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## ADHD & Addiction

van Emmerik-van Oortmerssen, Katelijne

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# **CHAPTER 12**

## SUMMARY AND GENERAL DISCUSSION



This thesis reports on the prevalence of ADHD in SUD patients, the comorbidity profile of this patient group, the validity of diagnosing ADHD in active substance abusing patients, and the development and efficacy of an integrated cognitive behavioral therapy for the treatment of patients with both ADHD and SUD. In this final chapter, the findings are summarized, integrated and discussed in the context of recent research findings, and conclusions are drawn. In the last two paragraphs, methodological considerations and clinical implications are provided together with recommendations for further research.

## SUMMARY

In Part I (**Chapters 1-2**), the context of our studies was presented.

In **Chapter 1**, a short introduction and an overview of the research questions of this thesis were presented. This was followed in **Chapter 2** by information on clinically relevant aspects of the comorbidity of ADHD in SUD patients, such as the neurobiology of ADHD, the clinical presentation of ADHD, screening and diagnostic assessment of ADHD in SUD patients, treatment and prognosis (**Chapter 2**). We described the symptoms of ADHD and showed that dysfunction of the motivational/reward system and impulsivity play a role in both ADHD and SUD. Because ADHD interferes with SUD treatment, we recommended that SUD patients be screened for ADHD, followed by a diagnostic assessment as soon as substance use has stabilized or stopped. We also summarized the treatment options for ADHD in SUD patients that were already investigated at the time, and concluded that most studies had focused on ADHD medication but that these studies did not provide convincing evidence for the efficacy of such medication. Finally, further research into other treatment options was recommended.

In Part II (**Chapters 3-6**), the prevalence of ADHD and additional comorbidities in SUD patients was investigated.

**Chapter 3** contains a meta-analytic review of the literature on the prevalence of ADHD in various SUD populations. A total of 29 studies reporting on 6,689 subjects were included in the analysis (4,054 adolescents and 2,635 adults), involving treatment seeking samples as well as community samples, with various types of SUD. Pooling the data in a meta-analysis yielded an overall prevalence estimate of ADHD in SUD patients of 23.1% (95% C.I. 19.4-27.2%): 25.3% (95% C.I. 20.0-31.4%) in adolescents and 21.0% (95% C.I. 15.9-27.2%) in adults. In a series of meta-regression analyses, the effect of age, gender, treatment setting, primary substance of abuse, recruitment method, abstinence duration, time-frame, ethnicity and assessment procedure on the prevalence of ADHD in SUD patients was evaluated. This resulted in two variables with a statistically significant effect: (1) ADHD assessment with the DICA (Diagnostic Interview for Children and Adolescents) or the SADS-L (Schedule for Affective Disorders and Schizophrenia-Lifetime Version) was associated with a higher prevalence of ADHD than assessment with the CAADID, K-SADS, DISC, GAIN, CHAMPS, DIS,

KID SCID, SSADDA, or Utah criteria, and (2) cocaine as the primary substance of abuse was associated with a lower prevalence of ADHD than all other primary substances of abuse. After adjusting for these variables, the overall ADHD prevalence remained unchanged, but the 95% C.I. became a little smaller (95% CI 19.9% to 26.7%).

In **Chapter 4** we presented the protocol of the IASP, the International ADHD in Substance use disorders Prevalence Study. The main aim of this study was to determine the prevalence of ADHD in treatment seeking SUD patients in different countries and different populations, using the same assessment method in all participating centers. Additional research questions for this study were to determine the reliability and validity of the ASRS as an ADHD screening instrument in treatment seeking SUD populations, to investigate the comorbidity profile of SUD patients with and without comorbid ADHD, to gain more insight into risk and protective factors in SUD patients with and without comorbid ADHD, and to shed some light on the relationship between ADHD and the onset and course of SUD. In this multi-center study in 10 countries, a total of 3,558 treatment-seeking SUD patients were screened for ADHD. These included both inpatients and outpatients from centers for alcohol and/or drug use disorder treatment. In a later stage, all participants in seven of the ten participating countries were contacted for a full diagnostic interview, consisting of a diagnostic evaluation for ADHD, major depression, (hypo)manic episode, antisocial personality disorder and borderline personality disorder. During this session, the screening instrument was re-administered. In this chapter, information on the procedure of the study, diagnostic instruments, data quality protection and the statistical analysis plan was presented, and a first description of the participating patients from the different countries was provided. Of the 3,558 participating patients, 1,276 participated in the full assessment; 1,319 patients dropped out after the screening and 963 patients were from countries that did not participate in the full assessment stage. Overall, 40.9% of all participating patients had a positive result on the ADHD screener. Alcohol was the main substance of abuse in about half of the patients (54.6% of the patients who participated in the full assessment stage), followed by stimulants (15.1%), opioids (10.8%), cannabis (10.8%) and other substances (8.6%). Because patients with a positive result on the ADHD screener were overrepresented in the full assessment stage (compared to the patients who dropped out), prevalence estimates of ADHD in further analyses were weighed with respect to the screening result.

