ADHD in treatment seeking patients with a substance use disorder
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Citation for published version (APA):

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CHAPTER 1

THE CONCEPTS OF SUD AND ADHD AND THE LINK BETWEEN THESE TWO DISORDERS
Substance Use Disorders: concepts, prevalence and treatment seeking

Concepts
Substance abuse and dependence are defined as maladaptive patterns of substance use leading to clinically significant impairment or distress (APA, 1994). Recently, Van den Brink and Schippers (2008) wrote a short history of the changing views on substance dependence. In their review, they more or less chronically listed the Moral Model (moral weakness constitutes the basis of habitual drunkenness and thus addiction is a choice and a person’s own responsibility), the Pharmacological Model (the addictive nature of the substance leads to addiction), the Symptomatic Model (substance abuse is not a disorder in itself, but it represents a symptom of an underlying character or personality disorder), the Disease Model (with uncontrolled substance use and tolerance as main concepts, leading to the view that abstinence should be the target for treatment), the Psychological Model (substance abuse is a form of learned maladaptive behavior, hence treatment is based on a remodeling of the behavioral patterns involved), and the Social Model (substance abuse is a normal reaction to abnormal circumstances and treatment should be directed to a change in the environment). In 1976, these different models were integrated in the Bio-Psycho-Social Model proposed by Edwards and Gross (1976.) using the concept of the substance dependence syndrome (Li et al., 2007). According to this model, addiction is the result of an interaction between genetic/biological vulnerabilities, psychological characteristics and environmental factors. Since the early 1990’s, the biological aspects of this model are considered to be of crucial importance, leading to the view that addiction is a disease of the brain (Leshner, 1997). In their landmark paper, McLellan et al., (2000) presented convincing evidence that substance dependence is a chronic disease like diabetes, hypertension, and asthma and that substance dependence “should be insured, treated and evaluated like other chronic illnesses” (McLellan et al., 2000, p.1689). Recently, however, Arria and McLellan (2012) noted that this approach has not resulted in sufficient changes in addiction treatment.

To summarize, addiction is currently conceptualized as a chronic relapsing brain disorder with a complex biopsychosocial etiology and the phenotype in current classification systems (DSM-IV; ICD-10) closely resembles the dependence syndrome developed by Edwards and Gross (1976). However, some changes have been made in the classification of addiction in the most recent edition of the DSM: DSM-5 (American Psychiatric Association, 2013).
The three most prominent changes in the description of the phenotype of addiction in DSM-5 are: 1) inclusion of behavioral addictions in the chapter of ‘Addiction and Related Disorders’; 2) removal of the ‘committing illegal acts’ criterion and addition of a ‘craving’ criterion from the menu of symptoms belonging to the core concept of addiction; and 3) elimination of the abuse/dependence dichotomy and combining the symptoms of these disorders into one disorder with different levels of severity. These changes are generally consistent with the original formulation of the dependence syndrome and are thought to be instrumental in the diagnosis and treatment of substance use and related disorders (O’Brien, 2011, p. 106). Since the main part of our studies was executed before the launch of DSM-5, in this thesis mainly DSM-IV Substance Use Disorders (SUD), including substance abuse and substance dependence, will be used.

It is beyond the scope of this thesis to fully discuss the etiology of SUD. Here we only mention those elements of the etiology that are of importance for the link between SUD and ADHD. Although there is growing knowledge about why some individuals become addicted when exposed to drugs or alcohol, whereas others do not, much is still unknown. The literature shows strong evidence for the role of genetic risks (Kendler et al., 2012), neurobiological vulnerabilities (Volkow et al., 2003; 2012), and certain developmental and environmental factors (Sloboda et al., 2012) influencing the genetic and neurobiological vulnerability for and the development of SUD.

Environmental factors are considered more important for initiation and less important for progression to dependence. The reverse is true for genetic factors (Kendler et al., 2012).

