during a task and increased during rest. Diminished suppression of the default network during tasks is related to attentional lapses. For a detailed account see Castellanos and Proal (Castellanos and Proal, 2012).

1.2.3.4 Genetics

Family and twin studies demonstrate a high genetic component in ADHD, with a mean estimated heritability of 77% in twin studies (Faraone et al., 2005). ADHD shows familial clustering with increased rates of ADHD among the parents and siblings of ADHD children, the risk being higher among the parents and siblings of individuals with persistent ADHD compared remitted ADHD (Franke et al., 2012). A number of risk genes for ADHD have been identified, but independently they signify only a relatively small risk for the disorder explaining up to 1% of the phenotypic variance (Plomp et al., 2009). Environmental risk factors e.g., maternal smoking or health complications early in life, may modulate the genetic risk for ADHD.

To conclude, the pathophysiology of ADHD has been suggested to involve fronto-striatal-cerebellar networks, and DA and NA neurotransmission (while not excluding other putative neurophysiological mechanisms). Results from imaging studies also support that several brain networks may be involved in ADHD symptomatology. ADHD has a strong genetic component, but with multiple genes of moderate effect, in complex interaction with environmental factors.
1.3 ADHD AND SUBSTANCE USE DISORDERS

1.3.1 ADHD as a risk factor for substance use disorders

Results emerging from longitudinal studies have elucidated the role of childhood ADHD in development of SUD. The role of conduct disorder (CD) as a mediator for the association between ADHD and SUD in children and adolescents has been debated. CD is characterised by antisocial behaviour, difficulties with authorities, and violation of rules and social norms. It is well documented that early antisocial behaviour is a predictor for substance use and abuse later in life (Odgers et al., 2008). As ADHD and CD frequently overlap, the question is if whether ADHD independently poses a risk for later substance use or whether the risk is entirely explained by the co-existing CD. Studies have found that CD rather than ADHD may account for the risk of developing SUD regardless of gender (Disney et al., 1999, Flory et al., 2003). However, other studies have reported that ADHD predicts earlier age of onset and presence of SUD after controlling for CD (Biederman et al., 1995, Milberger et al., 1997, Wilens et al., 1997).

Two extensive meta-analyses of ADHD as a risk factor for later SUD were published quite recently. A meta-analysis of 27 studies by Lee et al. (Lee et al., 2011) concluded that children with ADHD were more likely to have used nicotine and other substances except alcohol. They were also more likely to develop abuse or dependence of nicotine, alcohol, marijuana, cocaine, and other substances. A meta-analysis of 13 studies by Charac et al. (Charach et al., 2011) found ADHD associated with alcohol and drug use disorders in adulthood and with nicotine use in adolescence, however, association with drug use was influenced by one study. In a large USA based survey, NCS-R, including 5001 respondents, behavioural disorders such as ADHD predicted transition from substance abuse to dependence (Swendsen et al., 2010).

Results from a longitudinal study of 756 children, followed since 1975, suggest an association between ADHD and SUD mediated by CD (Brook et al., 2010) whereas results from the Minnesota Twin Family Study suggest that hyperactivity and CD independently contribute to all types of substance use and that, in comparison, inattention presents a smaller risk to develop SUD (Elkins et al., 2007). Girls with ADHD, when compared to controls, are at higher risk for developing SUD (Biederman et al., 2010b, Disney et al., 1999). An epidemiological study from Finland followed 1545 adolescents from ages of 11-12 years and found that both inattentiveness and hyperactivity were predictors for alcohol use in both sexes at age of 17.5, but more predictive of use of alcohol and illicit drugs in girls. Parent reports of inattention symptoms were a consistent predictor of illicit drug use during adolescence (Sihvola et al., 2011). Schubiner et al. (Schubiner et al., 2000) reported that women with ADHD had more treatment episodes for alcohol abuse compared to women without ADHD. It was also reported that CD and not ADHD explained most of the drug use severity measures and educational difficulties.

A twofold increased risk for SUD has been reported in adults with a childhood history of ADHD compared to controls (Biederman et al., 1998). ADHD has also been
associated with an earlier onset and more severe course of SUD, poorer treatment adherence, more difficulty reaching treatment goals, and higher rates of relapse (Carroll et al., 1993, Levin et al., 2004, Wilens et al., 1997, Wise et al., 2001).

In a sample of families with cocaine- or opiate-dependent sibling pairs Arias et al. (Arias et al., 2008) found that, compared with controls, individuals with ADHD had a significantly earlier age of onset of substance use, earlier age of first SUD diagnosis, were dependent on significantly more substances, and had been hospitalised more because of either substance or psychiatric problems. Johann et al. (Johann et al., 2003) reported that alcohol dependent individuals with ADHD symptoms lost control of drinking and developed tolerance at significantly younger ages compared with alcoholics without ADHD. Moreover, they were younger at the first treatment for alcohol dependence. These findings were most pronounced in alcoholics with ADHD plus ASPD. However, as discussed above, some studies have found CD rather than ADHD to explain the severity of SUD. A large overlap was found between ADHD, BPD, and CD in treatment-seeking polysubstance users in Australia (Torok et al., 2012). Rates of BPD and CD were higher in individuals with ADHD compared to those without ADHD. CD predicted all substance severity measures such as earlier onset of substance use, greater polydrug use, more frequent stimulant use and greater risk for stimulant dependence.

The self-medication hypothesis was proposed in context with SUD by Khantzian (Khantzian, 1985), suggesting e.g., that cocaine may be used to alleviate ADHD symptoms, later the assumption was phrased that ‘rather than simply seeking escape, euphoria, or self-destruction the addicts are attempting to medicate themselves for a range of psychiatric symptoms and emotional states’ (Khantzian, 1997). Self-medication, mainly for problems with mood or sleep, was acknowledged by approximately one third of 186 adolescent and young adults with substance use, while only approximately 25% had ‘getting high’ as motivation (Wilens et al., 2007). There was no difference between individuals with ADHD or without ADHD regarding self-medication, suggesting that self-medication is a more general feature among individuals with SUD and not limited to ADHD symptoms.

To summarise, ADHD with or without CD is a risk factor for SUD. Individuals with ADHD and SUD have more severe substance use and more psychiatric comorbidity compared to individuals without ADHD.

### 1.3.2 Prevalence of ADHD in substance use disorders

The prevalence rates of ADHD in individuals with SUD range from 3-54% (Hannesdottir et al., 2001, Ohlmeier et al., 2008). Methodological differences are central to this inconsistency, most importantly, studies relying solely on screening instruments report higher rates than studies including structured interviews. In addition, the rates are higher in clinical samples compared to community samples. Treatment-seeking substance users generally experience more psychiatric problems
than non-treatment seekers in the community; psychological distress is an important motivator for engaging in treatment. Thus, clinical samples will result in higher estimates than population samples.

Among patients in methadone maintenance treatment, prevalence rates range from 5.2-35.4% for lifetime and 4.2-24.9% for persistent ADHD (Arias et al., 2008, Carpentier et al., 2011, Davids and Gastpar, 2004, Eyre et al., 1982, King et al., 1999) In alcohol dependents seeking treatment the prevalence estimates range between 15-23.1% for lifetime (Clure et al., 1999, Johann et al., 2003, Ohlmeier et al., 2008) and from 8-33% for current ADHD (Clure et al., 1999, Ohlmeier et al., 2008). In cocaine users a lifetime ADHD rates ranged in community samples from 9.9-23.8% (Carroll et al., 1993, Falck et al., 2004) and in treatment seeking cocaine users from 24.9-34.9% (Rounsaville and Carroll, 1991, Ziedonis et al., 1994). The rate of adult ADHD ranged from 6-10% (Clure et al., 1999, Levin et al., 1998a) in clinical samples. The ADHD prevalence in cannabis users seeking treatment has been investigated in adolescents. Tims et al. (Tims et al., 2002) reported a 30% prevalence of ADHD in a sample of 600 adolescents (aged 12-18) seeking treatment for cannabis use disorders.

No gender differences were found in a sample of 304 treatment seekers for alcohol use disorders with 21.3% prevalence of adult ADHD (Johann et al., 2003). Likewise, a recent study in 269 polydrug users in Australia reported a 45% rate of adult ADHD with no gender differences (Torok et al., 2012). However, Schubiner et al. (Schubiner et al., 2000) reported a significantly higher ADHD prevalence for males compared to females, 28% vs. 19%, in adults seeking treatment for SUD.

Another recent study (Huntley et al., 2012), investigated a sample of 226 substance users entering detoxification units in South London, and found an ADHD prevalence of around 12%. Only one person had an existing ADHD diagnosis at admission while two had a record of childhood ADHD. Individuals with combined SUD and ADHD had significantly higher self-rated impairments across several domains of daily life, higher rates of substance abuse, alcohol consumption, suicide attempts, and depression compared to treatment seekers without ADHD.

Recently, a comprehensive meta-analytic review was published by van Emmerik-van Oortmerssen et al. (van Emmerik-van Oortmerssen et al., 2012) including 29 studies involving 6689 subjects, of which 12 studies (2635 subjects) concerned adults seeking treatment (10 studies) for SUD patients or adult substance users in the community (2 studies). Only studies using structured interview methods were included in the analysis. The primary substance of abuse in the adult studies was cocaine in six studies, various types of substances in four, alcohol in three and opioids in two studies. The pooled ADHD prevalence was 23.3% (95% CI 17.7–30.1%) irrespective of age or gender. There was an effect of interview method used, studies using SADS-L and DICA reported higher rates than the others. Cocaine use was associated with a lower rate of ADHD compared to other primary substances contrary to the self-medication hypothesis (Khantzian, 1985) and earlier findings of high rates of childhood ADHD in cocaine dependents (Rounsaville et al., 1991). The hypothesis that individuals with
ADHD choose a specific drug is not supported by the literature in adults (Clure et al., 1999) or in adolescents (Biederman et al., 1997).

1.3.3 ADHD, SUD and other co-occurring disorders
Both ADHD and SUD are frequently associated with other psychiatric disorders (Kessler, 2004, Kessler et al., 2006). The literature suggests that the co-occurrence of ADHD and SUD is associated with higher rates of other psychiatric disorders than each disorder on its own. King et al. (King et al., 1999) investigated the rate of ADHD and co-morbid disorders in 125 adult opioid dependent individuals admitted to methadone maintenance treatment. Individuals meeting diagnostic criteria for ADHD, compared to those without ADHD, had significantly higher rates of other current psychiatric disorders such as dysthymic disorder (48% vs. 18%), anxiety disorder (29% vs. 7%), social phobia (14% vs. 2%) and any axis II disorder (67% vs. 35%). ADHD cases had significantly earlier age of onset alcohol use (12.5 vs. 15.3), heroin use (17.7 vs. 21.4) and cocaine use (20.8 vs. 23.9). No association between ADHD and treatment outcomes was found. In a sample of 1761 individuals with cocaine and/or heroin dependence, individuals with ADHD had more psychiatric diagnoses, CD, ASPD, PTSD, intentionally self-injurious behaviour and suicide attempts, compared to SUD only. The authors suggest that ADHD could contribute to a more severe phenotype of SUD, with debut of substance use at earlier age and a more severe course of SUD (Arias et al., 2008). In a sample of 193 patients attending methadone maintenance treatment, Carpentier et al. (Carpentier et al., 2011) found higher problem severity scores, lower quality of life scores, more comorbid SUD and more psychiatric comorbidity; mood and anxiety disorders, PTSD, CD and ASPD, in individuals with ADHD compared to controls. Levin et al. (Levin et al., 2004) followed 135 cocaine-dependent individuals with ADHD entering a therapeutic community, and none of them graduated from the treatment compared to 9% of the individuals with another Axis I disorders and 19% of those without any Axis I disorders.

In summary, compared to individuals with SUD, individuals with combined ADHD and SUD appear to be more vulnerable for additional psychiatric disorders such as mood disorders, anxiety disorders and personality disorders and to have a lower quality of life.

1.4 TREATMENT OF ADULT ADHD

1.4.1 Psychosocial treatment
The subject of non-pharmacological treatment of ADHD is not within the scope of the present thesis but merits to be mentioned briefly. During the past two decades new treatment approaches for ADHD in children and adults are gaining support (for review see Skokauskas et al 2011) (Skokauskas et al., 2011). There is also growing evidence
for the usefulness of psychosocial treatment in adult ADHD, such as CBT (Emilsson et al., 2011, Saffren et al., 2005), DBT based treatment (Hirvikoski et al., 2011), or metacognitive therapy (Solanto et al., 2010). Young et al showed promising results of CBT in adult male detainees with ADHD and severe personality disorder. So far, no studies have been published on psychosocial treatment specifically targeting ADHD and SUD.

### 1.4.2 Pharmacotherapy, with focus on methylphenidate

A large body of studies has tested the efficacy and safety of ADHD pharmacotherapy in children and in the last two decades, the number of trials in adults with ADHD has been growing fast. All current pharmacotherapies for ADHD potentiate catecholamine transmission in the PFC (Arnsten, 2009). Stimulants, MPH in particular, have been the first-line treatment for ADHD for decades. Other medications such as atomoxetine and guanfacine have also shown efficacy in reducing ADHD symptoms. This section presents a short overview of RCTs evaluating the efficacy and safety of MPH. For an overview of studies regarding other compounds, see the review by Wilens et al. (2011).