**Chapter 5** reported on the main results of the IASP study, i.e. a prevalence estimation of ADHD in treatment-seeking SUD patients. A total of 3,558 patients were screened for ADHD and, as mentioned earlier, 1,276 of them (both screen positive and screen negative) participated in a full diagnostic evaluation of ADHD. Using the same assessment procedure in every center, the DSM-IV adult ADHD prevalence varied from 5.4% (95% C.I. 2.4-8.3) in a Hungarian center to 31.3% (95% C.I. 25.2-37.5) in a Norwegian center. This variability in prevalence was partly explained by center variation in the primary substance of abuse, with drug use disorders (compared to alcohol use disorder) associated with a higher prevalence of ADHD, and variations by country, with centers in Nordic countries having a higher ADHD prevalence than centers in non-Nordic countries. Moreover, inpatients had a higher ADHD

prevalence than outpatients. Prevalence estimates for ADHD using DSM-5 criteria were slightly higher than those for ADHD using DSM-IV criteria and varied from 7.6% (vs. 5.4%) to 32.6% (vs. 31.3%).

**Chapter 6** reported on the comorbidity profile of treatment-seeking SUD patients with or without a comorbid diagnosis of ADHD. A total of 1,205 SUD patients included in the IASP study were evaluated for the presence of ADHD, major depression (MD), (hypo)manic episode (HME), antisocial personality disorder (ASPD), and borderline personality disorder (BPD). This sample was slightly smaller than the sample of 1,276 patients in chapter 5, because in 71 patients, the diagnostic assessment was not fully completed. Overall, 13.9% of this sample met criteria for ADHD. Presentation of the results of the comorbid disorders were stratified by primary substance of abuse, if this variable modified the relationship between ADHD and the comorbid disorder. All comorbid disorders were more prevalent in the group of SUD patients with ADHD (ADHD+) than in the group of SUD patients without ADHD (ADHD-) ( $p < .001$ ), with an exception for current depression in SUD patients with drugs as their primary substance of abuse. Moreover, 75% of the ADHD+ group had at least one comorbid disorder compared to “only” 37% of the ADHD- group. Comorbidity patterns differed between ADHD subtypes with more MD in the inattentive and combined subtypes, more HME and ASPD in the hyperactive/impulsive and combined subtypes, and more BPD in all subtypes compared with SUD patients without ADHD.

In Part III (**Chapters 7-11**), we focused on the diagnostic assessment of ADHD in SUD patients and on the efficacy of a new integrated cognitive behavioral treatment for ADHD and SUD.

In **Chapter 7** we presented the protocol of an RCT comparing integrated cognitive behavior therapy for SUD and ADHD (CBT/Integrated) with standard cognitive behavior therapy for addiction (CBT/SUD). Both treatments consisted of CBT, with both treatments containing ten sessions for the treatment of SUD, to which five sessions for the treatment of ADHD were added in CBT/Integrated. The aims of the trial were to test the acceptance, feasibility, efficacy and cost-effectiveness of CBT/Integrated. Our primary research question was, whether adding CBT sessions directed at reducing ADHD symptoms to an existing CBT for SUD, would result in a decrease of self-reported ADHD symptoms in adults with SUD and comorbid ADHD compared to treatment as usual, i.e. CBT/SUD. In this chapter, the participants, the design of the study, the procedure, measures, and treatment protocols were described, as well as the statistical analysis plan.