Neurobiological features, such as motivation and reward and impaired ability to inhibit intentional actions, are highly relevant as vulnerability factors for the development of SUD (e.g. Goldstein and Volkow, 2002). In addition, some authors also suggest an association between anhedonia or reward deficiency (i.e. diminished pleasure following natural reward) and the development of stimulant dependence (Gawin & Kleber, 1986; Blum et al., 2000; Kalechstein et al., 2002; Leventhal et al., 2008). The dopamine system is strongly involved in expecting and experiencing pleasure, and in feeling good. Hence it is involved in conditioning via motivation and reward (Volkow et al., 2012). Impairments in the motivation and reward system and in the ability to inhibit intentional actions have mayor implications for social functioning, adding to the risk to develop a SUD (Goldstein and Volkow, 2002; Volkow et al., 2012; Chandler et al., 2009; Sanfey, 2007).
In discussing social factors and biological and psychological factors, Glantz and Pickens (1992; p. 9) state: “In general, drug use appears to be more a function of social and peer factors, whereas drug abuse appears to be more a function of biological and psychological processes”. The complex and individually tailored pattern of risk factors for the development of SUD is also discussed by Sloboda et al., (2012). They emphasize the interaction between vulnerabilities and (groups of) risk factors and conclude that "This interaction is bidirectional, i.e. it promotes social selection (e.g. forming friendships with peers having similar characteristics) and social contagion (e.g. influence of peers on individual behavior)” (Sloboda et al., 2012, p. 947).

**Prevalence**

**Alcohol use disorders**

There is a causal relationship between alcohol consumption and the global burden of disease: "The net effect of alcohol consumption on health is detrimental, with an estimated 3.8% of all global deaths and 4.6% of global disability-adjusted life-years attributable to alcohol. Disease burden is closely related to average volume of alcohol consumption, and is strongest in poor people and in those who are marginalized from society. The costs associated with alcohol amounts to more than 1% of the gross national product in high-income and middle-income countries, with the costs of social harm constituting a major proportion in addition to health costs" (Rehm et al., 2009; p. 2223).

In 2005, 45.8% of the adult world population was a lifetime alcohol abstainer, 13.8% had drank before but was currently abstaining from alcohol, and 40.6% was a current drinker. On average, current drinkers consumed 17.1 liters of pure alcohol per year (Shield et al., 2013). Shield and colleagues conclude that "lifetime abstention was most prevalent in North Africa, the Middle East and South Asia" and that "the prevalence of abstention, level of alcohol consumption and patterns of drinking vary widely across regions of the world", with Europe having the lowest abstention rates and the highest consumption levels (Shield et al., 2013, ahead of print, p. 2). In their study extrapolating German figures and costs on alcohol and nicotine consumption to the European Union, Effertz and Mann (2012) conclude that "substance use disorders rank on top of all disorders of the brain in Europe" (Effertz and Mann, 2012, p. 1). An alcohol use disorder is present in 14.6 million European citizens, representing 3.4% of the adult population (Wittchen et al., 2011).
Drug use disorders
Degenhardt and Hall (2012) estimated that 149–271 million people used an illicit drug worldwide in 2009 of which 125–203 million (75-85%) were cannabis users; 15–39 million (10-15%) were problem users of opioids, amphetamines, or cocaine, and 11–21 million (10-15%) injected drugs. They state that the levels of illicit drug use seem to be highest in high-income countries and in countries near major drug production areas. However, there are very limited reliable data for illicit drug use in low-income countries.

Treatment seeking
A large community study in the Netherlands showed a favorable course for DSM-IV alcohol abuse with a remission rate of 81% at 1 year follow-up and 85% at 3 years follow-up. In the same study, DSM-IV alcohol dependence showed a remission rate (no dependence) of 67% at 1 year follow-up and 74% at 3 years follow-up. The authors conclude that their "findings confirm that the 3-year course of alcohol dependence in the general population is far more favorable than findings from treatment-seeking populations" (de Bruijn et al., 2006, p. 391). Similar findings were reported for alcohol and drug dependence in a large community study in the USA (Dawson et al., 2005; Compton et al., 2013). Thus it can be concluded that the majority of AUD and DUD patients in the general population recover without treatment.

