ADHD in treatment seeking patients with a substance use disorder

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9.1 Summary

9.1.1 ADHD in treatment seeking SUD patients

In chapter 3 we reported on a Dutch project, running from 2000 to 2004, aimed at the development and practical testing of diagnostic procedures and treatments of adult ADHD in treatment seeking patients with a substance use disorder (SUD). This project was based mainly on professional experiences, because at that time, there was very little scientific evidence for effective screening, diagnosis and treatment of adult ADHD in SUD patients. In the Netherlands, as in many other countries outside the USA, there was concern to what extent intoxication and withdrawal would mimic ADHD symptoms and lead to false diagnoses of adult ADHD. Moreover, there was concern that stimulant medication may lead to relapse in Substance Abuse and to abuse and diversion of the medication.

Apart from the protocol for screening, diagnosis and treatment of SUD patients with comorbid ADHD (Van de Glind et al., 2004), which has been broadly used in the Netherlands since it was presented, the project had a variety of other important results:

1) For the first time, there was an estimation of the prevalence of adult ADHD in treatment seeking SUD patients in the Netherlands: 12%.
2) The practical experience from this project showed that ADHD patients can be identified and properly diagnosed in treatment seeking SUD patients.
3) The project indicated that psycho-stimulant medications could be used safely and reliably in this high risk patient group. Unexpectedly, professionals working with the protocol agreed on methylphenidate as the first line treatment.
4) Positive experiences were reported on the combination of medication with psycho-education and training procedures related to ADHD problems (like planning, financials, social network etc.).
5) Eight of 12 interviewed SUD patients diagnosed with ADHD reported that they were never diagnosed with ADHD before, suggesting that many adults in addiction treatment centers with adult ADHD, were not diagnosed nor treated for this disorder before this project.

Since this early project described in chapter 3, several papers contributed to the issues of diagnosis and efficacy and safety of pharmacological treatment of adult ADHD in SUD patients (e.g. Fatséas et al., 2012; Carpentier, 2012; Levin,
2007). In addition, Levin (2007) made us aware of the high rate of other comorbid disorders in ADHD patients, the presence of cognitive deficits in SUD patients and their influence on the ability to recall ADHD symptoms in childhood. Moreover, she warned us for the fact that intoxication and withdrawal symptoms may mimic ADHD symptoms and that patients may fake ADHD symptoms in order to get prescriptions for stimulant medication. Hence, it seemed that diagnosis and treatment of ADHD in this population is possible, but that it requires state of the art diagnostic procedures and scientifically informed treatment decisions.

Our initial conclusion on the safety of stimulant medication for treatment seeking SUD patients with comorbid adult ADHD was confirmed by recent reviews of the literature (Mariani and Levin, 2012; Pérez de Los Cobos et al., 2012; Wilens & Morrison, 2012; Kollins, 2008; Faraone & Wilens, 2007; Upadhyaya, 2007). These authors also stressed the importance of careful management of this treatment, of striving for abstinence of substance abuse before starting up medication treatment, titration, monitoring of therapeutic benefits and side effects, and monitoring of substance abuse in order to weigh the risk and benefits of stimulant treatment.

Later findings of pharmacological treatment of ADHD in SUD populations showed limited effects (Carpentier, 2012). In paragraph 9.3 (p. 159) we will further elaborate on the topic of treatment of patients with ADHD and SUD.

In chapter 4 we reviewed the literature on the size of the problem, i.e. the prevalence of adult ADHD in SUD populations. A total of 29 studies of good quality were included, including studies in adolescents (15 studies) and adults (14 studies) with some studies performed in the general population (3 studies) and others in addiction treatment centers (26 studies). Twelve of the 29 studies focussed on treatment seeking adult SUD patients. The prevalence of adult ADHD in this group was 23.3% (C.I. 17.7 – 30.1 %) ranging from 10.0 to 54.1% in individual studies. The studies that were included were published between 1983 (Wood et al., 1983) and 2009 (Daigre Blanco et al., 2009). Hence, these studies used different versions of the DSM (DSM-III, DSM-III-R, DSM-IV), although adult ADHD was mentioned first only in the DSM-IV (APA, 1994). In a meta-regression analysis, we showed that cocaine dependence was associated with a lower ADHD prevalence rate than alcohol dependence, opioid dependence and other addictions and that studies using the DICA or the SADS-L for the diagnosis of ADHD resulted in significantly higher comorbidity rates than studies using the KSADS, DISC, DIS or other assessment instruments (Van
Emmerik-van Oortmerssen et al., 2012). It was concluded that further studies were needed to better understand the variability in ADHD prevalence between the studies.

Our meta-analysis on the prevalence of ADHD in SUD patients failed to mention two other important issues:

1) The need for a feasible and valid instrument for the screening of adult ADHD in treatment seeking SUD patients in order to enhance case finding and treatment of subjects with SUD and adult ADHD;

2) The need for a better understanding of the overlap of ADHD, Antisocial Personality Disorder (APD), and other externalizing disorders such as Bipolar Disorder (BD) and Borderline Personality Disorder (BPD).

9.1.2 Background, methods and population characteristics of the International ADHD in Substance use disorders Prevalence (IASP) study.