In **chapter 8** we investigated whether the diagnostic assessment of ADHD can reliably be performed early in treatment, i.e. during active substance use. To do so, the results of a baseline assessment during intake were compared with the results of a second assessment after a period of drug use stabilization or abstinence. A total of 127 patients with a diagnosis of adult ADHD according to Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID) at baseline were assessed with the same instrument several weeks later. At this second

assessment, many patients were still using substances but in general, substance use had decreased with about 50%. Of the 127 patients with a diagnosis of adult ADHD at baseline, 121 (95.3%) also met criteria for adult ADHD at re-diagnosis. The subtype of ADHD was less stable though, with a change of subtype in 27% of the patients, but the number of ADHD symptoms in both childhood and adulthood corresponded well between both assessments. Sensitivity analyses in several subgroups, including patients who had become completely abstinent between intake and retest, yielded similar results with regard to the good diagnostic stability of ADHD.

In **chapter 9**, the main results of the RCT were presented. A group of 119 treatment seeking SUD outpatients with comorbid ADHD from a large addiction treatment center in Amsterdam were randomized to either integrated CBT for ADHD and SUD (CBT/Integrated) or standard CBT for addiction (CBT/SUD). No medication for ADHD was provided in this study, but five patients were already on ADHD medication before entering the trial; their dosages were kept stable during the study. At baseline, post-treatment and at 2-month follow-up, all patients were assessed for ADHD symptoms, substance use, depressive and anxiety symptoms, and quality of life. Generalized linear mixed models were fit to test whether the course of symptoms over time was different in the two treatment conditions. At post-treatment, self-reported ADHD symptoms (ARS total score) were significantly lower in the CBT/Integrated group than in the CBT/SUD group. At 2-months follow-up, the ARS total score was still lower in the CBT/Integrated compared to the CBT/SUD group, but the difference was just not statistically significant (probably due to reduced power). For all other measures, improvements were observed in both treatment groups, but there were no between-group differences in improvement. This first RCT with CBT for ADHD in SUD patients demonstrated that treatment of ADHD symptoms with CBT was possible and effective in SUD patients with comorbid ADHD.

In **chapter 10**, two cases were presented to illustrate the clinical use of the integrated cognitive behavioral therapy for the treatment of patients with SUD and comorbid ADHD in daily practice. The first patient was a 31-year old single man with alcohol dependence and ADHD. He received CBT/Integrated, and responded well: ADHD symptoms decreased from a score of 51 on the ARS to 21, he reported much better functioning at work at the end of treatment, and his alcohol use decreased from 23 heavy drinking days at intake to 1 heavy drinking day in the last month. This case clearly illustrated the potential benefits of CBT/Integrated. The second patient was a 25-year old man with cannabis dependence and comorbid ADHD. After a first treatment session, he did not return to the outpatient clinic and he did not respond to any attempts to contact him. This case illustrated the problem of high drop-out rate that we encountered, especially early in the treatment.

In **chapter 11**, we investigated potential predictors of early drop-out (before randomization) and treatment response in the RCT, and we explored variables that might be suitable for patient-treatment matching. The following patient characteristics were used as potential predictors in the analyses: demographic information (gender, age, level of education, employment status and relationship status), clinical characteristics (ADHD subtype and

symptom severity, primary substance of abuse and SUD severity, depression and anxiety symptoms, the use of ADHD medication), and measures on cognitive functioning (Stroop, Tower of London, and Balloon Analogue Risk Task).

We found that patients with drug use disorders (compared to patients with alcohol use disorder only) and patients with lower accuracy on the Tower of London were at higher risk of early treatment drop-out. Regarding the second research question, lower depression and anxiety symptoms and the absence of ADHD medication at baseline were found to be associated with fewer ADHD symptoms at the end of treatment and at follow-up. Remarkably, lower accuracy on the Tower of London at baseline was associated with lower substance use levels post-treatment/ at follow-up. Finally, there were no significant predictor by treatment interactions, indicating that there were no patient characteristics for which there was a specifically high or low benefit of CBT/Integrated over CBT/SUD.

## **INTEGRATION OF FINDINGS**

In this paragraph we will first elaborate on our findings focusing on the five research questions of this thesis that were outlined in the introduction (**chapter 1**). For each question, we will first describe what the studies in this thesis have shown, how the findings fit within the existing literature, and, if applicable, put them into the context of studies that have appeared more recently. In the subsequent paragraphs, we will discuss the methodological considerations and implications for clinical practice. Finally some recommendations for future research are made.