Treatment seeking patterns, based on a general population survey of people with a SUD diagnosis in the USA show that treatment seeking varies by region (Kessler et al., 2010). The authors conclude that "While treatment seeking has increased in recent years, it is not clear whether this is because of increased access, increased demand, increased societal pressure or other factors" (Kessler et al., 2010, p. 1065). In addition, Wang et al., (2005) concluded that 53-77% of all SUD patients in the general population in the USA eventually seek help for their problems. However, Gayman et al., (2011) reported that 68% of all young adults (18-23 years; n=672; USA) with SUD had not been seeking treatment yet. Moreover, the remaining 32% sought help with a delay of 1-7 years after initiation of the SUD. This discrepancy can be explained by differences in age as those with a late onset of SUD (> 30 years) are almost 4 times more likely to seek treatment than those with an early onset (Kessler et al., 2001). Also the presence or absence of specific symptoms of the disorder may be associated with the probability to seek treatment (Kessler et al., 2001). Finally, the primary substance of abuse affects the rate of treatment seeking, with the higher rates of treatment seeking in patients using heroin and cocaine compared to non-users of heroin and cocaine (Kessler et al., 2001). For those with an alcohol use disorders (AUD) the percentage of individuals seeking
treatment ranges from only 8% to 25%, (Van Amsterdam & van den Brink, 2012; Alonso et al. 2004).

Attention Deficit Hyperactivity disorder: concepts, prevalence and outcome

**Concepts**

Attention-Deficit/Hyperactivity Disorder (ADHD) is a multifactorial determined developmental neuropsychiatric disorder, based on a genetic predisposition and neurobiological dysregulations (Kieling and Rohde, 2012). The history of the concept goes back to the 18th century and is described by Lange et al., (2012). In 1798, the Scottish physician Alexander Chrichton wrote a book with the title “An inquiry into the nature and origin of mental derangement: comprehending a concise system of the physiology and pathology of the human mind and a history of the passions and their effects”. In the chapter “On Attention and its Diseases” he made a clear distinction between normal inattentive behavior and abnormal inattentive behavior, with the latter showing a large overlap with our modern concept of ADHD (Chrichton, 1798). In the mid 19th century, the German physician Heinrich Hoffmann wrote "Der Struwwelpeter" (Hoffmann, 1948; reprint of the 1844 original) or Fidgety Phil in the English version of 1846 (and many reprints thereafter). In both the famous drawings and the story, Fidgety Phil explicitly shows ADHD like behavior (see the drawings and texts on the next page).

The start of ADHD in modern science in the beginning of the 20th century is ascribed to Sir George Frederic Still (1868–1941) who presented 20 cases of children with a “defect of moral control as a morbid manifestation, without general impairment of intellect and without physical disease” (Still, 1902, p. 1079). He noted: "...a quite abnormal incapacity for sustained attention. Both parents and school teachers have specially noted this feature in some of my cases as something unusual” (Still 1902, p. 1166). Thirty years later, Kramer and Pollnow introduced the concept of Hyperkinetic disease of infancy (Kramer and Pollnow, 1932), and listed the inability to sit still for a second, run up and down the room (Kramer and Pollnow 1932, p. 7), climb about preferring high furniture (Kramer and Pollnow 1932, p. 10) and are displeased when deterred from acting out their motor impulses (Kramer and Pollnow 1932, p. 7), concluding that the abnormal motor activity is the main symptom in children with hyperkinetic disease (Kramer and Pollnow 1932, p. 7).
The Story of Fidgety Philip

"Let me see if Philip can
Be a little gentleman;
Let me see if he is able
To sit still for once at table."
Thus spoke, in earnest tone,
The father to his son;
And the mother looked very grave
To see Philip so misbehave.
But Philip he did not mind
His father who was so kind.
He wriggled
And giggled,
And then, I declare,
Swung backward and forward
And tilted his chair,
Just like any rocking horse;
"Philip! I am getting cross!"