Studies in children show response rates to stimulants of approximately 70% (Wilens et al., 2011). The results from adult studies are somewhat more inconsistent with a mean weighted response rate of 60% in short-term (range 25-78%) and 74% in longer-term. Studies using higher doses of MPH (>1.0 mg/kg/day) have reported more robust effects than lower doses (<0.7mg/kg/day), comparable results have been reported for amphetamine. However, this finding has not been consistent (Wilens et al., 2011). Two published meta-analysis found a dose response relationship for methylphenidate, with higher doses predicting better efficacy (Castells et al., 2011, Faraone et al., 2004). Faraone et al. (Faraone et al., 2004) found also significantly larger effects for physician ratings of outcome and use of higher doses. Castells et al. (Castells et al., 2011) reported that ER formulations and co-morbid SUD were related to decreased efficacy. Koesters et al. (Koesters et al., 2009) did not find any dose response relationship for MPH efficacy or for physician ratings vs. patient ratings. All three meta-analysis showed efficacy of MPH for treatment of ADHD symptoms. The estimated effect size for long acting stimulants across studies (published up to 2008) is 0.76 (Faraone and Glatt, 2010) and the number needed-to-treat is estimated at 2-3, implying that half or two thirds of the patients treated do not respond to the medication.

In a comprehensive review, Wilens et al. (Wilens et al., 2011) summarized 88 clinical trials regarding adults with ADHD, with both open label and double-blind design; 41 evaluating the effect of stimulants and 47 of other compounds such as atomoxetine and bupropion. The early studies evaluated the efficacy of immediate-release (IR) formulations of stimulants while more recent studies have largely concentrated on the ER formulations.

#### 1.4.2.1 Immediate release methylphenidate

The majority of the clinical trials have reported positive results, although Mattes et al. (Mattes et al., 1984) were not able to replicate the positive findings from Wood et al.
(Wood et al., 1976). Interestingly, Mattes et al. found that prior substance use was the only predictor for treatment response. Wender et al. (Wender et al., 1985) reported that MPH, compared to placebo, significantly improved inattention, motor overactivity, affect lability and impulsivity. Two of these early studies in adults used DSM-III diagnostic criteria for ADHD, whereas the diagnostic criteria in Wood et al. (Wood et al., 1976) are not described in detail.

Spencer et al. (Spencer et al., 1995) found that MPH (1.0 mg/day; mean 0.92 mg/day) was superior to placebo in reducing ADHD symptoms irrespective of gender or psychiatric comorbidity. The dose was not associated with plasma levels of MPH. Bouffard et al. (Bouffard et al., 2003) found that IR MPH, in doses of 30mg/kg and 45 mg/kg, compared to placebo, significantly reduced ADHD symptoms, both in subjective ratings and in the continuous performance test (CPT). The medication was well tolerated with minimal side effects. All RCTs mentioned above were short term studies (2-7 weeks) with a cross-over design, i.e. medication duration ranged only between 1-3 weeks.

Spencer et al. (Spencer et al., 2005) performed a larger (n=146), 6-week RCT with a parallel groups design, evaluating IR MPH in doses up to 1.3 mg/kg/day (1.1 ± 0.24 mg/kg). MPH compared to placebo, resulted in a statistically significant decline in ADHD symptoms (both inattention and hyperactivity) during the course of the trial. The response to MPH was not associated with depression, anxiety disorders, alcohol or drug abuse or dependence, antisocial personality, or number of comorbid disorders. Pulse, but not blood pressure increased significantly but moderately in the MPH group compared to the placebo treated. An RCT of MPH from Netherlands by Kooij et al. (Kooij et al., 2004) showed similar results using up to 1.0mg/kg/day.

Wender et al. (Wender et al., 2011) completed a 2-week crossover trial of MPH with a 12 month open label continuation for MPH responders. ADHD symptoms improved significantly (50% reduction of symptoms) in the MPH group (74%) compared to those receiving placebo (21%).

### 1.4.2.2 Extended release methylphenidate

In all, results from ten clinical trials of MPH-ER formulas (OROS, multilayer release, and extended release) in adults have been reported. The first RCT of OROS MPH in adults, performed by Biederman et al. (Biederman et al., 2006), testing dosage up to 1.3 mg/kg/day, reported significant reductions in symptoms of inattention and hyperactivity/impulsivity relative to placebo during the 6-week trial. In a randomized, double-blind, 8-week, cross-over trial by Reimherr et al. (Reimherr et al., 2007), OROS MPH (maximum dose 90 mg/day) was superior compared to placebo in reducing symptoms of inattention, hyperactivity/impulsivity and emotion dysregulation. Forty-nine percent of the participants receiving MPH were treatment responders as defined by >50% investigator rated improvement in WRAADDS, compared to 22% in the placebo group. Treatment responders averaged 57 ± 27 mg/day and non-responders 75 ± 21 mg/day.
Chronis-Tuscano et al. (Chronis-Tuscano et al., 2008) included 23 mother child dyads both diagnosed with ADHD and found an effect of MPH (36-90 mg/day) on maternal ADHD-symptoms and on measures of parenting such as inconsistent discipline.

In a large multinational placebo-controlled RCT trial (n=401), Medori et al. (Medori et al., 2008) tested the efficacy and safety of OROS MPH in 13 countries. This was a 5-week trial of three different dosages; 18mg, 36 mg and 72 mg. Treatment (in all dosages) resulted in a significant reduction in ADHD symptoms measured with observer-rated CAARS-O. No dose response effect was found.

In a 6-week randomized placebo-controlled dose-escalation study of OROS MPH in 226 adults, Adler et al. (Adler et al., 2009) reported that treatment with 36-108 mg/day of OROS MPH resulted in a statistically significant improvement in investigator-rated ADHD symptoms measured by AISRS.

Three longer-term (>12 weeks) studies using ER formulas of MPH have been reported. Rösler et al. (Rosler et al., 2009a) completed a 24-week multicentre RCT of MPH ER in 359 adults with ADHD. The dose ranged from 10 mg/day to 60 mg/day, depending on individual efficacy and tolerability. Mean daily MPH ER dose was 0.55 mg/kg. The authors reported significant reductions of ADHD symptoms, both clinician rated in WRAADDS and self-rated symptoms of inattention and hyperactivity/impulsivity in CAARS-S:L.

Biederman et al. (Biederman et al., 2010a) tested long-term efficacy and safety of OROS MPH (36 mg - 1.3 mg/kg/day) in a three-phase study. Phase 1 (n=227) was a double blind, randomized, 6-week, placebo controlled, parallel design study. Responders in phase 1 (MPH:n=62; placebo:n=34) were invited into phase 2, which lasted for 24 weeks, under continued double blind conditions. In phase 3, OROS MPH responders were randomized to continued active medication or placebo (placebo responders were not re-randomized to OROS MPH during phase 3). In phase 1, the MPH group showed significantly reduced ADHD symptoms, compared to the placebo treated. Responders in both groups continued at an improved level. In phase 3 no difference was found in ADHD symptoms between the MPH and the placebo treated. The attrition rate was 30%.

Most recently, Casas et al. (Casas et al., 2011) studied two different daily doses of OROS MPH (54 mg, 72 mg). OROS MPH 72 mg/day, but not 54 mg/day significantly reduced overall observer-rated ADHD symptoms compared to placebo. Interestingly, compared to placebo, both doses of MPH decreased inattention symptoms, but only 72 mg/day had an effect on hyperactivity symptoms.

To assess long-term medication adherence, Bejerot et al. (Bejerot et al., 2010) followed 133 adult psychiatric patients treated for ADHD: 80% of the patients were successfully treated at 6 and 9 month follow-up and 50% of continued with pharmacotherapy at 2-year follow-up. The best predictor for treatment adherence was the level of improvement during the first 6 to 9 months. Fifteen percent of patients dropped out due to lack of treatment effect.
The majority of the clinical trials mentioned above have excluded participants with a history of abuse or dependence on psychoactive substances during the past six months before the trial start.

All studies reported mild to moderate adverse events, the most common being dry mouth, insomnia, edginess, diminished appetite, weight loss, dysphoria, obsessiveness, tics, and headaches. Cardiovascular adverse effects of stimulant use in adults include a consistent increase in systolic and diastolic blood pressures (3-5 mmHg) and heart rate (5 bpm). Monitoring blood pressure and pulse at regularly is recommended (Wilens et al., 2011).

Taken together, both short and long-acting formulas of MPH have been efficacious in improving ADHD symptoms in adults with ADHD in short term. Much less is known about long-term effectiveness and medication adherence in adults with ADHD.

1.4.2.3 Regulatory guidelines in Sweden

In Sweden, OROS MPH (Concerta) was approved in 2002 for treatment of ADHD in children, to be prescribed by a child psychiatrist or a child neurologist with a special exemption of other closely related specialties. In 2008 this was extended to include adult psychiatry. The Swedish Medical Products Agency (MPA) www.lakemedelsverket.se) treatment guidelines from 2008 conclude that pharmacotherapy of ADHD should be a part of a multimodal treatment program, and introduced when other treatment measures have been insufficient. Individual treatment goals should be defined before the initiation of pharmacotherapy. Medication should be initiated in a context that facilitates treatment adherence and the need for support and aid should be taken to consideration. The patient and his/her family should be educated regarding the pharmacotherapy. MPH is recommended as the first line medication for treatment of uncomplicated ADHD, whereas atomoxetine should be considered in case of e.g., substance use disorders or risk for medication diversion. The clinician should evaluate the medication efficacy and safety on a regular basis (Läkemedelsverket, 2008). In Sweden, medications approved for the treatment of ADHD in children include different formulations of MPH (Concerta, Equasym depot, Medikinet, Ritalin and Ritalina) and atomoxetine (Strattera). Dexamphetamine (Metamina) and amphetamine are available on a license basis, for individual patients. The prescription of MPH for adults is allowed off-label.

1.4.3 Pharmacotherapy of ADHD with co-occurring SUD

Case reports and results from open label clinical trials have been promising and suggest that pharmacotherapy could reduce ADHD symptoms as well as drug use in adult patients with substance use and ADHD e.g., (Castaneda et al., 1999, Levin et al., 1998b, Somozza et al., 2004). In an open label pilot study by Levin et al. (Levin et al., 1998b), 12 cocaine dependent patients with ADHD received MPH (40–80 mg/day) combined with weekly sessions of relapse prevention therapy. Patients reported reductions in attention difficulties, hyperactivity, impulsivity and cocaine use. Self-reported cocaine use and craving decreased significantly during the course of 12 weeks
of treatment as did cocaine positive urine samples. Similar results were obtained in a 12 week single blind study in 12 cocaine dependent patients with ADHD testing bupropion (Levin et al., 2002). Castaneda et al. (Castaneda et al., 1999) treated 19 cocaine dependent patients with ADHD with good effect of pharmacotherapy (using several compounds e.g., MPH ER, fluoxetine, bupropion). Patients improved with regard to ADHD-symptoms and lower relapse rates to cocaine use.

There is little evidence from RCTs of the efficacy of stimulant pharmacotherapy to treat co-existing ADHD and SUD. Table 3 presents an overview of the RCTs in comorbid ADHD and SUD published to date. The utility of MPH has been evaluated in a RCT design in current (Levin et al., 2007, Levin et al., 2006b, Schubiner et al., 2002) and abstinent users (Carpentier et al., 2005). Results from these studies have been discouraging as to effect on ADHD symptoms and substance use although some secondary analyses have shown promising results.

Schubiner et al. (Schubiner et al., 2002) randomized 48 cocaine dependent patients; to placebo or a target dose of 90 mg/day of IR MPH (dose reduction was allowed). All participants received twice weekly CBT for cocaine dependence in groups of 2-6 patients and once weekly individual CBT for ADHD. Retention in the study did not significantly differ by group; 58% of the placebo group and 45% of the MPH group completed the trial. There was no difference in clinician rated ADHD symptoms, but the MPH group rated themselves as significantly better compared to the placebo group. There was no difference between the groups in the drug use measures, neither in the proportion of negative urine samples (placebo: 42% vs. MPH: 50%), nor in the mean longest continuous abstinence from cocaine. Carpentier et al. (Carpentier et al., 2005) found no effect of IR MPH (0.6 mg/kg/day) in 25 in-patients (with various primary drug of abuse) compared to placebo. The response rate to MPH was 36% and to placebo 20%.

In a three-armed RCT, Levin et al. (Levin et al., 2006a) evaluated effect of MPH (maximum dose of 80 mg/day) and bupropion (200 mg/day), compared to placebo, for treatment of ADHD in 98 patients currently on methadone maintenance. Fifty-three per cent of the sample also met criteria for cocaine dependence or abuse. Participants received weekly sessions of relapse prevention therapy as a part of the methadone maintenance program. A substantial number reduced their ADHD symptoms (placebo 46%, MPH 34%, bupropion 49%) from baseline. Drug use was measured as drug free weeks. None of the outcome measures for ADHD symptoms or drug use showed difference between the groups.