### ***1. What is the prevalence of ADHD in SUD patients and what are the factors that have an impact on the prevalence?***

#### *Prevalence*

In this thesis, a high prevalence of ADHD in SUD patients was demonstrated for the first time in a systematic review and meta-analysis of the existing literature. A pooled prevalence of 23.1% was found for adults and adolescents with SUD in different settings, both treatment seeking and community samples, using different instrument for the diagnosis of ADHD, and with most studies originating from the United States. This methodological heterogeneity may explain the broad range in ADHD prevalences reported in the different studies - ranging from 8% up to 54%. The estimated prevalence in adults was 21.0% (95% C.I. 15.9-27.2%). Second, we reported on findings from the IASP study, for a large part carried out in patients from European addiction treatment centers, all using the same diagnostic procedure and the same instruments. In this study, the prevalence of adult ADHD was calculated for each country separately rather than for all countries together, because the prevalence of ADHD was very different in the different countries and ranged from 5.4% in Hungary to 31.3% in Norway. Thus, the point estimate and the 95% confidence interval of the prevalence estimate for adult ADHD in the meta-analysis were well within the ADHD prevalence range that we found in the IASP study, but the broad range in ADHD prevalence was found in both



studies. In the next paragraph, we will discuss some potential factors that may affect the ADHD prevalence in SUD patients (see below).

Our findings of a high prevalence of ADHD in SUD patients were corroborated in two recent studies. In a study with 233 treatment seeking drug use disorder patients in Nigeria, the prevalence of ADHD was 21.5%,<sup>1</sup> which is very similar to the overall estimate of our meta-analysis in chapter 3. Furthermore, the prevalence of ADHD in an American sample of treatment-seeking patients with a cannabis use disorder was estimated to be between 34% and 46%, using a combination of different screening instruments and the CAADID as the gold standard.<sup>2</sup> This is even higher than the prevalence that we found in our studies and again suggests that the prevalence of ADHD in SUD patients is dependent on several factors; possibly, cannabis use disorders are associated with a higher prevalence of ADHD, but this observation needs replication.

### *Factors influencing the prevalence of ADHD in SUD*

In our meta-analysis, we found that the prevalence of ADHD among subjects with SUD was independently affected by the primary substance of abuse and by the instrument that was used to establish the presence of ADHD. In the IASP, we looked at the influence of setting (outpatients versus inpatients), country and primary substance of abuse. In this latter study, we found a higher prevalence of ADHD among inpatients than among outpatients and among Nordic SUD patients compared to non-Nordic SUD patients. The reason for this finding is still unclear, but an influence of solar intensity on ADHD prevalence has been reported with higher solar intensity putatively protecting against ADHD by regulating the circadian rhythm.<sup>3</sup> With regard to the influence of the primary substance of abuse we found in the IASP that ADHD was more prevalent in patients with a drug use disorder (including cocaine and cannabis use disorders) than in patients with an alcohol use disorder, whereas our meta-analysis unexpectedly indicated a lower ADHD prevalence among patients with a cocaine use disorder (compared to other substance use disorders). Unfortunately, the groups in the IASP study were too small and the substance use disorder diagnosis not specific enough for an in-depth analysis of patients with a cocaine use disorder versus patients with a cannabis use disorder and thus we do not know whether the higher ADHD prevalence in drug abusers was due to the higher prevalence in the subgroup of cocaine use disorder patients, the subgroup of cannabis use disorder patients or both. The recently reported high prevalence of ADHD in cannabis abusers in Nigeria<sup>1</sup> could provide an explanation for this combination of findings: cocaine abuse was associated with a relatively low prevalence of ADHD compared to alcohol and other drugs, whereas cannabis abuse (and thus drug abuse as an overarching group) was associated with a relatively high prevalence of ADHD. However, more specific studies are needed to draw final conclusions on this issue.

### *Prevalence of SUD in ADHD patients*

These high levels of comorbidity between ADHD and SUD are in line with several prospective studies that followed children, adolescents or young adults with ADHD and demonstrated

a higher risk of developing SUD in ADHD children and adolescents than in their non-ADHD peers.<sup>4-8</sup> Interestingly, one study found that having a history of early life maltreatment played a mediating role in the development of SUD, because youths with ADHD without a history of maltreatment were not at a higher risk of developing SUD than their peers without ADHD.<sup>9</sup> A large meta-analysis found that externalizing disorders such as ADHD, OD and CD confer a much larger risk on developing SUD than internalizing disorders do.<sup>10</sup> Below, we report on several factors that are relevant for the development of SUD in ADHD patients.