See the naughty, restless child,
Growing still more rude and wild,
Till his chair falls over quite.
Philip screams with all his might,
Catches at the cloth, but then
That makes matters worse again.
Down upon the ground they fall,
Glasses, bread, knives forks and all.
How Mamma did fret and frown,
When she saw them tumbling down!
And Papa made such a face!
Philip is in sad disgrace.
In the 1970s, Ross & Ross (1976) discussed brain damage in children with abnormal behavior and in 1980 the concept of *Minimal Brain Damage* was introduced by Kessler (1980). The same symptoms were, however, already described by Laufer et al., (1957) who mentioned that the same behavioral problems can also occur in children without any history or possible brain damage. This lead to the concept of *Minimal Brain Dysfunction*: "The term minimal brain dysfunction refers to children of near average, average or above average general intelligence with certain learning or behavioral disabilities ranging from mild to severe, which are associated with deviations of function of the central nervous system. These deviations may be manifested by various combinations of impairment in perception, conceptualization, language, memory and control of attention, impulse or motor function" (Clements, 1966, p. 9). Clements further distinguished “[impairment in] control of attention, impulse and motor function” (Clements 1966, p. 10).

With each iteration of the DSM (DSM-II, DSM-III and III-R), the nomenclature changed. DSM-II introduced the concept of *Hyperkinetic reaction of childhood* (APA, 1968), followed by *Attention deficit disorder: with and without hyperactivity* in DSM-III (APA, 1980), and then *Attention Deficit/Hyperactivity Disorder* without a separation between inattentive or hyperactive type in DSM-III-R (APA, 1987). In DSM-IV (APA, 1994), three subtypes were introduced: a predominantly inattentive type, a predominantly hyperactive-impulsive type, and a combined type with symptoms of both pathological dimensions (APA, 1994). This edition of the DSM also introduced the diagnosis of adult ADHD.

Though the existence of adult ADHD is widely accepted, the construct and diagnostic criteria of adult ADHD are still under debate (Fischer & Barkley, 2007; Solanto et al., 2012; Kessler et al., 2010). Some years ago, Barkley et al., (2008) highlighted several problems related to both childhood ADHD (focused on boys rather than girls; symptoms overlap with other psychiatric disorders) and adult ADHD (symptoms are related to children rather than to adults) in DSM-IV. According to Barkley et al. (2008), these problems resulted in the suggested underdiagnosis of adult ADHD due to the requirement of an equal number of symptoms (6 out of 9) for the symptom criterion for childhood and for adult ADHD (Barkley et al., 2008). Despite these serious problems, changes in ADHD-criteria for DSM-5 are relatively minor (American Psychiatric Association, 2013) and the wording of the 18 symptoms will not be changed, but for adults there will be examples related to adult behavior embedded in the description of symptoms. However, a rather important change for adult ADHD in DSM-5 is the higher *Age of onset criterion*: some of the symptoms must be present before age 12 (compared to age 7 in DSM-IV-TR) (Dalsgaard,
2013). In addition, the Number of symptoms criterion for adults has been changed to 5 out of 9 symptoms (compared to 6 out of 9 in DSM-IV-TR) for both of the inattentive and hyperactive/impulsive symptoms (American Psychiatric Association, 2013).

Etiology

As with SUD, it is beyond the scope of this thesis to extensively describe and discuss the etiology of ADHD. Instead, we will briefly present those etiological factors that may be of relevance for the observed link between ADHD and SUD. In general, as for all of the psychiatric and developmental disorders, there is no single factor causing ADHD. In the literature several interdependent biological (genetic/neurobiology) and psychosocial/environmental factors can be found (Nigg, 2012; Shaw et al., 2012; Thapar et al., 2012). Recent neuroimaging studies have shown an altered brain structure and function in specific brain circuits related to the regulation of attention, inhibition/cognitive control, motivation/reward, and emotion (Arnsten et al., 2012; Shaw et al., 2012). For example, children with ADHD showed prominent abnormalities in the inferior prefrontal cortex and its connections to striatal, cerebellar, and parietal regions (Arnsten et al., 2012; Cubillo et al., 2012).