The same research group investigated the efficacy and safety of 20-60 mg/day of IR MPH in cocaine dependent treatment seekers currently using cocaine. All participants visited the clinic three times a week and attended weekly individual CBT for cocaine dependence. The participants were compensated for transportation costs.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Population</th>
<th>Active substance</th>
<th>Additional treatment</th>
<th>Trial length</th>
<th>Outcome</th>
<th>Result</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schubiner et al. 2002</td>
<td>RCT placebo-controlled parallel 3-armed</td>
<td>48 cocaine dep.</td>
<td>IR MPH 30mg x 3/day</td>
<td>Group CBT for SUD 2 x week, Individual CBT for ADHD 1 x week</td>
<td>12 weeks</td>
<td>ADHD SC (clinician)</td>
<td>ns</td>
<td>the pemoline group (n=11) was excluded from the analysis due to slow recruitment to the study</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Outpatient</td>
<td></td>
<td>Group CBT for SUD 2 x week, Individual CBT for ADHD 1 x week</td>
<td>12 weeks</td>
<td>CGI-I (clinician)</td>
<td>21% PI, 77% MPH</td>
<td>Retention to treatment PI 58%, MPH 45%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Active users (used cocaine 13.5 days the last 30 days)</td>
<td></td>
<td>Craving Drug use</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>Abstinence required throughout the study Retention 78%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean age 37</td>
<td></td>
<td></td>
<td></td>
<td>Responders (&gt;30% improvement in ADHD-RS-IV)</td>
<td>ns, 23% PI, 36% MPH</td>
<td></td>
</tr>
<tr>
<td>Carpenter et al. 2004</td>
<td>RCT placebo-controlled multiple crossover 3-armed</td>
<td>25 SUD (52% AUD, 92% DUD)</td>
<td>IR MPH 15, 30 and 45 mg/day, fixed dose (up to 0.6mg/kg/day)</td>
<td>no</td>
<td>8 weeks</td>
<td>Responders (&gt;30% improvement in ADHD-RS-IV)</td>
<td>ns</td>
<td>Abstinence required throughout the study</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inpatient 3 weeks abstinent Mean age 32</td>
<td></td>
<td></td>
<td></td>
<td>Responders (&gt;30% improvement in ADHD-RS-IV)</td>
<td>ns</td>
<td>Retention 78%</td>
</tr>
<tr>
<td>Levin et al. 2006</td>
<td>RCT placebo-controlled parallel 3-armed</td>
<td>98 methadone maintained (53% cocaine dep.,/abuse)</td>
<td>IR MPH up to 400mg/day/BPR 300mg/day</td>
<td>Individual CBT for SUD 1xweek 3-weekly visits</td>
<td>12 weeks</td>
<td>&gt;30% reduction in AARS (self), &gt;30% reduction in AARS and CGI 3</td>
<td>46% PI, 34% MPH 49% BPR 39%</td>
<td>Stable methadone dose at least 3 weeks, 2-week PI led in Retention PI 76%, MPH 66%, BPR 70%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Outpatient</td>
<td></td>
<td></td>
<td></td>
<td>Responders (&gt;30% reduction in AARS (self), &gt;30% reduction in AARS and CGI 3,)</td>
<td>ns</td>
<td>Retention PI 76%, MPH 66%, BPR 70%</td>
</tr>
<tr>
<td>Levin et al. 2007</td>
<td>RCT placebo-controlled parallel 3-armed</td>
<td>100 cocaine dependent</td>
<td>IR MPH up to 60mg/day</td>
<td>Individual CBT for SUD 1x week 3-weekly visits</td>
<td>14 weeks</td>
<td>&gt;30% reduction in AARS (self), &gt;30% reduction in AARS and CGI 3</td>
<td>55% PI, 47% MPH</td>
<td>Retention PI 45%, MPH 43%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Active users</td>
<td></td>
<td></td>
<td></td>
<td>Drug free weeks Responders (&gt;30% reduction in AARS (self), &gt;30% reduction in AARS and CGI 3,)</td>
<td>ns</td>
<td>Retention PI 45%, MPH 43%</td>
</tr>
<tr>
<td>Wilens et al. 2008</td>
<td>RCT placebo-controlled parallel 3-armed</td>
<td>147 alcohol dependent</td>
<td>ATX 25–100 mg/dag</td>
<td>Weekly visits</td>
<td>12 weeks</td>
<td>ASRS (clinician)</td>
<td>p = .007, es=0.48</td>
<td>Additional 12 week open label phase, Retention PI 52%, MPH 44%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 days abstinent</td>
<td></td>
<td></td>
<td></td>
<td>Time to first heavy drinking day, Number of heavy drinking days</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Winhusen et al. 2010</td>
<td>RCT placebo-controlled parallel</td>
<td>255 smokers</td>
<td>ORDS MPH 72 mg/dag nicotine patch</td>
<td>10 min daily smoking cessation program</td>
<td>11 weeks</td>
<td>Prolonged abstinence</td>
<td>ns</td>
<td>No other SUD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ADHD-RS (clinician)</td>
<td>p&lt;0.001, p=0.008</td>
<td>Post-quit phase MPH group smoked less cigarettes/day</td>
</tr>
</tbody>
</table>

ADHD SC= ADHD Symptom Checklist, ASRS= ADHD Investigator Rating Scale, AUD= Alcohol Use Disorder, BPR= Bupropion, CBT= Cognitive Behaviour Therapy, CGI-I= Clinical Global Impression – Improvement, DUD= Drug Use Disorder, IR= Immediate Release, MPH= Methylphenidate, PI= Placebo, Targeted Adult Attention Deficit Disorder Scale (TAADDS), RCT= Randomized Controlled Trial
There was no difference between the groups regarding the primary outcome measure; the percentage of participants in each treatment group meeting 30% improvement in ADHD symptoms measured with AARS. In a secondary analysis, MPH treatment responders had significantly less cocaine positive urines compared to non-responders (Levin et al., 2007). Wilens et al. (Wilens et al., 2008) reported positive results from an RCT comparing atomoxetine (25-100 mg/day) and placebo in alcohol dependent patient who were abstinent (minimum four days, maximum 30 days) from alcohol. Atomoxetine was superior to placebo in reducing investigator rated ADHD symptoms. Time to relapse in heavy drinking did not differ between the groups, but cumulative heavy drinking days were reduced by 26% in the atomoxetine group compared to the placebo group. In an RCT of atomoxetine in 38 marijuana dependent patients, McRae-Clark et al. (McRae-Clark et al., 2010) found no statistically significant difference between the groups in self-reported ADHD symptoms, and no improvement in marijuana use outcomes. The atomoxetine group had greater improvement on the CGI-I than participants treated with placebo. A smoking cessation trial did not find difference in prolonged abstinence from cigarettes between MPH and placebo (Winhusen et al., 2010).

In adolescents with SUD (Riggs et al., 2004, Szobot et al., 2008), stimulants, compared to placebo, have shown efficacy in improving ADHD symptoms and related problems, but without effect on substance use. However, in two recently published trials in adolescents with ADHD and SUD, one with atomoxetine + MI/CBT (Thurstone et al., 2010) (n=70) and the other with OROS MPH + CBT (Riggs et al., 2011) (n=303) there was no difference between the MPH group and the placebo treated. In these studies, both treatment groups significantly improved their ADHD symptoms from baseline lending the authors to discuss the role of CBT in the symptom improvement and in the failure to show difference between the groups.

Ginsberg and Lindefors (Ginsberg and Lindefors, 2012) reported a 5-week cross-over RCT with 72 mg/day OROS MPH and a 47-week open label extension with up to 1.3 mg/kg/day. MPH significantly (with unusually large effect size, Cohen’s $d=2.17$) reduced observer-rated ADHD symptoms in 30 long-term male prisoners with previous SUD; the preferred substance of use was amphetamine in 63% of the cases, cocaine in 13% and alcohol in 13%. At randomization the participants were at least three months abstinent, verified by urine toxicology.

Taken together, clinical trials have so far not been able to show efficacy of MPH pharmacotherapy in co-existing ADHD and SUD. Atomoxetine has been efficacious in alcohol dependent, but not in marijuana dependent adults. Collectively, the trials report some improvement in ADHD symptoms but no effect on drug use. Importantly, the medication has been well tolerated and none of the trials reports worsening of drug use.
1.4.4 Methylphenidate

MPH hydrochloride (HCl) is a central nervous system stimulant. The immediate release (IR) formulation (Ritalin) has been used for treatment of ADHD in children since 1957. Methylphenidate increases the extracellular levels of DA and NA by inhibiting the re-uptake process, and increases extracellular DA and NA as a secondary effect although its mechanism of action is not yet entirely understood (Ramos-Quiroga et al., 2009). There are individual differences in response to MPH which may be related to individual differences in DA cell activity in spite of equivalent MPH induced DAT blockade (Volkow et al., 2002).

MPH is absorbed rapidly with the time to peak plasma concentration (t$_{max}$) somewhere between 1 and 3 hours (with individual variation) and elimination half-life [t$_{1/2}$] = 90 min. MPH is metabolized by the liver into ritalinic acid. Fifty per cent is excreted in the urine by eight hours and 90% after 48 hours post administration (Kimko HC, 1999).

Extended-release formulas were developed to allow a more stable concentration throughout the day. OROS MPH HCl (Concerta™) was designed to provide efficacy for approximately 12 hours and has a safety profile comparable to IR MPH. The OROS MPH HCl delivery system contains a drug overcoat of IR MPH (consisting of 22% of the active substance) designed to dissolve shortly after swallowing the capsule, resulting in an initial rapid increase in plasma concentration, and an osmotic release system which provides a gradual increase in plasma concentration that peaks approximately 6 to 8 hours after dosing. The plasma concentration then gradually declines, reaching the baseline values by 24 hours (Modi NB, 2000).

1.4.4.1 Abuse liability of MPH

An important factor in the treatment of SUD is the potential abuse liability of the medication. In a double-blind, placebo-controlled, randomised crossover study, 49 adults with a history of recreational drug use received either a single oral dose of placebo, 60 mg of IR MPH, or 108 mg OROS MPH. Twenty-four hours after dosing, blood was collected to determine plasma concentrations of MPH and subjects completed assessments of abuse liability. The abuse-related subjective effects of IR and OROS methylphenidate were statistically significantly different from placebo. Subjective effects were consistently lower for OROS compared with IR methylphenidate, particularly at early time points. Despite higher plasma concentrations of OROS MPH at the C$_{max}$, hardly any increase in subjective response was seen after the initial plasma peak (Parasrampuria et al., 2007).
To test the abuse potential of OROS MPH a single-dose, double-blind, randomised crossover study was performed in 49 healthy subjects (18-45 years old) with a history of recreational stimulant use. To test how the rate and the magnitude of drug delivery affected the abuse potential of OROS MPH, subjects received single doses of 54 and 108 mg of OROS MPH, 50 and 90 mg IR MPH, and placebo. Pharmacokinetic, pharmacodynamic and safety information was collected for 24 h post-dose. Both doses of IR MPH and the higher dose of OROS MPH produced significantly higher subjective effects compared with placebo on all measures. The low dose of IR MPH resulted in higher ratings of subjective effects than the higher dose of OROS MPH (McBurnett and Starr, 2011, Parasrampuria et al., 2007) suggesting that, compared to IR formulations of MPH, OROS MPH has a lower abuse potential.

In addition, Volkow et al. (Volkow et al., 2010) reported that methylphenidate induced craving in cocaine abusers only when given together with cocaine-cues and suggested that this finding highlights the context dependency of methylphenidate’s effects.

To summarise, MPH is a powerful CNS stimulant with an abuse potential. However, therapeutic use of extended release formulas in well-structured clinical settings should minimize the risk for craving or relapse in individuals with co-morbid ADHD and SUD.
2 AIMS

2.1 GENERAL AIM

The overall aim was to examine the prevalence of ADHD in substance using populations and to investigate the feasibility and efficacy of methylphenidate pharmacotherapy for treatment of co-existing ADHD and SUD.

2.1.1 Specific aims

- Study I aimed to estimate the prevalence of ADHD in adults, seeking treatment for SUD.
- Study II aimed to estimate the prevalence of ADHD and SUD in incarcerated women in Swedish prisons.
- Study III aimed to test the feasibility of using methylphenidate to treat comorbid ADHD and amphetamine dependence.
- Study IV aimed to test the efficacy and safety of methylphenidate, in doses up to 180 mg, in amphetamine dependent individuals with ADHD.
3 METHODS

This thesis addresses two important aspects of co-existing ADHD in SUD: How common is it? Can it be treated using stimulant pharmacotherapy, also in the presence of a severe SUD? Studies I and II investigate the rate of ADHD in SUD, studies III and IV evaluate the treatment of ADHD in an amphetamine dependent population.

3.1 STUDY I

3.1.1 Design and procedure
Study I was a cross sectional multicentre study involving treatment centres for SUD in ten countries: Belgium, France, Hungary, the Netherlands, Norway, Spain, Sweden, Switzerland and USA. The study had two stages: 1) screening and 2) assessment. Seven countries (France, Hungary, the Netherlands, Norway, Spain, Sweden, and Switzerland) participated in both stages of the study. In stage one all treatment seeking substance users starting a new treatment episode were asked to take part in a short screening. Stage two comprised of a clinical assessment by a trained clinician (medical doctor or psychologist).