In Chapter 5 we reported on the background, methods and population characteristics of the IASP study. The IASP study is an international cross-sectional two-staged and multi center study. A total of 10 countries participated in the study: three countries only in stage 1 [USA (n=130), Belgium (n=371) and Australia (n=462)] and seven countries in stage 1 and stage 2 [France (n=216), Hungary (n=343), the Netherlands (n=403), Norway (n=487), Spain (n=432), Sweden (n=325), Switzerland (n=389)]. Non-participation in the stage 2 assessment resulted in the following numbers for stage 2: France (n=157; 72.7%), Hungary (n=226; 65.9%), the Netherlands (n=129; 32.0%), Norway (n=220; 45.2%), Spain (n=222; 51.4%), Sweden (n=168; 51.7%) and Switzerland (n=154; 39.6%). Thus the total number of ASRS screenings was 3,558 for all 10 countries: 963 in those countries participating only in stage 1, and 2,595 in the countries participating in both stage 1 and stage 2. Of the latter subjects, 1,319 dropped out and 1,276 completed the second stage ADHD-diagnostic interview (CAADID).

The ASRS (Kessler et al., 2005, 2007) is an 18 item self-report questionnaire. The first 6 items are used for screening for adult ADHD. The CAADID is a frequently used semi-structured diagnostic interview for diagnosing adult ADHD (Arcos-Burgos et al., 2010; Daigre et al., 2009; Epstein et al., 2001; Epstein & Kollins, 2006; Medori et al., 2008; Ribasés et al., 2009).
The overall prevalence of ASRS positives in all 3,558 SUD patients was 40.9%, which is fully in line with previous research in SUD subjects using the ASRS (Adler et al., 2009; Daigre et al., 2009; Chiasson et al., 2011). However, the prevalence of ASRS positives varied from 20.1% in Switzerland to 60.0% in Norway.

Several potential causes for bias in the prevalence estimates in the included sample were discussed. Three issues are related to selection bias (a, b, c) and one to information bias (d):

a) Are the included addiction treatment centers representative for the country? This issue could not be solved, as the information is not available in most of the participating countries. There was no funding available for a structured and top-down selection of representative addiction treatment wards. So addiction treatment sites wanting to participate were included. Most participating sites confirmed that their center was not specifically geared to the recruitment, diagnosis and treatment of SUD patients with comorbid ADHD, but there were no data available to show that these centers were indeed representative for the country. As a consequence, the country specific rates need to be interpreted with great caution.

b) Is the included sample representative for the addiction treatment center? There are no measures available to control for this. The participating wards were asked to draw a random sample of subjects starting a new episode of treatment. This procedure differed in each center, and was influenced by the number and flow of patients, and availability of trained staff. Thus we need to be careful in our generalization of the center specific findings.

c) Are the samples included in stage 2 representative for the full samples included in stage 1? To control for this, differences on several variables, such as age, gender, primary substance of abuse, and also level of ASRS screen positives were measured in both the included sample and the drop out sample. With the exception of age (significantly higher in Norway and Spain in the included sample) and the percentage of ASRS positives (significantly higher in the included sample: 40.1% vs.36.3%), no differences were observed. Given the relatively small differences between the stage 2 sample and the drop outs, it can be concluded that the subsample included in stage 2 is representative for the full sample. However, given the limited but important difference in the percentage of ASRS positives between stage 2 and those that drop out after stage 1, most of the analyses in chapter 6 and 7 are weighted for the ASRS outcome.

d) Are the instruments used in the same way in all centers? As many languages were involved, a thorough interviewer reliability test was considered too
expensive and not feasible. A structured training in all of the instruments for the local project leaders and those interviewers fluent in English was performed in all participating countries by the PI of the IASP study (GvdG).

The reported overall rate of ASRS positive cases at stage 1 (40.9%; n=3,558) in our study is in line with findings in other studies in SUD populations. The observed range in the level of ASRS positives in this sample was 20.1% in Switzerland to 60.0% in Norway. This raised additional questions: Is the ASRS a reliable and valid screening tool for the detection of adult ADHD in populations of treatment seeking SUD patients from different countries? Given a similar reliability and validity of ASRS in the different countries, what are causes for the variability in prevalence of adult ADHD between the different countries and centers?

9.1.3 Case finding of ADHD patients in treatment seeking SUD patients using the ASRS

In chapter 6 we investigated the psychometric quality of the ASRS using the Conner's’ ADHD Adult Diagnostic Interview for DSM-IV (CAADID; Epstein et al., 2001) as the gold standard. IASP data were used to assess the psychometric quality of the ASRS. The ASRS was selected for two reasons: 1) the instrument showed moderate sensitivity of 68.7% and high specificity of 99.5% (Kessler et al., 2005), high internal consistency (Adler et al., 2006) and good test-retest reliability (Matza et al., 2011) in general population samples; and 2) the 6-item version is the shortest test available and thus feasible and easy to use and can thus be implemented easily in the field of addiction treatment.

We included those patients having a score on the ASRS at stage 1, a score on the ASRS at stage 2, and a score for the CAADID. This resulted in a sample of 1,138. As mentioned in chapter 5, the results were analyzed using weighted data.