In a recent comprehensive review it is stated that ADHD is familial and highly heritable (Thapar et al., 2013). However the question by what route or routes (exposure to psychosocial/ environmental factors) the vulnerability for ADHD leads to inattentive and/or hyperactive/impulsive behavior, and ultimately to the disorder, has not yet been answered. Even more, it is concluded that "there is a large literature documenting associations between ADHD and a wide variety of putative environmental risks that can, at present, only be regarded as correlates" (Thapar et al., 2013, p. 3). Finally, a significant association between anhedonia and inattentive symptoms of ADHD has been found, suggesting a reward insensitivity problem in ADHD (Meinzer et al., 2012).

Prevalence of ADHD.

The worldwide prevalence of ADHD is estimated to be about 5% in children and adolescents and it is concluded that geographic location plays a limited role in variability of ADHD/HD prevalence estimates worldwide: "This variability seems to be explained primarily by the methodological characteristics of studies" (Polancyk et al., 2007; p. 942). Taking these factors into account, the worldwide prevalence of adult ADHD is estimated in a meta-analysis by Simon et al., (2009) to be 2.5%. Faraone and colleagues performed a meta-analysis on longitudinal studies in ADHD children followed up into adulthood. They reported that when defining only those meeting full criteria for ADHD as having
‘persistent ADHD’, the rate of persistence is low: 15% at age 25 years. But when including cases consistent with DSM-IV’s definition of ADHD in partial remission, the rate of persistence is 65%. They conclude that estimates of ADHD’s persistence heavily rely on how persistence, hence adult ADHD, is defined. They also conclude that, regardless of definition, the prevalence of ADHD becomes lower with age (Faraone et al., 2006). However in a recent general population study in the Netherlands among 1,494 subjects older than 60 years, an ADHD prevalence of 2.8% was reported (Michielsen et al., 2012), i.e. a prevalence fully in line with the 2.5% prevalence reported by Simon et al. (2009) in his meta-analysis in a pooled sample with a weighted mean age of 34 years.

The comparison of the prevalence of ADHD in children/adolescents and adults shows that the disorder disappears in adulthood in many cases. Part of this can be explained by true remission of the disorder. However, Barkley et al., (2008) questioned whether a group of children outgrew their ADHD or outgrew the DSM-IV criteria, suggesting that the ADHD criteria as mentioned in the DSM-IV did not fit adult patients with the disorder.

In summary, the precise persistence rate of childhood ADHD into adulthood is yet unclear. The variability in persistence rates seems to be mainly related to methodological differences between studies and to yet unclear criteria for the condition in adult subjects.

**Long term outcome of ADHD**

Extensive research has shown that the adult prognosis for many ADHD-children is poor. Poor outcome was reported in educational performance (higher rates of being disciplined at school; drop out from school; leaving school without diploma; decreased level of higher educational levels), frequent comorbid disorders (including SUD), increased probability of development into antisocial behavior and crime, more frequent and more severe motor vehicle accidents, and higher levels of divorce and underemployment (Barkley et al., 2008; Nigg, 2012). Furthermore, decreased work productivity was reported: 22 more work loss days per year in ADHD subjects compared to non ADHD subjects according to the WHO World Mental Health Survey Initiative, with data from 10 countries (De Graaf et al., 2008).
ADHD in treatment seeking SUD patients, why is research on this topic important, and what do we already know?

Why is this important?
There are several reasons why we spent so much attention to the comorbidity of SUD and ADHD.