3.1.2 Measurements

3.1.2.1 Screening
The screening included the ASRS v. 1.1. (Kessler et al., 2005) and a short questionnaire on demographics and substance use.

3.1.2.2 Assessment
The assessment phase included: a) the M.I.N.I. Plus version 5.0.0 (Sheehan et al., 1998); a structured interview to assess prior and current episodes of mood disorders (current and lifetime depression, manic episode/hypomania), SUD and ASP, b) the borderline module of the SCID II (Williams et al., 1992) to assess BPD, and c) CAADID (Epstein and Kollins, 2006) as the gold standard for ADHD diagnosis. CAADID is a semi structured interview in two parts. CAADID Part I collects information on demographics, developmental course, ADHD risk factors, and psychopathology and was filled out by the patient before the interview. CAADID Part II evaluates the presence of DSM-IV ADHD criteria in childhood and in adulthood. The M.I.N.I. Plus interview was completed first, followed by SCID-II and finally the CAADID-II.

3.1.3 Recruitment and participants
All patients aged 18 to 65, seeking treatment for SUD on the participating sites, and starting a new treatment episode during the study period were informed about the study and asked to participate. Patients who did not speak the language were excluded from the study. Patients who were intoxicated or not able to participate as a result of severe
mental distress or physical illness were asked to join the study as soon as their clinical condition improved.

### 3.1.4 Statistical analysis
The prevalence estimates were calculated on weighted data. The proportion of ASRS positives participating in the assessment stage differed from the proportion of ASRS positives in the screening stage. Because this effect was different for the different countries weights were constructed based on the proportion of ASRS positives, CAADID cases, and country. To prevent biased standard errors, these weights were constructed in such a way that the overall number of participants did not change. SPSS 20 was used for analysing the data.

### 3.2 STUDY II

#### 3.2.1 Design and procedure
Study II was a cross-sectional study using similar methodology as in Study I, a two stage approach, but some additional instruments:

1) Screening for ADHD using ASRS 1.v.1. and for substance use during the 12-month period prior to incarceration using AUDIT (Bergman and Kallmen, 2002, Saunders et al., 1993) and DUDIT (Berman et al., 2005).

2) Diagnostic assessment for ADHD (CAADID), for other psychiatric disorders using MINI Plus, SCID-II module for BPD and a short neuropsychological assessment using a short form of WAIS-III (Vocabulary and Block Design) (Ringe et al., 2002, Wechsler, 1997)and CPT-II.

The CAADDID part I, used as an interview was completed first, followed by the other instruments in the order described above. The interviewers were blind as to the initial screening result.

The screening was administered by prison staff at each site during a two week period in September to October 2008. The interviews were conducted within a 2-month period following the screening. The interviews were completed by trained clinicians from the Stockholm Centre for Dependency Disorders, a university clinic, either licensed clinical psychologists or psychologist in the last phase of their internship. All interviewers were experienced in the assessment of ADHD in individuals with SUD and received recommended training (3 hours) to administer CAADID interview (Epstein and Kollins, 2006). To attain an inter-rater agreement, the interviewers met on several occasions during the course of the study to discuss diagnostic issues.

#### 3.2.2 Recruitment and participants
The project staff visited five of the six Swedish prisons for women: Färingsö, Hineberg, Sagsjö, Ystad and Ringsjö, to inform and coach the staff on how to manage the screening. The sixth prison, Ljustadalen, an open site with 20 beds, was contacted.
by phone, but was excluded from the sample due to practical difficulties during the screening.

Exclusion criteria were: insufficient language skills, repatriation after served sentence and unwillingness to sign an informed consent. All women who were physically present at the prison facilities were asked to participate and fill out the screening instruments. Participation was voluntary. The women could decline or participate anonymously by returning an empty questionnaire in a sealed envelope. They were instructed to write their name on the screening questionnaire if they agreed to take part in the interview. The participants were then to enclose the questionnaires in an envelope and seal the envelope that was sent to the project leader in Stockholm.

### 3.2.3 Statistical analysis

The population was described regarding demographics for full sample and for the screened and interviewed respectively. Analyses used for statistically significant differences were chi-square and Fisher’s exact test. For all analyses, $p>.05$ was regarded as statistically significant.

All statistical analyses were performed with SPSS v. 17 and 18.

For the test statistics following calculations were made:

- **Sensitivity** = $a/(a+c)$, *proportion of true positives who are test positive*
- **Specificity** = $d/(b+d)$, *proportion of true negatives who are test negative*
- **PPV** = $c/(c+d)$, *proportion of test positives who are true positive*
- **NPV** = $b/(c+d)$, *proportion of test negatives who are true negatives*

<table>
<thead>
<tr>
<th>Disease</th>
<th>Positive</th>
<th>Negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>A</td>
<td>B</td>
<td>$a+b$</td>
</tr>
<tr>
<td>Negative</td>
<td>C</td>
<td>D</td>
<td>$c+d$</td>
</tr>
<tr>
<td>Total</td>
<td>$a+c$</td>
<td>$b+d$</td>
<td>$N$</td>
</tr>
</tbody>
</table>

### 3.3 STUDY III

#### 3.3.1 Design and procedure

This study was a randomised double-blind, placebo-controlled trial with parallel-groups-design. Twenty-four participants were randomised to either placebo or MPH. Participants were required to stay abstinent of any psychoactive substances (except nicotine) for a minimum of two weeks prior to inclusion and this was verified with both patient self-report and urine toxicology. Trial duration was 13 weeks including baseline measurements and 12 weeks of treatment.

Subjects visited the clinic twice a week. A research nurse dispensed the study medication (in blisters of 6-8 tablets) and supervised urine sampling.
Once a week all subjects participated in an individual skills training programme to improve coping with ADHD symptoms and with the risk for relapse to drug use (Nordell and Konstenius, unpublished). Therapy sessions were led by trained psychologists familiar with the dual diagnosis of ADHD and amphetamine dependence.

3.3.1.1 Medication
All patients started with an 18 mg/day dose of OROS MPH (Concerta™)/placebo titrated over a period of 10 days to the maximum dose of 72 mg. For subjects who did not tolerate a dose increase the dosage was adjusted and continued at the tolerated level.

<table>
<thead>
<tr>
<th>Dose scheme Study III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1-3</td>
</tr>
<tr>
<td>Day 4-6</td>
</tr>
<tr>
<td>Day 7-9</td>
</tr>
<tr>
<td>Day 10-84</td>
</tr>
</tbody>
</table>

3.3.2 Measurements
3.3.2.1 ADHD and psychiatric symptoms
ADHD symptoms were assessed once a week with a CAARS: SV self-rating scale including a total of 30 items; nine of inattention, nine of impulsivity/hyperactivity and 12 with ADHD frequently co-occurring problems scored from 0 (not at all, never) to 3 (very much, very frequently). The therapists rated the participant’s ADHD symptoms in connection to the weekly therapy session using CAARS:O (Conners, 1999).
At baseline, week 6 and 12 symptoms of depression were measured by BDI-II (Beck, 1996), and symptoms of anxiety by Beck’s Anxiety Inventory (BAI) (Beck, 1993).

3.3.2.2 Substance use
Weekly assessments included: self-reported drug consumption using the Time Line Follow Back (TLFB) interview (Sobell et al., 1992) and a 7-point Likert scale measuring craving for amphetamine adapted from the Tiffany craving scale (Jayaram-Lindstrom et al., 2008, Tiffany et al., 1993).

All urine samples were analysed for amphetamines, benzodiazepines, cannabis, cocaine [bensoylecgonine], dextropropoxyphene and opiates. The urines were screened for amphetamine by an immunoassay method with a cut off level of 500 ng/ml. The confirmation analyses of the positive samples comprised amphetamine, methamphetamine, 3, 4-methylenedioxyamphetamine and 3, 4-methylenedioxymethamphetamine (reporting limit 300 ng/mL) and were performed using a liquid chromatography-tandem mass spectrometry method.

3.3.2.3 Safety assessment
Adverse effects monitoring, including rating of intensity and duration, was carried out weekly by the research nurse using a standardised form with open end questions. Blood pressure, pulse and weight were monitored weekly.
3.3.2.4 Neuropsychological measures
Reaction time and directed attention was assessed at baseline, week 6 and 12 by STROOP test (Golden and Freshwater, 2002).

3.3.3 Recruitment and participants
Participants were recruited from outpatient addiction treatment centres in the Stockholm metropolitan area. Clinicians were informed to ask all amphetamine dependent patients, newly diagnosed with ADHD, about participation in the trial. Initial eligibility was ascertained via phone interviews with the referring clinician who then referred the patient for an interview.

The study included 19 men and five women who met the DSM IV criteria for ADHD and amphetamine dependence and had used amphetamine for a minimum of 12 days during the last 12 months. Exclusion criteria included: 1) current or past DSM IV diagnosis of any other substance dependence except amphetamine or nicotine, 2) history of any major psychiatric disorder except substance use (e.g., schizophrenia or psychosis) or any current psychiatric condition requiring medication, 3) use of any medication with opiates or use of illicit opiates during the last month, 4) current use of benzodiazepines, 5) traces of any illicit substance in urine (amphetamine, benzodiazepines, cannabis, cocaine [bensoylecgonine], dextropropoxyphen, opiates during the last two weeks before inclusion, 6) serious somatic disease (e.g., severe hypertension, seizure disorder, glaucoma, arteriosclerosis, hyperthyroidism), 7) pregnant or lactating women, 8) known hypersensitivity for methylphenidate and 9) IQ<70. Potential participants underwent a physical examination including laboratory tests for haematology and liver functions.

3.3.4 Statistical analysis Study III
All continuous data was analysed using unpaired t-test. The Mann-Whitney test was used for continuous data with non-Gaussian distributions. Patients were compared on baseline characteristics using chi-square and Fischer’s exact test for categorical data and t-tests for continuous data in order to assess homogeneity between the two treatment groups. The primary outcome measure was the difference in CAARS: SV scores between baseline and LOCF comparing MPH and placebo treated patients according to completers’ analysis. A completer was defined as participant who had received ≥75 % of the study medication. A secondary analysis of the same variable was performed according to the ITT approach. The observer rated ADHD symptoms in CAARS:O were analysed for completers and for ITT. Treatment responder was defined as somebody who had at least 30% reduction in CAARS:SV (in line with earlier studies (Levin et al., 2006a). The additional secondary outcome measures were 1) relapse to amphetamine use measured as proportion of negative amphetamine urines during 12 weeks of treatment; all missing urine samples were imputed as positive, 2) retention to treatment; rate of continuous abstinence from amphetamine was analysed using Kaplan-Meier survival analysis, where the time-dependent survival (non-relapse as measured by negative amphetamine urine samples) probabilities for both treatment groups were calculated according to ITT principle, 3) duration of longest period of...
abstinence 4) self-reported use of amphetamine, alcohol and other drugs in TLFB, 5) craving for amphetamine, 6) change in psychiatric symptoms in BDI and BAI, 7) change in STROOP-test.

3.4 STUDY IV

3.4.1 Design and procedure
Study IV was a randomised placebo-controlled trial with parallel groups design. Fifty-four incarcerated men with ADHD and amphetamine dependence were randomised to either MPH or placebo between March 2007 and February 2011. Patients were required to abstain from any illicit substances during the two weeks preceding the inclusion, verified by patient self-reports and supervised urine toxicology. The medication started within 14 days before release from prison (two participants started three days, one five days and one seven days before release) and continued for 24 weeks. All participants were released on supervised probation involving mandatory meetings with a probation officer.

The subjects were picked up by a prepaid taxi at the prison gate on the day of their release and taken to the outpatient clinic. The participants then received study medication for two to four days and were asked to provide a supervised urine specimen. During the 22-week outpatient treatment phase, the participants visited the clinic twice weekly to get the study medication and provide a supervised the urine sample. Compliance to the trial was defined as consumption of 75% of the study medication as assessed by pill count, and verified by analysing MPH in the urine at the end of the trial.

Once weekly, for the first 12 weeks, the participants attended individual manual-based cognitive behavioural therapy targeting relapse (Caroll, 1998). In the case of a relapse lasting longer than three weeks (six consecutive positive urines), the participant was excluded from the trial.

The randomisation list was generated by an independent pharmacist using the computer-based program Design by Trombult Programmering. Fifty-four subject numbers were randomised into two parallel groups with the block size two. Block randomisation was used because of the length of the trial and the nature of the medication effect. The block size was unknown to the principal investigator and all the study staff. The randomisation code was retained by the Karolinska Pharmacy and disclosed after the end of the trial. No interim analysis was performed.

The primary outcome measure was relapse to any screened drug, secondary measures included: relapse to amphetamine, relapse to other drugs, self-reported relapse in TLFB, change in ADHD symptoms in CAARS:SV, CGI, change in CPT-II.
The first urine sample in each week was analysed for all drugs and the second sample for amphetamines only. The participants assumed that both weekly urine samples were analysed for all drugs.

3.4.1.1 Study medication
Placebo was produced by Apoteket Produktion & Laboratorier by filling identical capsules with Concerta™ or placebo. The start dose was 18 mg MPH/placebo titrated over a period of 19 days (with three day increments of 36 mg) to the optimal dose (maximum 180 mg/day). For participants who did not tolerate a dose increase, the dosage was adjusted and continued at the tolerated level, a dose adjustment could be repeated during the trial.