The overall prevalence of adult ADHD in this sub-sample was 13.0%. Sensitivity and specificity of the ASRS measured at intake using DSM-IV criteria (0.84 and 0.66, respectively) were very similar to sensitivity and specificity when using DSM-5 criteria for adult ADHD (0.83 and 0.68, respectively). The alternative scoring algorithm did not improve the performance of the ASRS. No differences in performance of the ASRS were observed for gender and treatment setting. Also no significant differences in sensitivity were observed for patients with
alcohol as their primary substance of abuse (0.80) compared to patients with drugs as their primary substance of abuse (0.85). However, specificity of the ASRS in patients with alcohol as their primary substance of abuse was better (0.76) than in patients with other primary drugs of abuse (0.56). The ASRS was not a very good screener for BPD (sensitivity 0.63, specificity 0.64), APD (sensitivity 0.65; specificity 0.66) and BD (sensitivity 0.70; specificity 0.62), indicating that the ASRS is sensitive for ADHD and not for externalizing disorders in general.

The results on the stability of the performance of the ASRS were mixed: 84% of the patients showed similar ASRS results at the two measurements, but also 8% switched from ASRS positive to ASRS negative and another 8% from ASRS negative to ASRS positive.

Given the low time burden for both patients and professionals, the benefit of using the ASRS is that it had good sensitivity, resulting in an acceptable low number of falls negatives. However, many of the screen positives turn out to not have adult ADHD. The literature so far does not provide a clear superior alternative. To our knowledge the study of Dakwar et al., (2012) is the only study comparing several screening instruments for adult ADHD in treatment seeking SUD patients: Conners’ Adult ADHD Rating Scale (CAARS), Wender Utah Rating Scale (WURS) and the ASRS. They reported better sensitivity and specificity for the CAARS and the WURS compared to the ASRS, but mentioned that the ASRS, being the simplest and shortest instrument of the three, was probably best for screening in large populations.

9.1.4 Variability in prevalence of adult ADHD in treatment seeking SUD patients

The meta-analysis of Van Emmerik-van Oortmerssen et al., (2012; chapter 3) showed a broad variation in prevalence rates of adult ADHD in treatment seeking SUD patients in different studies, ranging from 10.0% to 54.1%. In the IASP study we investigated whether the use of the same instruments and the same diagnostic procedure in all treatment centers would result in a smaller variation in prevalence rates.

In chapter 7 of this thesis we presented the answer to this research question. The prevalence of adult ADHD-DSM-IV ranged from 5.4% in Hungary to 31.3% in Norway. Based on DSM-5 criteria the prevalence rates for adult ADHD were slightly (but not significantly) higher, ranging from 7.6% in Hungary to 32.6% in Norway. Since country was strongly confounded with setting (inpatient vs.
outpatient) and by primary substance of abuse (alcohol vs. drugs) with only one country (Norway) including both inpatients and outpatients and one country (Switzerland) including almost only patients with alcohol use disorders, we were not able to statistically adjust for country. Therefore, the analyses were stratified by the setting (inpatient vs. outpatient) and primary substance of abuse. These analyses showed an important and significant effect for Nordic countries (Sweden and Norway) vs. non-Nordic (other) countries, for setting (inpatient vs. outpatient) and for primary substance of abuse (alcohol vs. drugs).

**Outpatient-Alcohol**
The prevalence of adult ADHD based on DSM-IV criteria in *outpatient* settings for patients with *alcohol* as their primary substance of abuse ranged for non-Nordic countries from 4-10% and for Nordic countries from 13% (Sweden) to 14% (Norway).

**Outpatient-Drugs**
The prevalence of adult ADHD based on DSM-IV criteria in *outpatient* settings for patients with *illicit drugs* as their primary substance of abuse ranged for non-Nordic countries from 12-30% and for Nordic countries from 37% (Sweden) to 41% (Norway).

**Inpatient-Alcohol**
The prevalence of adult ADHD based on DSM-IV criteria in *inpatient* settings for patients with *alcohol* as their primary substance of abuse ranged from 5% for non-Nordic countries like Hungary and Switzerland to 22% for Norway.

**Inpatient-Drugs**
The prevalence of adult ADHD based on DSM-IV criteria in *inpatient* settings for patients with *drugs* as their primary substance of abuse ranged from 16% for the non-Nordic country Hungary to 57% for Norway.

This important effect of Nordic versus non-Nordic countries on the prevalence of adult ADHD remained significant after adjustment for age, gender, occupational status, housing and marital status.

A possible explanation for this country effect was discussed: region affecting circadian rhythm via level of sun-intensity, as ADHD prevalence rates in general population studies significantly decreased in states with high solar intensity compared to those states with low solar intensity in a general population study in the USA (Arns et al., 2013).

Not explored explanations for the variability of prevalence rates in this population include culture specific issues. These include the way addiction treatment is organized, the system of referral to specialized treatments, views
on SUD and ADHD by professionals and the general population and the level of treatment of ADHD in primary care and mental health services. In other words, SUD patients with ADHD might find their way to addiction treatment in different percentages based on these issues.

Three important conclusions can be drawn:
1) The prevalence of comorbid adult ADHD is moderately high in treatment seeking SUD patients with alcohol as their primary substance of abuse (5-22%) and higher in treatment seeking SUD patients with illicit drugs as their main problem substance (12-57%);
2) Applying DSM-5 criteria does not increase the range of prevalence rates dramatically and remains within the ranges for ADHD-NOS based on DSM-IV criteria;
3) Differences in regional solar intensity, differences in cultural values and differences in referral and treatment systems may result in large differences in prevalence rates of adult ADHD in treatment seeking SUD patients.