First, the literature on SUD and ADHD is limited when compared to the literature on SUD and other psychiatric syndromes and personality disorders. Depression (Lev-Ran et al., 2013; Conway et al., 2006; Swendsen et al., 2000), anxiety (Lev-Ran et al., 2013; Conway et al., 2006; Lev-Ran et al., 2012; Cheung et al., 2010), Post Traumatic Stress Disorder (PTSD; Antshel et al., 2013; Gielen et al., 2012; Driessen et al., 2008; Bonin et al., 2000), psychosis (Lev-Ran et al., 2013; Addington & Addington, 2007; Degenhardt & Hall, 2001; Jenkins et al., 1997) and personality disorders (Lev-Ran et al., 2013; Langås et al., 2012; Chen et al., 2011; Torrens et al., 2011) are all linked to SUD. For each of these disorders and their link with SUD the knowledge on prevalence, etiology and treatment options is substantial (Lev-Ran et al., 2013; Langås et al., 2012).

Altogether, the quantity of research and as a result, the options for evidence based prevention of SUD development in ADHD patients and for evidence based detection, diagnosis and treatment of ADHD in SUD patients are scarce (Wilens & Morrison, 2012; Carpentier, 2012).

Second, in anxiety, depression and psychotic disorders we may speak of substance induced depression, or substance induced psychosis. Contrary to this, there may be ADHD-like symptoms induced by substance abuse. However, ADHD as a disorder is by definition present before the onset of SUD. Therefore detection, diagnosis and treatment of ADHD may prevent the onset of SUD.

Third, CD and APD are very important risk factors for the development of SUD, and it is well known that ADHD is a risk factor for development of CD and APD (Ivanov et al., 2008; Manuzza et al., 2004). A common pathophysiology for ADHD, other externalizing disorders, APD and SUD as stated in the review by Ivanov et al., (2008) and a more dimensional typology of psychiatric and personality disorders as defined by Kendler et al., (2011) distinguishing between internalizing and externalizing disorders, are both compatible to the National Institute of Mental Health (NIMH) strategy 1.4: “Develop, for research purposes, new ways of classifying mental disorders based on dimensions of observable behavior and neurobiological measures” (NIMH, 2013). Further
research that helps identifying elements of the underlying pathophysiology and risk and protective factors involved in the pathway from childhood ADHD symptoms and from in- and externalizing disorders towards SUD may contribute to these "new ways of classifying mental disorders" as proposed in the NIMH strategy.

What do we know already?
The following four questions will be explored in this paragraph:
1) What is the prevalence of ADHD in treatment seeking SUD populations?
2) a) What is known about the causes of the relation between ADHD and SUD? b) What explanatory models are available?
3) What is known about the accuracy of instruments for the detection of ADHD in treatment seeking SUD populations?
4) What is known about comorbidity patterns in treatment seeking SUD populations with and without ADHD?

1) Prevalence
Recently, Van Emmerik-van Oortmerssen et al., (2012) presented the results of a meta-analysis on 12 prevalence studies in adult treatment seeking SUD patients. Eight out of 12 studies were conducted in the USA. A prevalence of ADHD in these individual studies was reported, ranging from 10.0% to 54.1%. The variability in findings was partly explained by the primary substance of abuse and by the difference in diagnostic instrument. The meta-analysis is part of this thesis and for further results and discussions the reader is referred to chapter 4.

2a) Risk for the development of SUD in ADHD children
In their review of longitudinal studies of ADHD children followed up into adulthood, Lee et al., (2011) summarized the increased risk of SUD in ADHD children compared to non-ADHD controls as follows:
- ever having used nicotine (OR=2.08, CI=1.66-2.60, p<.001);
- ever having used marijuana (OR=2.78, CI=1.64-4.74, p<.001);
- marijuana abuse or dependence (OR=1.58, CI=1.16-2.14, p=.003);
- alcohol use disorder (OR=1.74, CI=1.38-2.20, p<.001);
- cocaine abuse or dependence in adolescence/adulthood (OR=2.05, CI=1.38 3.04, p<.001); and
- overall drug abuse/dependence based on studies without an explicit specification of the primary substance of abuse (OR=2.64, CI=1.77-3.94, p<.001).
2b) Explanatory models
As this thesis focuses on prevalence, screening and comorbidity, explanatory models for the link between ADHD and SUD will be mentioned only briefly.