<table>
<thead>
<tr>
<th>Dose scheme Study IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 1-3</strong> 18 mg 1x1</td>
</tr>
<tr>
<td><strong>Day 4-6</strong> 36 mg 1x1</td>
</tr>
<tr>
<td><strong>Day 7-10</strong> 36 mg 2x1</td>
</tr>
<tr>
<td><strong>Day 11-14</strong> 36 mg 3x1</td>
</tr>
<tr>
<td><strong>Day 15-18</strong> 36 mg 4x1</td>
</tr>
<tr>
<td><strong>Day 19-168</strong> 36 mg 5x1</td>
</tr>
</tbody>
</table>

While in prison, participants received the study medication under supervision of a prison nurse.

3.4.2 Recruitment and participants
The study participants, all males between 18 and 65 years, were recruited from three medium security prisons in Stockholm County: Häga, Storboda and Täby. A short advertisement was placed on the prison billboard to inform the inmates about the study. The prison staffs were instructed to give further information to anyone interested. Potential participants were then screened in person by the study physician and the study psychologist. Participation was voluntary and in no way affected the prison sentence.

To be included the participant were to: a) meet the DSM-IV diagnostic criteria for ADHD, b) meet the DSM-IV diagnostic criteria for amphetamine dependence during the last 12 months prior to the current incarceration, and have used amphetamines on a minimum of 12 occasions during the last 12 weeks preceding the current incarceration c) be registered for census purposes and reside in Stockholm county and d) have a place to live in (not only shelter). The study exclusion criteria were: a) a DSM-IV diagnosis of any other substance dependence except nicotine, currently or during the 12 months prior to incarceration, b) a major psychiatric disorder (e.g., schizophrenia, severe depression), c) current antipsychotic medication, d) current use of bensodiazepines, e) traces of any of the following substances in urine: amphetamine, bensodiazepines, cannabis, cocaine, dextropropoxyphene, opiates, i) serious somatic disease (e.g., moderate to severe hypertension >150/95 mm Hg, seizure disorder, glaucoma, hyperthyroidism), and g) known hypersensitivity to methylphenidate. Prior to inclusion in the trial, potential
participants underwent a physical examination including laboratory tests for haematology and liver function.

3.4.2.1 The assessment of ADHD
At screening none of the eligible participants had been evaluated for ADHD (one person had a Minimal Brain Dysfunction diagnosis as a child), therefore the assessment of ADHD was completed by the project staff if the initial screening indicated ADHD and none of the exclusion criteria were present (with the exception of drug screening and housing that often took time to get organised).

3.4.3 Measurements
3.4.3.1 Substance use measurements
Urine samples were screened by CEDIA immunoassay: amphetamines [cutoff 500 ng/ml], cocaine [benzylecgonine; cutoff 150 ng/ml], cannabis [THC-COOH; cutoff 25 ng/ml], opiates [morphin, codeine, 6-AM; cutoff 300 ng/ml], buprenorphine [buprenorphine and norbuprenorphine; cutoff 5ng/ml], benzodiazepines [oxazepam, temazepam, diazepam, 7-aminofluorizepam, 7-aminonitrazepam, 7-aminodiazepam, α-hydroxyalprazolam; cutoff 200 ng/ml], and dextropropoxyphene [cutoff 300 ng/ml]. Verification of amphetamine positive urines included amphetamine, methamphetamine, 3, 4-methylenedioxyamphetamine and 3, 4-methylenedioxy-methamphetamine [cut off 300 ng/ml] using liquid chromatography-tandem mass spectrometry. The above mentioned drugs, MPH and ritalinic acid in urine [cutoff 300 ng/ml] were analysed using a similar mass spectrometric method (Andersson, 2008, Gustavsson et al., 2007).

Drug consumption was also assessed with bi-weekly self-reports using the TLFB (Sobell et al., 1992). Craving for amphetamine was measured using a 7-point Craving for Amphetamine Scale (adapted from Desire for Alcohol scale DAQ) (Love et al., 1998).

3.4.3.2 ADHD and psychiatric measurements
ADHD symptoms were measured with the CAARS: SV (see 4.3.2 Measurements Study III) (Conners, 1999). The participants rated their ADHD symptoms at baseline, once weekly the first four weeks and once every four weeks thereafter.

Severity of symptoms and improvement of patients clinical condition was rated using CGI-S scale, a 7-point Likert scale, comprised of three parts; patient’s own rating of the severity of the clinical condition and clinician’s rating of the severity, and CGI-improvement (CGI-I) a combined rating of patients clinical improvement. At baseline, week 12 and week 24, patients filled out Outcome Questionnaire 45 (OQ45) (Lambert, 1996) to measure psychiatric symptoms and were interviewed using ASI (McLellan et al., 1992).
3.4.3.3 Safety assessment

Adverse events monitoring was carried out weekly by a research nurse using a standardised form with open questions, rating intensity and duration of the event. Blood pressure, pulse and weight were monitored weekly.

3.4.3.4 Neuropsychological measurements

CPT-II v. 5 (Conners, 2002) was completed at baseline, week 12 and week 24. As a part of the assessment IQ estimate was completed, based on two tests (Vocabulary and Block Design) from WAIS-III (Ringe et al., 2002, Wechsler, 1997).

3.4.4 Statistical analysis

The primary outcome measure was the proportion of urine samples negative for any of the following drugs of abuse: amphetamines, cocaine, cannabis, opiates, buprenorphine, benzodiazepines and dextropropoxyphene. The data was analysed for the ITT population as the primary analysis, and for completers in a secondary analysis. Missing urine samples were imputed as 0.9 (9/10 missing samples interpreted as positive) with the exception of a refused urine sample that was imputed as 1.0 (positive).

The data were analysed using unpaired t-tests or the Mann-Whitney test for continuous data with non-Gaussian distributions. For repeated measures, missing data were completed using the LOCF method. Chi-square was calculated for the categorical variables and frequencies, M and SD for the demographics. Retention to treatment (defined as time to six consecutive positive urines, or to not showing up) and time to relapse (calculated as time [days] to first positive urine sample [any drug]), were analysed using Kaplan-Meier survival analysis. Sensitivity analyses were carried out by changing the missing urine data to from 0.9 to 1.0, 0.8, 0.7 and 0.6 before re-analysing the data. All statistical analyses were performed using IBM SPSS20.

3.5 ETHICAL CONSIDERATIONS

All studies were approved by the Stockholm Regional Ethical Review Board. Participation in the studies was voluntary; all participants received oral and written information about the study at hand and signed a written consent. Participants were informed that they at any time before or in the course of the study could retract their participation.

However, some issues need clarification as the study recruited potentially vulnerable individuals, particularly the incarcerated men and women who during their prison sentence loose much of their autonomy. Both declining to participate and participation in the study may raise situations possibly harmful for the individual. The potential participants could experience (intended or unintended) pressure from the prison staff, family or their social workers “to do something about their situation”. This in mind, measures were taken so that declining to participate would not affect the person’s situation or treatment in any way. In the prevalence study in female prisoners, women were able to mask their attendance at the screening stage if they wished to do so. Issues concerning the voluntary aspect of participation were discussed with the staff on several occasions. Participation in the prison-based clinical trial could raise situations
Theoretically harmful for the participants e.g., more frequent urine samples could lead to conflicts with the staff. However, efforts were made to regard situations related to the study protocol as separate from prison routines so that e.g., refusal of a urine sample for the trial would not lead to subsequent penalty. The participants did not receive financial compensation in any of the studies except for a free taxi-ride to the clinic on the day of the release in study IV.

Individuals who were screened but not enrolled in the study were referred to an appropriate psychiatric or SUD treatment programme or somatic care if it was clinically meaningful and they so desired.
4 RESULTS

4.1 STUDY I

The prevalence of ADHD was examined in a clinical sample of individuals seeking treatment for SUD in a multinational study. In total 3558 patients were screened and 1276 patients participated in the assessment phase. Table 1 in the Study I manuscript summarises the demographics and substance use characteristics for those screened.

The primary substance of abuse varied between the countries. Alcohol was the most frequent primary substance in the total sample (54.6%). There was a significant country effect for all demographic and clinical characteristics (p<.001; adjusted for multiple testing) except for the housing status.

Table 4 presents prevalence estimates of childhood and adult ADHD for DSM-IV and DSM-5 criteria. The 95% CI for adult ADHD largely overlaps for DSM-IV and DSM-5. The rate of adult ADHD, according to DSM-IV criteria varied across countries, from 5.4% in Hungary to 31.3% in Norway. The proportion of persistent ADHD also differed between countries.

Data was analysed stratified on setting and primary substance of abuse (see Table 3 in the manuscript). The exact binomial confidence intervals were calculated for these results using a method proposed by Morisette and Khorram (Morisette and Khorram, 1998).

Prevalence rates ranged from 5-22% in inpatient participants and 4-14% in outpatients whose primary problem was alcohol. Among inpatients whose primary substance of abuse was an illicit drug, prevalence rates ranged from 5-52% and, among outpatient illicit drug users, from 10-33%. After adjustment for age, gender, occupational status, housing and marital status there was a statistically significant effect of Nordic (Norway and Sweden) versus non-Nordic countries. After post-hoc stratification on Nordic versus non-Nordic countries the differences in prevalence of ADHD within the Nordic and within the non-Nordic countries were no longer significant (Table 3 and 4 in the manuscript).

4.2 STUDY II

Study II examined the rate of ADHD and SUD in female prisoners in Sweden. At the time of the study, 264 women were registered in a Swedish Prison and Probation Services central database as serving a prison sentence. Of these, 184 (69%) were physically present in the prisons. Those serving the last part of their prison sentence in a treatment home, on leave or for other related reasons not physically present at the time of the screening were not included in the sample. Due to deficient language skills, women who were to be extradited (n=0) were excluded from the sample. An open site (n=15) was excluded for practical reasons. The
Table 4. Prevalence of childhood (retrospective) and adult (current) ADHD according to DSM-IV-TR and proposed DSM-5 adjusted criteria for adults in patients seeking treatment for substance use disorders.

<table>
<thead>
<tr>
<th></th>
<th>France (n=157)</th>
<th>Hungary (n=226)</th>
<th>Netherlands (n=129)</th>
<th>Norway (n=220)</th>
<th>Spain (n=222)</th>
<th>Sweden (n=168)</th>
<th>Switzerland (n=154)</th>
<th>Total (N=1276)</th>
<th>range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Childhood ADHD DSM-IV-TR %</strong></td>
<td>21.3 (14.9-27.7)</td>
<td>12.9 (8.6-17.3)</td>
<td>15.0 (8.9-21.2)</td>
<td>41.0 (34.5-47.5)</td>
<td>10.6 (6.5-14.6)</td>
<td>27.7 (20.9-34.5)</td>
<td>15.1 (9.4-20.8)</td>
<td>21.0 (18.8-23.2)</td>
<td>10.6-41.0</td>
</tr>
<tr>
<td><strong>Childhood adjusted criterion 2 age of onset &lt;12 % (CI 95 %)</strong></td>
<td>23.2 (16.6-29.8)</td>
<td>12.9 (8.6-17.3)</td>
<td>15.0 (8.9-21.2)</td>
<td>42.3 (35.7-48.8)</td>
<td>13.0 (8.5-17.4)</td>
<td>29.1 (22.2-36.0)</td>
<td>15.6 (9.8-21.3)</td>
<td>22.1 (19.8-24.3)</td>
<td>12.9-42.3</td>
</tr>
<tr>
<td><strong>Adult ADHD DSM-IV-TR %</strong></td>
<td>11.2 (6.3-16.2)</td>
<td>5.4 (2.4-8.3)</td>
<td>10.1 (4.9-15.3)</td>
<td>31.3 (25.2-37.5)</td>
<td>9.2 (5.4-13.0)</td>
<td>19.7 (13.7-25.7)</td>
<td>6.1 (2.3-9.9)</td>
<td>13.8 (11.9-15.6)</td>
<td>5.4-31.3</td>
</tr>
<tr>
<td><strong>Adult adjusted 1</strong> age of onset criterion &lt;12 % (CI 95 %)**</td>
<td>13.1 (7.8-18.4)</td>
<td>5.4 (2.4-8.3)</td>
<td>10.1 (4.9-15.3)</td>
<td>32.1 (26.0-38.3)</td>
<td>10.6 (6.6-14.7)</td>
<td>21.0 (14.9-27.2)</td>
<td>6.6 (2.6-10.5)</td>
<td>14.6 (12.7-16.5)</td>
<td>5.4-32.3</td>
</tr>
<tr>
<td><strong>ADHD adjusted 2</strong> % symptoms criterion 5/9 (CI 95 %)**</td>
<td>14.4 (8.9-19.8)</td>
<td>7.6 (4.1-11.1)</td>
<td>11.8 (6.2-17.3)</td>
<td>31.7 (25.6-37.9)</td>
<td>9.2 (5.4-13.0)</td>
<td>21.0 (14.9-27.2)</td>
<td>7.3 (3.2-11.4)</td>
<td>15.1 (13.2-17.1)</td>
<td>7.3-31.7</td>
</tr>
<tr>
<td><strong>ADHD adjusted 3</strong> Combined: age of onset &lt;12 and # symptoms 5/9 % (CI 95 %)**</td>
<td>16.2 (10.5-22.0)</td>
<td>7.6 (4.1-11.1)</td>
<td>11.8 (6.2-17.3)</td>
<td>32.6 (26.4-38.8)</td>
<td>10.6 (6.6-14.7)</td>
<td>22.4 (16.1-28.7)</td>
<td>7.7 (3.5-12.0)</td>
<td>16.0 (14.0-18.0)</td>
<td>7.6-32.6</td>
</tr>
<tr>
<td><strong>Adult ADHD adjusted 4</strong> % symptoms criterion 4/9 (CI 95 %)**</td>
<td>15.0 (9.4-20.6)</td>
<td>8.9 (5.2-12.7)</td>
<td>12.3 (6.7-18.0)</td>
<td>33.6 (27.4-39.9)</td>
<td>9.2 (5.4-13.0)</td>
<td>21.0 (14.9-27.2)</td>
<td>7.7 (3.5-12.0)</td>
<td>15.9 (13.9-17.9)</td>
<td>7.7-33.6</td>
</tr>
<tr>
<td><strong>Adult ADHD adjusted 5</strong> (DSM-IV-TR ADHD-NOS) Combined: age of onset &lt;12 and # symptoms 4/9 % (CI 95 %)**</td>
<td>16.9 (11.0-22.7)</td>
<td>8.9 (5.2-12.7)</td>
<td>12.3 (6.7-18.0)</td>
<td>34.5 (2.2-40.7)</td>
<td>10.6 (6.6-14.7)</td>
<td>22.4 (16.1-28.7)</td>
<td>8.2 (3.9-12.5)</td>
<td>16.7 (14.7-18.8)</td>
<td>8.2-34.5</td>
</tr>
</tbody>
</table>