Given these conclusions it seems important not to rely on an overall or average adult ADHD prevalence estimate in treatment seeking SUD populations. Such an estimate needs to be country specific, may be setting specific and is primary substance of abuse specific. However, regardless of country or setting, ADHD is overrepresented in both AUD and DUD patients, also in countries outside the USA. It therefore can be concluded that the increased prevalence of ADHD in treatment seeking SUD patients is not a USA specific phenomenon.

9.1.5 Comorbidity in treatment seeking SUD patients with and without adult ADHD

In chapter 8 we looked at psychiatric comorbidity patterns in treatment seeking SUD patients with and without comorbid adult ADHD with special attention to the three subtypes of ADHD. For these analyses we included subjects who completed the CAADID, the MINI-plus modules Major Depression (MD), (Hypo)Manic Episode (HME), and Antisocial Personality Disorder (APD), and the SCID-II module for Borderline Personality Disorder (BPD), resulting in a sample of 1,205 SUD patients.

SUD patients with ADHD had at least one additional comorbid disorder in 75% of the cases, whereas this was “only” 37% in SUD patients without ADHD. All
other psychiatric disorders were significantly (p<.01) more prevalent in SUD patients with adult ADHD compared to SUD patients without adult ADHD.

The relation between ADHD and some of the other comorbid disorders was modified by the primary substance of abuse. The odds ratios adjusted for age, gender, marital status, housing and employment status were as follows: for current MD (alcohol OR= 4.1; drugs OR=1.2), for BPD (alcohol, OR=7.0; drugs OR = 3.4), for APD (OR 2.8) and for current HME (OR 4.3).

Comorbidity patterns differed between ADHD subtypes with increased MD in the inattentive and combined ADHD subtype (p<.01), increased HME and APD in the hyperactive/impulsive ADHD subtype (p<.01) and the combined ADHD subtype (p<.001) and increased BPD in all three subtypes (p<.001).

The finding of increased comorbidity in SUD patients with compared to SUD patients without ADHD is in line with previous studies (Huntley et al., 2012; Santucci, 2012). We noted that this high prevalence may reflect the presence of some underlying pathophysiology. Our study is the first to determine the comorbidity patterns in the three ADHD subtypes.

The pattern of MD being overrepresented in subjects with alcohol as their primary substance of abuse, in the ADHD inattentive and combined ADHD subtype, but not in the hyperactive/impulsive subtype may indicate the presence of a common underlying internalizing genetic vulnerability and/or pathophysiology. In contrast, externalizing disorders like HME and APD were overrepresented in the hyperactive/impulsive and combined ADHD subtypes but not in the inattentive ADHD subtype suggesting the presence of a common underlying externalizing genetic vulnerability and/or pathophysiology. BPD was overrepresented in all ADHD subtypes, but more in subjects with alcohol as their main problem. Together these findings might be related to the distinction between internalizing and externalizing psychiatric and personality disorders as proposed by Kendler et al., (2011). We will further elaborate on this in paragraph 9.2 in the section: Treatment seeking SUD patients with ADHD showed more psychiatric comorbidity than those without ADHD (p. 163).
9.2 Integration of findings and future research

In their guidelines for the pharmacological management of substance use disorders and comorbidity, Lingford-Hughes et al., (2012) state that in SUD patients (symptoms of) psychiatric disorders such as depression, anxiety and psychosis are the rule rather than the exception. This high level of comorbidity in SUD patients has been recognized and led to development of National guidelines for treatment of comorbidity in SUD patients (NICE, 2011; Mills et al., 2009). However, currently little evidence is available for the efficacy of such treatments (Lingford-Hughes et al., 2012). With highly prevalent and severe disorders like Major Depression, Bipolar Disorder, Schizophrenia and Anxiety disorders in treatment seeking SUD patients, one may ask what the relevance of ADHD is in this field? This thesis provides some answers to this question, which will be discussed below. In addition suggestions for future research will be given.

9.2.1 The variability in prevalence rates is high, and is related to region and primary substance of abuse

Our first study (chapter 3) resulted in an estimate of the prevalence of 12%. In our meta-analysis of existing studies (Van Emmerik-van Oortmerssen et al., 2012) presented in chapter 4 the best overall estimate was 23%, with a range from 10% to 54% in individual studies. In our international cross-sectional study (chapter 6) we found a range of 4% to 10% of DSM-IV ADHD in outpatient AUD subjects and a range of 12% to 30% in outpatient DUD subjects in non-Nordic countries, with slightly higher rates for DSM-5, and substantial higher rates for Nordic countries (Sweden and Norway).

Even in participating centers with the lowest prevalence estimate of adult ADHD (5% in an AUD treatment center in Hungary and Switzerland), the rates were twice the pooled prevalence rate for adult ADHD in the general population: 2.5% (Simon et al., 2009).

Eight of the twelve included studies in the meta-analysis by Van Emmerik-van Oortmerssen et al., (2012) were studies from the USA. Our study documents increased prevalence rates of adult ADHD in treatment seeking SUD patients in eight European countries and Australia.