Pathway via development of Antisocial Personality Disorder
In their review, Flory and Lynam (2003) presented several models for the relation between externalizing disorders, SUD and the role of ADHD:
- ADHD is not an independent risk factor, and the risk related to ADHD is attenuated or disappears after controlling for the presence of Conduct Disorder (CD). Thus, the development of SUD is accounted for by comorbid Oppositional Defiant Disorder (ODD) and/or Conduct Disorder (CD) (Barkley et al., 1990; Molina et al., 2002; Harty et al., 2011; Tuithof et al., 2012);
- ADHD is an important and independent risk factor for the development of SUD, especially for nicotine use and dependence (Hartsough & Lambert, 1987; Milberger et al., 1997; Disney et al., 1999);
- ADHD is a risk factor for the development of CD and then SUD development in subjects with CD kicks in (Flory and Lynam, 2003);
- The combination of ADHD and CD accounts for more severe patterns of SUD than either one of these disorders alone; a model that was recently confirmed in heroin dependent patients (Carpentier et al., 2011, 2013; Flory and Lynam, 2003).

It is not known yet which model or which combination of models represents the real world relationship between ADHD and SUD in the most comprehensive way. However, the important, but non-replicated, results reported by Elkins et al. (2007) provide at least a good start in our thinking about the relationship between ADHD and SUD. They included 1,404 11 year old general population children (694 boys) and assessed them three times: at baseline (11 years), at 14 years and at 18 years. They looked for categorical diagnoses of ADHD and CD and for dimensional measures of ADHD (inattentive vs. hyperactive/impulsive scores) and CD and tested how these categorical and dimensional measures influenced the presence of SUD at age 18. Interestingly the categorical diagnosis of ADHD at 11 years predicted only nicotine dependence at age 18, but when adjusted for the presence of CD, the significance of this finding disappeared. However, the dimensional measures of hyperactivity/impulsivity predicted the presence of both nicotine dependence and cannabis abuse and dependence and these effects remained significant after controlling for CD (Elkins et al., 2007). They also reported significant values for the prediction of SUD for even 1 symptom of ADHD or CD. These findings were supported by
results of a recent study in adolescents with ADHD, with hyperactive/impulsive symptoms predicting smoking (Foster et al., 2012).

Lee and colleagues concluded that the current prospective literature on the link between ADHD and SUD and the role of CD is too scarce to conclude that ADHD does not play an important independent role in the development of SUD (Lee et al., 2011).

The literature suggests that ADHD is probably an independent risk factor for tobacco dependence and probably Drug Use Disorders (DUD), but this might not be the case for Alcohol Use Disorders (AUD). However, the greatest risk is of the development of SUD is for youngsters with a comorbid diagnosis of CD and ADHD, leading to greater a risk for almost every SUD than the presence of a diagnosis of either CD or ADHD alone (Ivanov et al., 2008).

**Neurobiological model of overlap between ADHD and SUD**

Recent studies have shown common genetic vulnerabilities for SUD, ADHD and other externalizing disorders (Arcos-Burgos et al., 2012). As presented in some of the previous paragraphs, also similar brain functions and brain-structures are involved in both SUD (Volkow et al., 2003; 2012) and ADHD (Arnsten et al., 2012; Cubillo et al., 2012; Shaw et al., 2012), including brain areas involved in inhibition, motivation and reward and more general the dopamine system.

In addition, there are similarities in ADHD and SUD in terms of dysfunctional inhibitory processes. What remains unclear is whether the lack of inhibition among those with ADHD is what increases risk for SUD. What is probably true is that once someone has a SUD, dysregulation of the inhibitory system is exacerbated by the excessive use of alcohol and/or drugs (Ivanov et al., 2008).