* Prerequisite: Diagnosed Childhood ADHD based on CAADID retrospective diagnosis; DSM-IV criteria for Childhood ADHD; ** Prerequisite: Diagnosed Childhood ADHD based on CAADID retrospective diagnosis; adjusted age of onset <12 criterion for childhood
remaining 169 prisoners were invited to participate in the study, and 96 (57%) agreed to take part in the screening phase. Of these 96 screened 60 women were included in the assessment phase and 56 completed the full assessment.

One in five of the screened women reported childhood contact with psychiatry, the corresponding rate in adulthood was 65%. However, almost half (42%) of the women had not answered these questions. Six women had received methylphenidate treatment as children. There were no significant differences in these measures or in demographics including age, employment status, marital status, and housing between women who participated only in the screening and those who also participated in the assessment phase.

4.2.1 ADHD Prevalence

4.2.1.1 Screening

Fifty-one per cent of the total sample (mean age 38 years) screened positive for ADHD in the ASRS screener. Forty-five percent of the women met the criteria for “highly probable ADHD” (a score ≥24 in the inattentive or the hyperactive-impulsive symptom dimension) using the full 18-item ASRS. A majority (53%) of those had a score ≥ 24 in both symptom dimensions, 35% had a score ≥24 only in the inattentive dimension and 12% only in the hyperactive-impulsive dimension.

4.2.1.2 Assessment

Sixteen women (29%) of the 56, who fulfilled the assessment phase, met DSM-IV criteria for persistent ADHD in the CAADID interview (Table 5). Of these 16 women, 11 (69%) met the diagnostic criteria for the combined subtype, three (19%) for the inattentive subtype and one (6%) for the hyperactive-impulsive subtype. One additional person met the diagnostic criteria for the combined subtype, but had a later age of onset (at 10) and another person met the criteria for childhood ADHD but not for adult ADHD (she had four out of nine symptoms of inattention).

<table>
<thead>
<tr>
<th>ADHD measures</th>
<th>Screening only n = 40</th>
<th>Full Assessment n = 56</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASRS 6-item screener</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screen pos (4/6-item part A)</td>
<td>51%</td>
<td>53%</td>
</tr>
<tr>
<td>ASRS 18-item</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highly probable ADHD</td>
<td>45%</td>
<td>43%</td>
</tr>
<tr>
<td>CAADID Adult ADHD</td>
<td>na</td>
<td>29 %</td>
</tr>
<tr>
<td>Combined subtype</td>
<td>na</td>
<td>20 %</td>
</tr>
<tr>
<td>Inattentive subtype</td>
<td>na</td>
<td>5 %</td>
</tr>
<tr>
<td>Hyperactive-impulsive subtype</td>
<td>na</td>
<td>2 %</td>
</tr>
<tr>
<td>NOS</td>
<td>na</td>
<td>2 %</td>
</tr>
</tbody>
</table>

Note: NOS = Not otherwise specified (symptom debut after age of seven)
4.2.1 SUD and Other Psychiatric Disorders

Of the 96 women screened 43% had AUDIT scores indicating harmful use or dependence on alcohol and 68% had DUDIT scores indicating either harmful use or dependence on drugs. Co-occurring alcohol use disorder and drug use disorder were found in 12% of the women (Table 6).

**Table 6.** Demographics, preferred substance of use, prevalence of substance use problems and psychiatric disorders, IQ, and their co-variance with ADHD.

<table>
<thead>
<tr>
<th>Comparisons between ADHD and non-ADHD</th>
<th>Full Sample (n=96)</th>
<th>ADHD (n=16)</th>
<th>No ADHD (n=40)</th>
<th>Fisher’s exact 2-tailed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>39.7</td>
<td>40.8</td>
<td>39.9</td>
<td>.587</td>
</tr>
<tr>
<td>Married/co-habitant</td>
<td>32.0%</td>
<td>19%</td>
<td>35%</td>
<td>.338</td>
</tr>
<tr>
<td>Works for living</td>
<td>17.7%</td>
<td>6%</td>
<td>20%</td>
<td>.248</td>
</tr>
<tr>
<td>Homeless</td>
<td>42.7%</td>
<td>56%</td>
<td>42%</td>
<td>.193</td>
</tr>
<tr>
<td>Alcohol use (AUDIT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harmful use (6-17 points)</td>
<td>21%</td>
<td>13%</td>
<td>20%</td>
<td>.710</td>
</tr>
<tr>
<td>Alcohol dependence (&gt;18 points)</td>
<td>22%</td>
<td>33%</td>
<td>18%</td>
<td>.274</td>
</tr>
<tr>
<td>Use of illegal drugs (DUDIT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harmful use (&gt;2-24 points)</td>
<td>23%</td>
<td>21%</td>
<td>28%</td>
<td>.735</td>
</tr>
<tr>
<td>Dependence (&gt;25 points)</td>
<td>45%</td>
<td>71%</td>
<td>31%</td>
<td>.012</td>
</tr>
<tr>
<td>Preferred substance of use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stimulants</td>
<td>57%</td>
<td>87%</td>
<td>43%</td>
<td>.016</td>
</tr>
<tr>
<td>Cannabis</td>
<td>40%</td>
<td>44%</td>
<td>38%</td>
<td>.765</td>
</tr>
<tr>
<td>Opiates</td>
<td>12%</td>
<td>13%</td>
<td>15%</td>
<td>1.0</td>
</tr>
<tr>
<td>Alcohol</td>
<td>33%</td>
<td>40%</td>
<td>30%</td>
<td>.752</td>
</tr>
<tr>
<td>MINI Plus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>40% a</td>
<td>53%</td>
<td>33%</td>
<td>.235</td>
</tr>
<tr>
<td>Alcohol dependence</td>
<td>30% a</td>
<td>44%</td>
<td>23%</td>
<td>.189</td>
</tr>
<tr>
<td>Drug dependence</td>
<td>30% a</td>
<td>100%</td>
<td>58%</td>
<td>.001</td>
</tr>
<tr>
<td>Depression current</td>
<td>21% a</td>
<td>25%</td>
<td>20%</td>
<td>.726</td>
</tr>
<tr>
<td>Depression, lifetime</td>
<td>44% a</td>
<td>56%</td>
<td>38%</td>
<td>.249</td>
</tr>
<tr>
<td>Manic episode/hypomania</td>
<td>7% a</td>
<td>13%</td>
<td>5%</td>
<td>.570</td>
</tr>
<tr>
<td>ASPD</td>
<td>45% a</td>
<td>81%</td>
<td>30%</td>
<td>.001</td>
</tr>
<tr>
<td>SCID-II</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPD</td>
<td>18% a</td>
<td>25%</td>
<td>15%</td>
<td>.448</td>
</tr>
<tr>
<td>Age matched estimated IQ</td>
<td>89</td>
<td>87</td>
<td>89</td>
<td>.971</td>
</tr>
</tbody>
</table>

Note: a, based on number of participants in the assessment phase (N=56).
According to the MINI Plus psychiatric interview, 40% of the participants in the assessment phase (n=56) fulfilled criteria for alcohol dependence during lifetime, whereas the corresponding number for dependence on illegal drugs (stimulants and cannabis being the most frequent) was estimated to 30%.

Drug dependence was significantly more common in the ADHD cases (100%) compared with the non-ADHD cases (56%). All, but one of the ADHD cases with co-occurring drug dependence reported amphetamine as their main substance of use.

Significantly more women in the ADHD group (81%) met diagnostic criteria for ASPD compared with the non-ADHD group (30%). Overall, women with ADHD showed higher rates of substance use problems and co-occurring psychiatric disorders compared to women without ADHD. For example, manic episodes/hypomania was more common among ADHD cases (13%) than in non-ADHD cases (5%), a similarly BPD (ADHD cases 25% vs.15 % non-ADHD cases), however, these differences were not statistically significant.

### 4.2.2 Validity of the ASRS
The ASRS 6-item screener generated a sensitivity of 1.0, a specificity of 0.66, a positive predictive value (PPV) of 0.55, and a negative predictive value (NPV) of 1.0. The full 18-item ASRS generated a lower specificity (0.45) and a lower PPV (0.42) when the ‘highly probable ADHD’ definition (i.e., having a score ≥24 in either the inattentive or the hyperactive-impulsive symptom dimension) was used.

### 4.3 STUDY III

#### 4.3.1 ADHD measures
The primary outcome measure, change in self-reported ADHD-symptoms in CAARS:SV, did not show any difference between the two conditions in the ITT analysis (p=0.137) or in the completers analysis (p=0.686). Both groups improved their ADHD symptoms from baseline to week 12 (MPH=-19.1, SD=13.2; placebo M=-8.5, SD=19.8) in the ITT analysis (Fig. 2) There was no difference between the groups regarding the proportion of treatment responders (defined as at least at least 30% reduction of ADHD symptoms).
4.3.2 Substance use and other measures

There was no difference between the treated groups in the proportion of urines negative for amphetamine or for other drugs, in time to relapse, in cumulative abstinence, in days of drug and alcohol use (>60 g/day) in TLFB, or in craving. Alcohol use < 60 g/day was significantly less frequent in the MPH group than in the placebo group. Retention in treatment was higher in the MPH group than in the placebo group (84% vs. 59% of the participants were defined as completers) but this difference was not significant. There was no difference in any of the other secondary measures between the two treatment groups.

4.3.3 Safety and Tolerability

Reported adverse events were mild and reversible. Most common were headache and nausea. Only one severe AE was reported in the MPH group, blurred vision, which temporarily occurred in one participant. This was reversible and disappeared with dose reduction. Another participant in the MPH group required reduced dosage due to nervousness.