Professionals, managers and policy makers interested in the prevalence of adult ADHD in their addiction treatment centers, should bare in mind the
differences between AUD and DUD, the possible differences in region related to solar intensity and cultural specific issues like the organization of addiction treatment services and the attitude towards ADHD in the general population.

As our study was conducted in adults, additional research in adolescent populations of (treatment seeking) SUD patients is needed.

Conclusion: Despite the variability in prevalence of ADHD in treatment seeking SUD patients, the presented ranges of rates in both alcohol and drug use disorders indicate the necessity of screening every SUD patient for ADHD. For this purpose a validated screening instrument for ADHD with good sensitivity and specificity for this population is warranted.

9.2.2 The ASRS is a minimally intrusive, brief instrument that can detect the majority of ADHD patients in treatment seeking SUD populations

The ASRS is a sensitive screener for the detection of adult ADHD in treatment seeking SUD patients, but additional state of the art diagnosis by qualified professionals is warranted in ASRS positive patients. It should be noted, however, that the ASRS has only moderate specificity in this population with the lowest specificity in populations with illicit drugs as their primary substance of abuse, resulting in a low Positive Predictive Value. Recent research compared several adult ADHD screening instruments (Dakwar et al., 2012), with better specificity. However the authors also stressed the advantages of a short screener (as the ASRS) over the other instruments. Future research should investigate how to combine the advantages of the different screening instruments. For example, the ASRS only addresses the first DSM ADHD criterion (presence of ADHD symptoms), whereas the other DSM criteria for ADHD, more specifically the pervasiveness and the impairment criterion, are not measured with the ASRS. These omissions may be responsible for the relatively high number of false positives and the low specificity in our study.

Chapter 7 showed that changes in the age of onset criterion and changes in the number of symptoms criterion in DSM-5 did not lead to an increase in the prevalence of ADHD beyond the rate of ADHD-NOS based on DSM-IV criteria. Therefore, changes in these items of the DSM-5 probably have little effect on ASRS performance. It should be noted, however, that four of the six ASRS items are related to attention deficit symptoms, whereas only hyperactive/impulsive ADHD symptoms independently predict the development of SUD (Elkins et al.,
ADHD symptoms independently predict the development of SUD (Elkins et al., 2007; Foster et al., 2012). This suggests that the ASRS might be less suitable for identifying true ADHD cases in SUD populations.

Given these findings, future research should try to develop and test the performance of a short screening tool, using the 6-item ASRS as the basis, while adding hyperactive/impulsive items as well as items related to pervasiveness and impairment. These additional questions might improve specificity, while maintaining a high level of sensitivity.

9.2.3 Treatment seeking SUD patients with ADHD showed more psychiatric comorbidity than those without ADHD

Antisocial personality disorder, borderline personality disorder, current major depression and current (hypo)manic episode were all significantly more prevalent in SUD patients with ADHD compared to SUD patients without ADHD. In SUD patients with ADHD 75% had at least one additional comorbid disorder compared to "only" 37% of SUD patients without ADHD.

Our study was the first to look at comorbidity patterns in ADHD subtypes in treatment seeking SUD patients. Comorbidity patterns differed between ADHD subtypes with increased MD in the inattentive and combined ADHD subtype \((p<.01)\), increased HME and APD in the hyperactive/impulsive ADHD subtype \((p<.01)\) and the combined ADHD subtype \((p<.001)\) and increased BPD in all three subtypes \((p<.001)\). These differences were in line with research suggesting underlying pathophysiology for SUD and comorbid disorders (Pani et al., 2010; Ivanov et al., 2008) and research showing empirical evidence for the distinction between internalizing and externalizing psychiatric and personality disorders (Kendler et al., 2011).

Both childhood and adolescent ADHD are independent risk factors for the development of a variety of psychiatric disorders, including bipolar disorder, generalized anxiety disorder, post-traumatic stress disorder, specific phobia, and narcissistic, histrionic, borderline, antisocial and schizotypal personality disorders (Bernardi et al., 2012; Meinzer et al., 2013). In addition childhood and adolescent ADHD are associated with impaired functions, i.e. engagement in behaviors reflecting lack of planning and deficient inhibitory control, with high rates of adverse events, lower perceived health, social support and higher perceived stress (Bernardi et al., 2012).
In this thesis phobic anxiety, generalized anxiety disorder and PTSD were not addressed. Anxiety and SUD are positively related (Conway et al., 2006; Lev-Ran et al., 2012; Cheung et al., 2010), whereas anxiety plays a specific and complex role in the relationship between ADHD and CD (Bilgiç et al., 2013; Gielen et al., 2012). Moreover, Dore et al., (2012) reported increased levels of Post Traumatic Stress Disorder in SUD patients, whereas Antshel et al., (2013) reported an increased level of PTSD in adult ADHD subjects. Internalizing disorders are often seen in adolescent and young adult female SUD patients (Couwenbergh et al., 2006). Finally, there are indications that girls with ADHD are vulnerable for the development of SUD via early engagement in sexual activities, Post Traumatic Stress Disorder (PTSD) and or BPD (Van der Gaag & van Wijngaarden-Cremers, 2009). Therefore, in future studies on comorbidity patterns in SUD patients with ADHD, phobic anxiety, generalized anxiety disorder and PTSD should be included in the assessment.