**3) Accuracy of instruments**

In clinical samples of treatment seeking adult SUD patients, the prevalence of adult ADHD ranges from 10.0% to 54.1% (Van Emmerik-van Oortmerssen et al., 2012). According to these authors, this broad range of prevalence rates is partly explained by the use of different diagnostic instruments.

So far there is only limited data on the accuracy of screening instruments for ADHD in SUD patients (Dakwar et al., 2012). Screening for adult ADHD is not routine practice in many if not most drug and alcohol treatment services (McAweeney et al., 2010). As ADHD is one of many disorders that are present in treatment seeking SUD patients a screening procedure for this disorder should also focus on practical and feasibility aspects, such as complexity of the tool (both for patients and for treatment staff) and time involved. More information on psychometric features of screening tools for adult ADHD in the
population of treatment seeking SUD patients is warranted, both for scientific and clinical reasons.

4) Comorbidity patterns
SUD in treatment seeking subjects is often comorbid with other psychiatric disorders such as Major Depression, Bipolar Disorder, Anxiety Disorders, Borderline, Schizophrenia and Antisocial Personality Disorder (Chen et al., 2011; Chan et al., 2008; Peles et al., 2007; Compton et al., 2000). Adult ADHD is also associated with high rates of comorbid disorders such as Mood and Anxiety Disorders, and Antisocial Personality Disorders (Sobanski, 2006; Wilens & Dodson, 2004; Kessler et al., 2006). Moreover, for those with both ADHD and SUD there is an even further increased risk for comorbidity with Mood and Anxiety Disorders and for Antisocial Personality Disorders (Carpentier et al., 2011; Wilens et al., 2005; King et al., 1999; Levin et al., 1998).

Conclusions of chapter 1
SUD is a brain disease affecting millions of people worldwide with different patterns of remission and treatment seeking behavior for AUD and DUD. Its etiology consists of genetic vulnerabilities and neurobiological abnormalities interacting with personal and environmental conditions.

Eventually the majority of patients with a DUD seek treatment, but often after a delay of many years. In contrast, only a small minority of patients with an AUD seeks treatment. The more severe and deviant the course of SUD, the more likely it is that treatment is sought.

ADHD is a chronic developmental disorder, with a prevalence of about 5% in children and adolescents and about 2.5% in adults with a chronic course in many of them.

ADHD is highly prevalent in treatment seeking SUD patients. However, current prevalence estimates of ADHD in treatment seeking SUD patients vary greatly. Moreover, most studies on the prevalence of ADHD in SUD population have been performed in the USA. So far, variability in prevalence rates are mainly ascribed to differences in populations and to methodological issues and inconsistent criteria for the condition in adulthood.
Many children with ADHD grow up with serious consequences such as educational problems, other psychiatric disorders, social/relationship problems, occupational problems, motor vehicle accidents, suicidal behavior and suicide, and excessive substance use or SUD in later life. Prospective studies of children with ADHD, with a follow up into adulthood, show this increased risk for SUD. However there is debate on the role of comorbid CD and the development of Antisocial Personality Disorder (APD). Some of the researchers therefore conclude that ADHD is not an independent risk factor for the development of SUD and that comorbid CD during adolescence and APD in adulthood fully account for this risk. A growing consensus emerges that ADHD affects the course of SUD in such a way that the latter has a more chronic, complex and severe course in CD+ADHD subjects than in subjects with either CD or ADHD only (Flory & Lynam, 2003; Lee et al., 2011). A minority of studies conclude that ADHD is an independent risk factor. However, so far only one of the studies differentiated between the causal role of ADHD subtypes, i.e. the different role of inattention and hyperactive/impulsive symptoms. This study found that impulsive/hyperactive symptoms of ADHD were a strong independent risk factor for SUD development (Elkins et al., 2007).

Finally, it should be noticed that the literature on screening for adult ADHD in treatment seeking SUD populations is scarce.

This thesis tries to improve our knowledge on these issues.