4.4 STUDY IV

Most of the participants were Swedish-born, chronic intravenous amphetamine users, about 40 years of age and with 9 years of education. The two treatment groups were comparable in terms of the demographics and baseline characteristics.
Table 7. Baseline measures for severity of substance use, psychiatric disorders and criminality for the Methylphenidate (MPH) and Placebo Groups (PL)

<table>
<thead>
<tr>
<th></th>
<th>MPH</th>
<th>PL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, M(SD) y</td>
<td>41 (7.5)</td>
<td>42 (11.7)</td>
</tr>
<tr>
<td>Substance use measures a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age of onset in substance use, M(SD)</td>
<td>13.0 (1.8)</td>
<td>12.2 (2.2)</td>
</tr>
<tr>
<td>Age of onset amphetamine use, M (SD)</td>
<td>18.2 (4.5)</td>
<td>19.3 (7.2)</td>
</tr>
<tr>
<td>Amphetamine use by injection</td>
<td>23 (89%)</td>
<td>25 (93%)</td>
</tr>
<tr>
<td>Age of onset use by injection, M (SD)</td>
<td>20.5 (6.2)</td>
<td>20.8 (5.4)</td>
</tr>
<tr>
<td>Amphetamine use (years) lifetime, M (SD)</td>
<td>20.6 (10.2)</td>
<td>18.3 (12.7)</td>
</tr>
<tr>
<td>Substance use treatment, M (SD)</td>
<td>3.5 (3.1)</td>
<td>4.2 (5.0)</td>
</tr>
</tbody>
</table>

Psychiatric measures-SCID a

<table>
<thead>
<tr>
<th>Additional DSM-IV diagnosis</th>
<th>MPH</th>
<th>PL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axis I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Axis I diagnoses, M (SD)</td>
<td>1.4 (0.7)</td>
<td>1.5 (0.8)</td>
</tr>
<tr>
<td>Axis II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Axis II diagnoses M (SD)</td>
<td>1.9 (1.9)</td>
<td>3.0 (2.3)</td>
</tr>
<tr>
<td>Antisocial personality disorder</td>
<td>17 (63%)</td>
<td>11 (41%)</td>
</tr>
<tr>
<td>Attempted suicide in lifetime</td>
<td>4 (15%)</td>
<td>9 (35%)</td>
</tr>
</tbody>
</table>

Criminality measures b

<table>
<thead>
<tr>
<th></th>
<th>MPH</th>
<th>PL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at the first prison sentence, M (SD)</td>
<td>28.7 (8.7)</td>
<td>27.4 (9.6)</td>
</tr>
<tr>
<td>Prison sentences, M (SD)</td>
<td>10.5 (7.3)</td>
<td>12.3 (8.8)</td>
</tr>
<tr>
<td>Total length of prison sentences, M (SD) months</td>
<td>22.4 (30.9)</td>
<td>14.9 (10.0)</td>
</tr>
<tr>
<td>Length of current prison sentence, M (SD) months</td>
<td>5.30 (3.76)</td>
<td>6.89 (6.07)</td>
</tr>
</tbody>
</table>

a Interview data, b Register data

4.4.1 Substance use measures

Figure 3a shows the proportion of drug negative urine samples for the two treatment groups. The ITT analysis of the primary efficacy variable showed a significant difference in the proportion of drug negative urines in the MPH group (Md=23%, n=27) compared to the placebo group (Md=16%, n=27) (U=250, z=-1.985, p=0.047, r=0.27). Similarly, the secondary analysis (Fig. 3b) showed significantly more amphetamine negative urine samples in the MPH group (Md=23%, n=27) compared to the placebo group (Md=14%) (U=230, z=-2.340, p=0.019, r=0.32). The same pattern was obtained when analysing for other drugs only (MPH group: Md=44%, n=27; placebo group: Md=29%, n=27) (U=242, z=-2.136, p=0.032, r=0.29) (Fig. 3c). Completer's analysis was omitted due to lack of statistical power.
Figure 3. The proportion of negative urine-toxicology after release from prison (week 3 to week 24) for the two treatment groups; methylphenidate (MPH) and placebo over 24 weeks of treatment: (3a) any drugs (amphetamine + other drugs), mean difference 95% CI 0.05-0.32, (3b) amphetamines only, mean difference 95% CI 0.07-0.36 and (3c) other drug, mean difference 95% CI 0.02-0.25.

To test the robustness of the results, we conducted several tests of sensitivity. Firstly, urine samples that were missing in prison (due to administrative aberrations e.g., shortage of staff, staff not complying with study protocol etc.), were omitted and only the urines in the outpatient phase were analysed. Secondly, samples during the prison phase were recoded as negative (refusal was still coded as positive). These imputations of outcome measures did not change the results.

Median retention to treatment, defined as time to six consecutive positive or missing urines, for the MPH group was 162 days compared to 33 days for the placebo group (U=176, z=-3.269, p=0.001, r=0.44). Time (days) to first positive urine for any drug was significantly shorter for the placebo group (Md=15 days, n=27) compared to the MPH group (Md=29 days, n=27) (U=199, z=-2.879, p=0.004, r=0.39), as was time to
first amphetamine positive urine (MPH: Md=25; placebo: Md=16) (U=188, z=-3.068, p=0.002, r=0.42).

4.4.2 Subjective measures

Compared to the placebo group, the MPH group showed significantly greater improvement in ADHD symptoms in CAARS:SV; all symptoms (95% CI: -14.18 to -3.28) (p=0.002) (Fig. 4a in ), inattention (95% CI: -7.0 to -1.59; p=0.026) and hyperactivity (95% CI: -6.95 to -1.59; p=0.002) Seventeen patients (65%, n=26) in the MPH group, decreased symptoms of inattentiveness or hyperactivity by at least 30%, considered as clinically relevant reduction, compared to 7 patients (27%, n=26) in the placebo group (p=0.012).

In addition, in the ITT analysis, clinician-rated severity of symptoms in CGI-S were significantly decreased (p=0.039) from baseline to LOCF, in the MPH group, but not in the placebo group (p=0.688), however, there was no significant difference between the treatment groups in clinician rated improvement in CGI-I.

Changes in other psychiatric symptoms did not differ between the groups.

Twenty-one patients (79%) in the MPH group and 16 patients (59%) in the placebo group completed the titration period. In the MPH group, 17 patients (63%) were stabilized on 180mg, three (11%) on 144 mg and two (7%) on 96 mg/day.

The two treatment groups did not differ with regard to craving at week 12 or 24 using LOCF. During the medication titration (week 1-4), the MPH group decreased their craving scores more compared to the placebo group (Fig. 4b). This difference reached significance (95% CI -15.30 to -0.11, p=0.047) at week three and showed a strong trend at week four (95% CI -14.78 to 0.11, p=0.053).

Changes in other psychiatric symptoms did not differ between the groups.

Figure 4. Change in ADHD symptoms (4a) and craving (4b) over 24 weeks of treatment.
4.4.3 Safety measures

Adverse events were generally mild to moderate. Nausea, stomach pain, sweating, loss of appetite and interrupted sleep were reported more often in the MPH group (Table 8). There were no reports of any unexpected adverse events. At week 5 in treatment, one participant in the placebo group reported suicidal ideation and was taken out of the study. Two others in the placebo group required dose reduction because of high blood pressure and one because of palpitations. In the MPH group, the dosage was reduced for three participants for following reasons: high blood pressure, tense jaw and feeling edgy.

Table 8. Frequency of adverse events in respective treatment group.

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>MPH n=27</th>
<th>Placebo n=27</th>
<th>MPH n=27</th>
<th>Placebo n=27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Sleep problems</td>
<td>6</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>7</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Depressed mood</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Increased blood pressure</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Sweating</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Craving</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Chest pain</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Blood pressure, pulse or weight did not change significantly from baseline to LOCF in the MPH group (Table 9) and there were no significant difference in these measures between the groups.

Table 9. Blood pressure, pulse and weight for the methylphenidate group from baseline to LOCF.

<table>
<thead>
<tr>
<th>Methylphenidate group</th>
<th>Baseline</th>
<th>LOCF</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic mmHg</td>
<td>129.6±11.2</td>
<td>134.4±16.2</td>
<td>.901</td>
</tr>
<tr>
<td>Diastolic mmHg</td>
<td>83.7±8.1</td>
<td>83.7±12.4</td>
<td>.163</td>
</tr>
<tr>
<td>Pulse bpm</td>
<td>71.9±4.5</td>
<td>91.7±12.5</td>
<td>.090</td>
</tr>
<tr>
<td>Weight kg</td>
<td>86.1±11.6</td>
<td>84.1±12.8</td>
<td>.383</td>
</tr>
</tbody>
</table>

In the MPH group, the compliance to the study medication was 0.83 (SD 0.25), calculated as the mean proportion of MPH positive urines of all the urine samples.
provided in this group (missing urines excluded). At week 12, 29% of the participants in the MPH group visited the clinic compared to 7.4% in the placebo group.
5 GENERAL DISCUSSION AND CONCLUSIONS

The present thesis investigates two important aspects of co-existing ADHD and SUD; prevalence and treatment. The included studies show that ADHD is prevalent in adults seeking treatment for SUD and that the rates of substance use and ADHD are high in incarcerated women. In addition, the results suggest that MPH pharmacotherapy for ADHD and co-existing amphetamine dependence is feasible and safe and that higher doses of MPH result in better outcomes compared to placebo.

5.1 EPIDEMIOLOGY

The bidirectional relationship of ADHD and SUD is acknowledged in the literature. Higher rates of psychiatric comorbidity, including ADHD, are reported in clinical compared to population samples of individuals with SUD. However, comparison between studies is difficult because of methodological differences resulting in a wide range of prevalence estimates. Study I, to our knowledge, is the first multinational study of the prevalence of ADHD in adult treatment seeking SUD patients, aiming to overcome some of these obstacles by using similarly structured methods of assessing ADHD across countries.

As expected, the total rates of both childhood ADHD and persistent ADHD (13.8%; 95% CI: 11.9-15.6%) were considerably higher in treatment seeking SUD patients than estimates in the general population (6-9% childhood; 2.5% adult) (Kessler et al. 2005, Simon et al. 2009). This finding, DSM-IV ADHD-NOS excluded, is lower compared to the ADHD prevalence of 23.3% (95% CI 17.7-30.1%) in adult treatment seeking SUD patients reported in a recent meta-analysis (van Emmerik-van Oortmerssen et al., 2012). The rigorous methodology (extensive psychiatric interview and requirement of childhood ADHD for diagnosis of adult ADHD) used in Study I may explain why our finding is at the lower end of the range of prevalence rates reported previously.

The rate of adult ADHD based on the DSM-IV-TR NOS criteria (allowing for a later age of onset) was almost identical with the proposed DSM-5 criteria (age of onset <12 and 5/9 symptoms in individuals aged >17) (http://www.psych.org/practice/dsm/dsm5). Hence, the proposed DSM-5 adaptations of the diagnostic criteria seem not to have any practical impact on the prevalence rates of adult ADHD in SUD.

Our results show large country variation of adult ADHD rates (ranging from 5.4% in Hungary to 31.3% in Norway). Post-hoc analyses showed that this large variation was mainly caused by the high prevalence rates in the Nordic countries (Norway and Sweden) independent of gender, age, occupational status, housing and marital status. Given that this is a true difference, there may be several explanations. One hypothesis that has been forwarded is that geographical latitude may be related to circadian rhythm.
(Friborg et al., 2012), which in itself might be related to ADHD (Snitselaar et al., 2013) and substance use (Kosobud et al., 2007). This is supported by a recent meta-analysis by Arns et al. (Arns et al., 2013) who found that solar intensity (SI) explained 34%-57% of the variance in ADHD prevalence rates (in USA and 9 non-US states). High SI was a protective factor possibly via improving circadian clock disturbances (Arns et al., 2013). Another explanation may be differences in the recognition of ADHD as frequently coexisting with SUD, resulting in higher treatment availability for co-occurring ADHD and SUD in certain countries. This may influence the population seeking treatment. Lastly, the difference in ADHD rates between the participating countries may be an artefact of methodological deviances in spite of the efforts made to standardize the assessment procedure between the participating sites.

Another interesting finding in Study I was the higher rates of ADHD in treatment seekers with illicit drugs as their primary substance compared to primary alcohol users. However, the notion that substance users with ADHD would explicitly choose certain type of drugs such as illicit stimulants to self-medicate ADHD symptoms has not been supported by the data; rather, various substances are used for self-medication related to psychiatric symptoms in a broad sense (Wilens et al., 2007). No substance of choice in individuals with ADHD and SUD has been identified (Biederman et al., 1995, Clure et al., 1999). Drug use patterns seem more culturally and sub-culturally defined. In the present study subsamples of participants with different primary drug were too small to draw conclusions as to prevalence rates by preferred drug.

The high rate of ADHD in drug users is also evident in incarcerated women of Study II. All women with ADHD also met criteria for SUD and all but one were amphetamine dependent. This is not so surprising as amphetamine is the most frequently used i.v. drug in Sweden and common in male and female prisoners (Hakansson et al., 2009). Drug use was frequent in the whole sample of incarcerated women as was the rate of psychiatric comorbidity. This is in line with prior studies reporting high rates of SUD and other psychiatric disorders (such as post traumatic stress disorder, ASPD and major depression) in female offenders, rates that are higher than in their male counterparts (Lewis, 2006). However, at the time of planning and completion of Study II, few estimates of ADHD in adult female offenders were available. There may be several explanations for this lack of focus on ADHD in women prisoners. ADHD was previously regarded exclusively as a childhood disorder affecting mainly boys. Moreover, the proportion of women in correctional services is much smaller compared to men (in Sweden 10:1) explaining the socio-economic incentives to focus firstly on male offenders. With growing awareness of the often persistant nature of ADHD more studies regarding the disorder in female offenders are emerging. The estimates vary between studies, but they all report highly elevated rates of ADHD in both female and male criminal offenders compared to general population surveys e.g (Cahill et al., 2012, Edvinsson et al., 2010, Eyestone and Howell, 1994, Ginsberg et al., 2010, Gunter et al., 2008, Hennessey et al., 2010, Rasmussen et al., 2001, Rosler et al., 2004, Rosler et al., 2009b, Young et al., 2011).
Collectively, these findings suggest that worldwide, a significant number of individuals with SUD are afflicted with ADHD. It is important that more attention is given to adult ADHD in addiction treatment centres and in criminal justice systems in order to address the clinical needs of this population.

5.2 PHARMACOTHERAPY

The high rate of ADHD in SUD populations and the negative outcomes associated with both disorders, separately and in co-existence, emphasise the necessity of developing effective treatments for ADHD with co-occurring SUD.