An important statement on the link between SUD and the 'psychic structure' of subjects was made by Pani and colleagues: "We postulate that addiction reaches beyond the mere result of drug-elicited effects on the brain and cannot be peremptorily equated only with the use of drugs despite the adverse consequences produced. We infer that mood, anxiety and impulse-control dysregulation is at the very core of both the origins and clinical manifestations of addiction and should be incorporated into the nosology of the same, emphasizing how addiction is a relapsing chronic condition in which psychiatric manifestations play a crucial role" (Pani et al., 2010; p.185).

Kendler et al., (2011) analyzed both genetic and environmental risk factors related to Axis I and Axis II disorders (Kendler et al., 2011). In the genetic factors model, both alcohol and drug abuse and dependence were placed in a group with Axis 1 Externalizing disorders (Kendler et al., 2011, figure 1, p. 34). However, in the environmental factors model, alcohol abuse and dependence were placed in the group with Axis 1 internalizing disorders (together with generalized anxiety disorders, dysthemia, major depression), whereas drug abuse and dependence were placed in the Axis 1 externalizing group (Kendler et al., 2011, figure 2, p. 36).

These two studies (Kendler et al., 2011; Pani et al., 2010) suggest the existence of networks of co-occurring disorders.

Based on our findings in chapter 8 and on the patterns proposed by Kendler et al., (2011) and Pani et al, (2010), we suggest the following networks of co-occurring disorders: 'ADHD-SUD-MD', 'ADHD-PTSD-SUD', 'ADHD/BPD-PTSD-
SUD’, ‘ADHD-Generalized Anxiety Disorder-SUD, and of course the 'ADHD-CD-APD-SUD' link (Flory and Lynham, 2003; Lee et al., 2011). These networks need further (prospective) investigation. In these studies, special attention should be given to underlying mechanisms in order to learn more about causal pathways and possibilities for the treatment of these co-occurring disorders. An excellent overview of such underlying factors is presented by Ivanov and his colleagues (Ivanov et al., 2008). They identified inhibitory control deficits as an important risk factor for development of ADHD, ODD, CD and APD, but also for SUD. Studying causes, consequences and treatment options for inhibitory control deficits, thus targeting both prevention of the development of SUD in patients with ADHD and treatment of both ADHD and SUD, is highly relevant for future research.

Furthermore, new behavioral addictions and co-occurring disorders and problems are emerging with the internet and game revolution of the past two decades, with patients having psychiatric disorders being more vulnerable for internet and game addiction (Cho et al., 2012) and ADHD as a specific risk factor (Weinstein & Weizman, 2012). This also implies future lines of research, expanding the topic of ADHD-SUD to other forms of addictive behavior.

9.3 The relevance of the findings in this thesis

Our findings regarding the psychometrics of the ASRS, the range of prevalence rates in different SUD populations and the extent and the patterns of comorbid disorders are only relevant if the following objectives can be achieved:

1) Effective treatment of those individuals with both SUD and ADHD, resulting in positive effects on at least ADHD outcomes and preferably also on SUD outcomes, resulting in a better quality of life for these subjects;
2) Effective strategies to prevent the development of SUD in ADHD children, adolescents and (young) adults.

9.3.1 Treatment of patients with ADHD and SUD

Efficacy of the pharmacological treatment in adult ADHD is well documented and reviewed, concluding that such treatment has robust positive effects on reducing ADHD symptoms (Bitter et al., 2012; Fredriksen et al., 2012; Faraone & Glatt, 2010) with better effects for stimulant medication compared to non-
stimulant medication (Faraone & Glatt, 2010). In contrast, data on the non-pharmacological treatment of ADHD in adults is limited but also indicates positive effects of non-pharmacological treatment options (Philipsen, 2012; Solanto et al., 2010; Safren et al., 2006). The NICE practice guideline on ADHD concludes on treatment of adult ADHD: "Currently there is good evidence supporting the effectiveness of methylphenidate in people with ADHD symptoms and associated impairment. However, there is insufficient evidence on whether non-drug treatments could have specific advantages in some important aspects of the life of a person with ADHD. Given the strong association of ADHD in adults with substance misuse, personality disorder and involvement in the criminal justice system, a health economic approach would be essential" (NICE, 2013; p. 45-46).

However, stimulant treatment of adult ADHD in patients with SUD is much less effective than in adult ADHD patients without SUD in the reduction of ADHD symptoms and it also has little effect on substance use (Carpentier, 2012). In his review, Carpentier (2012) looked at all controlled studies in this population and found a small effect for stimulant medication on ADHD symptoms in only one study in adults (Schubiner et al., 2002), in only one study in adolescents (Riggs et al., 2004) and small effects on secondary ADHD outcome measures in one study in adolescents (Riggs et al., 2011). Carpentier (2012) also reported a moderate effect of atomoxetine on ADHD symptoms in one study in adults with alcohol dependence (Wilens et al., 2008). The same study was also the only one with a small effect on alcohol use. Two studies reported small effect sizes on secondary outcome measures for SUD outcome, one in adults (Levin et al., 2007) and one in adolescents (Riggs et al., 2011). Four studies showed no significant result in neither ADHD nor SUD (Carpentier et al., 2005; Levin et al., 2006; Thurstone, 2010; Konstenius, 2010). Explanations for these results have been proposed but scarcely tested.

Carpentier (2012) points to several possible explanations for these results: 1) the high prevalence of additional comorbidity in populations with ADHD and addiction; 2) diagnostic inaccuracy; 3) effects of long-term psychoactive substances on the brain and on its responsiveness to ADHD medication; 4) inadequate medication dosages; and 5) the "classic pattern of dual disorder treatment" in which "active treatment alleviates the comorbid disorder but does not directly influence the SUD" (Carpentier, 2012, p. 19). Crunelle et al., (2013) tested whether a low dopamine transporter occupancy by methylphenidate could be a possible reason for reduced treatment effectiveness in ADHD patients with and without cocaine dependence, using single photon emission computed tomography (SPECT). However, they had to
reject their hypothesis, suggesting that higher doses of methylphenidate are not very likely to improve the effectiveness of stimulants in patients with ADHD and comorbid SUD.

To the best of our knowledge, there are no results of non-pharmaceutical treatment options for ADHD in SUD patients available. Recently, van Emmerik-van Oortmerssen and colleagues proposed integrated CBT treatment for this population (van Emmerik-van Oortmerssen et al., 2013).

In addition to the above mentioned reasons for the small or absent effects in the treatment of ADHD in SUD patients (Carpentier et al., 2012; Crunelle et al., 2013), the chosen outcome measures and the duration of trials should be considered. The current outcome measures (e.g. level of ADHD symptoms; abstinence of substance use; level of substance use at a given moment) in all controlled research so far (Riggs et al., 2004; Schubiner et al., 2002; Wilens et al., 2008; Carpentier et al., 2005; Levin et al., 2006; Thurstone, 2010; Konstenius, 2010) may not be the most suitable and sensitive in this specific population. Other outcome measures such as criminality (Lichtenstein et al., 2012) and injuries (van der Ban et al., 2013) may be of importance. Moreover, so far only fixed dosages have been used in previous trials (Carpentier, 2012). Individually tailored dosages of ADHD medication are known to be of importance in treatment of adult ADHD (Benkert et al., 2010). Using titration, but also using responders and non-responders may be considered in developing designs and methods for future trials.

Hence, we should seek for clever and novel research designs and new outcome parameters to test and, if needed, develop effective treatments for subjects suffering from both ADHD and SUD.

9.3.2 Prevention of SUD development in ADHD children and adolescents

In an extensive systematic review and meta-analysis, investigating the long-term outcome of ADHD subjects with and without pharmacological treatment, Shaw and colleagues (2012) conclude, that those without treatment had poorer outcome (including more SUD), when compared to those who were treated for ADHD, although significant differences remained also for this group when compared to healthy controls (Shaw et al., 2012). Fredriksen et al., (2012)
reviewed the literature on the effect of stimulant treatment of ADHD children/adolescents for the development of SUD. There is a clear protective effect, but this effect seems to decrease over the years, due to so far unknown reasons. Family related factors, other environmental factors, and limited adherence to the medication are all possible explanations (Fredriksen et al., 2012).

An important line of research is the detection and treatment of inhibitory control deficits (Ivanov et al., 20089). Also research on the changes and/or persistence of attention deficit symptoms and hyperactive/impulsive symptoms in the development of a child via adolescence to adulthood might result in clues on risks for the development of SUD in ADHD children and adolescents.

### 9.3.3 Consequences for clinical practice

Intensive collaboration between clinical practice and science in the IASP study resulted in important scientific findings with major implications and challenges for clinical practice.

The phenomenon of ADHD presence in treatment seeking SUD patients can no longer be attributed to a USA hype or to biased USA scientific work. Hence, professionals and managers of addiction treatment centers worldwide should work on the detection, diagnosis and treatment of these patients. The severity and consequences for quality of life of both disorders demand this. In addition, in the field of adolescent addiction treatment, professionals should be aware of possible comorbid ADHD.

Short term and long term collaboration between clinical practice and science is warranted for a further improvement of the quality and effectiveness of existing and new diagnostic and treatment procedures, both in adolescents and adults.

Finally, in the fields of child and adolescent psychiatry and youth care professionals should be aware of the risk for development of SUD in ADHD children and adolescents. Together with people from the clinical field, scientists should develop and test methods for prevention of SUD in children, adolescents and in (young) adults with ADHD.
9.4 Remarks on under- and overdiagnosis of ADHD, medicalization of normal behavior, and interpreting long term outcome of research.

9.4.1 Overdiagnosis of ADHD

In the Netherlands, media and politicians constantly raise questions about the steep increase in annual numbers of ADHD and stimulant prescriptions. The number of individuals receiving a prescription for ADHD medication in 2011 was 200,000, and for 2012 an additional increase of 10% is expected. It should be noted that these figures include prescriptions for other than ADHD disorders (e.g. narcolepsy), and also one time prescriptions (Stichting Farmaceutische Kerngetallen, 2012).