In this thesis, the efficacy and safety of two different dose regimes, 18-72 mg/day and 18-180 mg/day, of OROS MPH was investigated for treatment of ADHD in amphetamine dependent individuals. The study populations in in Study III were men and women seeking treatment at an addiction clinic and incarcerated men in Study IV. Individual CBT was provided as part of the treatment in both treatment arms in both trials, although the focus of CBT was slightly different; ADHD in Study III and relapse prevention in Study IV. In Study III both the MPH and the placebo group improved in their ADHD symptoms but no significant difference was found between the two treatment arms either in ADHD-symptoms or in drug use. These findings are in line with results from other studies investigating MPH in ADHD and co-occurring SUD (Carpentier et al., 2005, Levin et al., 2007, Levin et al., 2006a, Schubiner et al., 2002).

The previous lack of treatment efficacy for MPH in ADHD populations with SUD may have several explanations. The published RCTs of MPH for ADHD in adult SUD populations in outpatient settings (Levin et al., 2007, Levin et al., 2006a, Schubiner et al., 2002) have all provided additional CBT treatment along with the medication. CBT in adults with ADHD has shown to be effective with moderate effect size (Safren et al., 2006) therefore, it has been suggested that the improvement as a result of psychosocial treatment would mask the medication effect (Riggs et al., 2011, Thurstone et al., 2010, Wilens and Morrison, 2012). CBT trials in adults with ADHD have included participants on medication (Safren et al., 2005, Solanto et al., 2010). Up to date no trials of psychosocial treatment in comorbid ADHD and SUD have been reported.

An important factor to consider is a requirement of abstinence from illicit drugs before the medication is started, as a negative urine sample at intake to a treatment program is found to predict better outcome in psychosocial treatment (Stitzer et al.2007). Compared to placebo, atomoxetine improved ADHD symptoms in abstinent (minimum 4 days) alcohol dependent patients with co-existing ADHD (Wilens et al. 2008). However, 0.6 mg/kg/day MPH compared to placebo, failed to show efficacy in inpatients with various types of SUD and ADHD with a minimum of three weeks of abstinence (Carpentier et al. 2005), whereas a similar dose level of MPH showed efficacy in adults without SUD (Wender et al., 2011). Although there was no
significant difference in improvement of ADHD symptoms or drug use between the MPH and placebo arms in Study III (with a minimum of two weeks abstinence at randomization), the MPH group improved their ADHD symptoms more than the placebo treated, with an effect size of 0.6, indicating that given a larger sample size this difference might have reached significance. Results from these studies suggest that although abstinence as a prerequisite for medication may be an important factor, it is not sufficient to explain the poor treatment effect in trials evaluating MPH in co-morbid ADHD and SUD.

A common denominator in clinical trials of MPH in adults with ADHD and SUD conducted to date has been the dose (60-90 mg/day) tested. While this dose level may be effective in patients without a history of SUD, it could be an insufficient dosing for the SUD population and might explain the poor treatment effects seen in earlier clinical trials (Levin et al., 2007, Levin et al., 2006a, Schubiner et al., 2002). Evidence from brain imaging studies suggest that long-term drug use may down-regulate brain dopamine systems in chronic drug-dependent individuals (Volkow et al., 2004) leading to increased tolerance to stimulants. Thus, a patient with a long history of daily illicit use of up to several grams of amphetamine is likely to need a higher dose of MPH to reduce ADHD symptoms, than previously stimulant-naïve patients. Clinical experience indicates a significant individual variation in clinically effective doses (Wilens et al., 2011) with some individuals requiring a higher dose of stimulants to achieve a clinical response. Taken together, this suggests that a wider range of doses is needed to evaluate the efficacy and safety of MPH in substance dependent patients with ADHD.

Consequently in Study IV, the MPH doses evaluated ranged from 18 to 180 mg/day. Compared to placebo, MPH significantly reduced relapse to substance use (including amphetamine, the primary drug of abuse), decreased self-reported ADHD symptoms, decreased clinician rated severity of symptoms, and resulted in higher retention to treatment. Although the primary drug of abuse in this population was amphetamine, the effect of treatment with MPH was also investigated for other illicit substances since individuals with SUD often use more than one type of drug. By screening for other commonly used drugs (in addition to amphetamine), the aim was to detect any potential risk of patients diverging in their drug use pattern to other illicit drugs while in treatment.

A minimum of two weeks abstinence was a prerequisite to be included in the trial, as it was hypothesised that treatment of ADHD would be more clinically meaningful in abstinent individuals, both in order to measure the risk for a relapse and any change in ADHD-symptoms which may otherwise have been confounded with drug-induced symptoms. It may also be considered clinically less meaningful to assess the level of functional impairment with regard to ADHD in individuals who are currently using drugs.
The clinical concern of potentially inducing craving and thereby triggering relapse during titration of stimulant medication in abstinent substance-dependent individuals is not supported by results from Study III or IV. Instead, in Study IV craving decreased significantly in the MPH group compared to the placebo group during the titration phase. This is also corroborated by a laboratory study of MPH in cocaine-dependent patients (Volkow et al., 2010), where there was no increase in cocaine craving suggesting that the context of use may influence the subjective effects and abuse potential.

Another important factor to consider in the treatment of ADHD in co-existing SUD is the medication formula. The reinforcing effects of stimulants are associated with rapid changes in serum concentration (Volkow et al., 2004), and extended release preparations of MPH are associated with less stimulant-like drug effects (Spencer et al., 2006). The OROS MPH is more difficult to use via a non-oral route (e.g., injection or intranasal use), thereby lowering the risk of abuse and diversion. However, abuse and diversion of medication should always be a concern in SUD treatment and measures should be taken to provide a treatment setting that enhances medication compliance.

The adverse events of MPH are generally mild to moderate, but long-term safety data for MPH or other stimulant medications for ADHD in adults is largely lacking. There is a concern from earlier studies for an increased risk of cardiovascular events (Hammerness et al., 2009). In the present studies, there was no significant difference with regard to changes in blood pressure or pulse rate. A recent study by Stevens et al (Stevens et al., 2010) found no association between high doses of OROS MPH with unusually elevated plasma concentration of MPH, or clinical toxicity. However, some individuals are sensitive to the cardiovascular effects of MPH, and blood pressure and pulse should always be carefully monitored.

Taken together, the results from the present clinical trials show that MPH given in structured settings is efficacious and safe to use in currently abstinent amphetamine dependent individuals with ADHD. A flexible dose range with a higher maximum dose improved ADHD symptoms, clinical condition and retention in treatment, and reduced the risk for relapse to illicit drug use.

Further research is needed to identify predictors for treatment response in this comorbid population. Although a majority of patients with ADHD (without SUD) benefit from pharmacotherapy, substantial numbers of individuals experience little or no effect. Our results suggest that higher doses of MPH are efficacious in this comorbid population but these results need to be replicated. Studies also need to systematically evaluate the neurocognitive and neurobiological effect of different doses, including long term follow up. With new medication formulas and compounds with less abuse liability resulting in less concern about medication deviation, pharmacological treatment may become more accessible also in this comorbid population. Importantly, non-pharmacological treatment alternatives should also be studied in this population. Even though pharmacotherapy improves ADHD symptoms and every day
functioning, individuals with ADHD have persistent difficulties that need to be addressed. Considering that individuals with ADHD present a heterogeneous clinical picture, often with additional symptoms such as emotional dysregulation, a broad range of treatments is warranted.

5.3 METHODOLOGICAL ASPECTS

This section provides reflections of the strengths and limitations of the studies included in this thesis.

Strengths of Study I include a large sample based on a similar recruitment strategy across different countries and sites, using identical instruments for the assessment of adult ADHD in several countries. However, there are several limitations to consider. Because of the lack of information about the initial number of referred patients and the dropout rates in some countries, it remains unclear to what extent the sample is representative of adults seeking treatment for SUD. Although the participants dropping out from the full assessment stage of the study were very similar to those who participated, the possibility that there were ADHD related differences that could have biased the estimates of ADHD cannot be fully discounted. In addition, requiring sustained abstinence as a criterion for inclusion might have resulted in more reliable information, but would have potentially excluded others, such as the more severely dependent participants, thereby leading to a possible underestimation of the prevalence of ADHD. Moreover, the selection of treatment centres within the various countries was not random and the observed differences in prevalence might be a result of selection bias at the centre level. Finally, we had limited data on reliability among interviewers in diverse locations. However, all interviewers at all sites were extensively trained using the same training manuals for all assessment instruments.

Strengths of the study II were the sound methodology for diagnosis of ADHD, and that the entire female prison population was targeted. The dropout rate in Study II was high and it is therefore difficult to generalise the results, however, Edvinsson et al (Edvinsson et al., 2010) found almost identical rates of ADHD in a sample of incarcerated women in one of the prisons for women (Hinseberg), supporting the assumption that the dropout in our study was random.

Study III and IV have important limitations to be considered when interpreting the results. The sample sizes were relatively small and the findings need to be replicated. The attrition rate in Study IV, although significantly lower in the MPH group, was overall high although confounded by per protocol exclusion following 6 consecutive positive urines. Release from prison is a critical time-point with a high risk of relapse in substance use. The investigators had no means of checking whether the dropouts, although chronic amphetamine users, in fact relapsed to substance use for the remaining trial period. In SUD treatment trials, missing data are generally assumed to be positive, i.e. to represent
relapse to drug use. By weighing the missing data by 0.9, in study IV, we aimed to decrease a potential positive bias in favour of active medication.

Another limitation concerns the blinding. Although efforts were made to maintain blinding, 48% of the participants receiving MPH in Study IV, and 48% of the placebo treated correctly identified their medication during the titration phase or after reaching the maximum dose. However, many of the participants in both treatment groups remained uncertain (41% MPH, 26% placebo) or were wrong (11% MPH, 26% placebo) about which treatment arm they were allocated to.

Strengths of the present RCTs include predefined definitions of compliance, strict adherence to protocol, no interim analysis and one single objectively verifiable primary outcome measure. Additional strengths in Study IV were the trial length, dose range and highly clinically relevant outcome measure.

In Study IV the completer rate (how many pills were received) is, to some extent, influenced by the safety measures taken during the trial. If a participant had relapsed in amphetamine use he sometimes did not receive the study medication because of safety reasons, this decision being based on clinical judgment.

To conclude, although rigorous methodology used in the studies there are several limitation to consider when interpreting the data.

5.4 CLINICAL IMPLICATIONS

- High prevalence rates of ADHD in individuals at addiction treatment centres and in prisons highlight the need for screening for and diagnosing of ADHD. ASRS appears useful as a screener in these populations.

- With knowledge of the difficulties individuals with ADHD face in everyday life, treatment should be easily accessible and accommodate these difficulties i.e. provide flexibility but in structured settings.

- Abstinence before initiation of MPH pharmacotherapy and a larger dose range appears to result in better efficacy.

- Efficient treatment strategies that take ADHD-symptoms into account could enable the offenders to better access the psychosocial treatment programmes provided in prison.
6 SVENSKSPRÅKIG SAMMANFATTNING

Alkohol- och narkotikaberöende är ofta förknippat med negativa livserfarenheter och psykiskt lidande. Detsamma gäller ADHD (uppmärksamhetsstörning med hyperaktivitet). Det övergripande syftet med denna avhandling var att undersöka förekomst och behandling av ADHD bland personer med substansberoende.


**Studierna III och IV** var kliniska prövningar av läkemedlet metylfenidat (Concerta™) för behandling av ADHD hos personer med amfetaminberoende. Deltagarna i studierna randomiserades till placebo (sockerpiller) eller Concerta™. Studie III pågick under 12 veckor och undersökte en daglig dos av 18-72mg/dag Concerta™ för patienter (män och kvinnor) som sökte vård på en beroendeklinik. Det primära utfallsmåttet var förändring av ADHD-symptom. Studie IV var en 24-veckors klinisk prövning som undersökte 18-180 mg/dag Concerta™ för amfetaminberoende män som var intagna på en kriminalvårdsanstalt. Deltagarna påbörjade behandlingen inom två veckor före frigivning från fängelset och fortsatte behandlingen som öppenvårdspatienter på Beroendecentrum Stockholm. Det primära utfallsmåttet var återfall i missbruk mätt med övervakade urinprov. I studie III förbättrades båda behandlingsgrupperna med avseende på ADHD-symtom jämfört med baslinjemätningen men det fanns ingen statistiskt säkerställd skillnad mellan grupperna, varken i förändring av ADHD-symptom eller avseende återfall i missbruk. I studie IV resulterade behandling med metylfenidat i fler negativa urinprover (utan spår av narkotika), förbättring av ADHD-symtom och att flera stannade kvar i behandling.

Sammanaget visar resultaten från de epidemiologiska studierna att en avsevärd andel av personer med missbruk/beroende även uppfyller diagnostiska kriterier för ADHD. För att kunna bemöta behovet av behandling och stöd hos personer med ADHD är det viktigt att detta uppmärksammas av vårdgivare, framförallt beroendevården och kriminalvården. Resultatet från läkemedelsprövningarna visar att behandling med metylfenidat under strukturerade förhållanden kan vara ett säkert behandlingsalternativ för personer med samtidig ADHD och amfetaminberoende. Individuellt anpassad dos, med högre maximal dos, resulterade i minskade ADHD symtom, bättre kliniskt allmäntillstånd och högre kvarstannade i behandling. Dessutom minskade risken för återfall i missbruk hos denna grupp personer med mångårig beroendesjukdom.
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