The Netherlands in 2012 had 16,730,000 inhabitants. Of these 3,894,000 were younger than 20 years, 10,119,000 were between 20 – 65 years and 2,716,000 were older than 65 years (CBS, 2013). The internationally accepted prevalence rates are 6-9% for ADHD in childhood and adolescence (Kessler et al., 2005) and 2.5% in adults (Simon et al., 2009). For calculating the number of expected individuals (children, adolescents and adults) with an ADHD diagnoses in the Netherlands, we use 6% for children and adolescents (Kessler et al., 2005), and for adults we use the recently reported 2.1% prevalence of adult ADHD based on Netherlands general population data (de Graaf et al., 2012). For adults older than 65 we use the reported prevalence rate of 2.8% by Michielsen et al., (2012), both in line with the 2.5% reported by Simon et al., (2009).

- 6% of 3,894,000 is 233,640 inhabitants under 20 years;
- 2.1% of 10,119,000 is 212,499 inhabitants between 20-65 years;
- 2.8% of 2,716,000 is 76,048 inhabitants older than 65 years.

Taken together this is 522,187 inhabitants who are expected to have ADHD.

Given the figure of 220,000 individuals with an ADHD medication prescription, including those who received one prescription only, and prescriptions for non-ADHD treatment, this number is an overestimation of those receiving treatment for ADHD on a regular basis. Nevertheless, the number represents 42% of the expected 522,187 inhabitants who are expected to have ADHD.
9.4.2 Medicalization of normal behavior

Although there is clear neurobiological and genetic data supporting the validity of adult ADHD, there remains an ongoing debate on the validity of the diagnosis of (adult) ADHD (Batstra & Frances, 2012). However, the following issues might be overlooked:

1) In ADHD the symptoms are present already in childhood; DSM-5 age of onset criterion is prior to the age of 12;
2) The criterion of pervasiveness, meaning that the ADHD symptoms should be present in more than one social context, i.e. not only at home, or only at school;
3) The criterion of impairment, meaning that the symptoms must lead to impairment in education, social functioning etc.

So a happy busy kid, jumping and climbing, but without impairment should not be diagnosed with ADHD, nor should an adult with 5 inattentive symptoms, but no evidence of pervasiveness or impairment, be diagnosed with adult ADHD.

Furthermore, the presence and magnitude of 'overdiagnosis of ADHD' has never been properly researched. This should be done, before decisions to resolve this assumed problem are taken. In addition, if the scale at which this happens is significant, this means that even more children, adolescents and adults with ADHD (based on all criteria) do not receive the diagnose or treatment they need. As shown in the previous paragraph on overdiagnosing, the number of individuals getting prescriptions for ADHD medication is only 42% of the number of expected ADHD cases, based on all DSM criteria.

Finally, the fact that "mind and brain altering" medication is prescribed for patients, in many cases young children, is reason for concern.

I share this concern.

Therefore, researchers, professionals, parents and teachers should work on non-pharmaceutical treatment options. However, given the fact that these are not sufficiently available yet, these same groups of persons need to balance between the disadvantages of medication and no medication. Barkley and colleagues (Barkley et al., 2008), and Shaw and colleagues (Shaw et al., 2012) and many others indicate that ADHD in children often results in poor outcome on all aspects of life, including abuse of substances and addiction. The effect of stimulant medication on postponing substance abuse in ADHD adolescents (Fredriksen et al., 2012) is of great importance. In addition, the study by Lichtenstein et al., (2012), shows more than 30% decrease of criminal activities in ADHD patients during periods on ADHD medication compared to periods of
no medication use; a finding that may contribute to balancing risks and benefits of medication as a treatment option for ADHD.

9.4.3 Long term outcome of ADHD treatment

ADHD is for many patients a chronic and lifelong disturbing disorder. It is unclear to what extent treatment of ADHD has long term effects. The literature on this topic is scarce, as it is very difficult to organize long term follow-ups. A serious attempt was made in the famous Multimodal Treatment study of children with ADHD (MTA). In this study a large group of children was randomly assigned to treatment as usual, medication, non-pharmacological treatment and combined medication-non-pharmacological treatment groups. The short term results were in line with previous reports showing evidence for effectiveness of both medication and combined treatment. However, in the 8 year follow up study, these effects seemed to have disappeared (Molina et al., 2009; Swanson et al., 2008).

The way the study was developed and reported, unfortunately easily leads to misinterpretation of the findings. As the participating children only received the prescribed treatment under controlled circumstances during the initial period (first 14 months of the study), and were not medically followed after that, many children dropped out of either or both treatments. Thus, the study suggests that when treatment is not carefully monitored, and medication is not maintained, the therapeutic benefits of treatment disappear. This is exactly what would be expected in the case of a chronic disorder. What would have happened if children would have received the treatment, according to the treatment group they were assigned to, for a long period of time is unfortunately unknown.

What we do know, however, is that too many ADHD children/adolescents wind up in treatment for an addiction. And we know that throughout the world only a limited number of treatment seeking SUD patients receive a proper screening, diagnosis and treatment for ADHD.

I hope this thesis will contribute to 1) a decrease of the numbers of ADHD patients who develop a SUD, 2) as a result, increased quality of life for children and adolescents with ADHD at risk for development of SUD and 3) increased quality of life for adolescents and adults suffering from both ADHD and SUD.
As this thesis can provide only a modest contribution to the field, future collaboration on many levels, and in many disciplines is necessary.