### ***ADHD subtypes and the development of SUD***

A growing number of studies focused on how the different subtypes of ADHD are associated with the development of SUD. In a cross-sectional study with 413 adult ADHD patients, lifetime substance abuse or dependence was 26%. Patients with the inattentive subtype (in adulthood) were less likely to abuse cocaine than patients with the combined subtype of ADHD.<sup>11</sup> Similarly, in the NESARC study (n=33,588), hyperactive/impulsive symptoms were more strongly associated with SUD than inattentive symptoms.<sup>12</sup> On the other hand, inattention symptoms and not hyperactivity symptoms were a significant predictor of nicotine dependence in a large prospective population-based study following 1,803 children. The strongest predictor of SUD in this study, however, was oppositional behavior during elementary school.<sup>13</sup> In a recent study by Zohsel et al., again conduct/oppositional behavior problems in childhood and inattention problems during adolescence were found to be predictive of problematic cannabis use during young adulthood.<sup>14</sup> Thus, although inattention symptoms and co-occurring behavioral problems seem to confer the main risk of SUD in some studies, the role of these symptoms is restricted in others and it is still unclear which symptoms are mainly responsible for the risk of SUD.

### ***Mechanisms underlying the comorbidity between SUD and ADHD***

Numerous studies have tried to elucidate the reasons for the high co-occurrence of SUD and ADHD. First of all, temperament traits such as behavioral control are known to contribute to addiction vulnerability. These traits are closely linked to ADHD symptoms or might even be considered as ADHD (related) behaviors. Thus, temperament traits clearly link the two disorders.<sup>15</sup> Furthermore, several studies have focused on a genetic basis for the comorbidity of SUD and ADHD by demonstrating that shared genetic factors underlie both SUD and ADHD.<sup>16-18</sup> For example, in a study with 6,024 Dutch twins, ADHD symptoms and problem drinking were significantly correlated, and genetic influences explained 61-100% of this association.<sup>18</sup> From a neurobiological point of view, Frodl examined whether similarities exist in neuro-imaging findings between patients with ADHD and those with addiction-related craving, and found similarities in PET and fMRI studies, but not in structural MRI and MR spectroscopy, suggesting that there is some evidence for a common pathophysiological substrate for the two disorders.<sup>19</sup> Next, as we saw before, comorbid behavioral problems are reported to increase the risk of SUD in ADHD patients.<sup>13,14</sup> Data from cognitive and neurophysiological research suggested that impulsivity plays a key role in the development of SUD among ADHD patients. A review of the literature on different

impulsivity-related constructs indicated that ADHD and SUD share neurophysiological deficits such as abnormal brain activity in areas involved in inhibition and complex cognitive-emotional processes.<sup>20</sup> However, in a systematic review of neuroimaging research focusing on impulsivity as hypothesized mechanism underlying SUD risk, dysfunction of cognitive functions including the inhibitory control network seemed to play only a minor role, but dysfunction of the motivation-reward processing network was predictive of a high risk of SUD in ADHD patients.<sup>21</sup> This dovetails nicely with the findings of a prospective follow-up study by Groenman et al., who found that inhibition tasks and other so-called 'cold' executive functions did not predict later SUD in children with ADHD. 'Hot' executive functions such as reward processing were not included in this study but were theorized to be more relevant.<sup>22</sup> These findings, however, do not seem to match very well with data on the protective effects of stimulant medication on development of later SUD in ADHD patients, because stimulants mainly exert a beneficial effect on attention and inhibition in ADHD patients but not on motivation-reward processes. Clearly, there are more factors involved in this complex issue. The self-medication hypothesis proposing that substances are used to alleviate negative affect (for example depressive symptoms as a result of frequent experiences of failure), to improve executive functioning (cocaine use to reduce impulsivity) or to alleviate sleeping problems (cannabis use to fall asleep), provides a bio-psychological explanation for the high amount of SUD problems in ADHD patients,<sup>23</sup> although the evidence for this model is limited. A recent study exploring the reasons why ADHD patients are using substances found that a strong yearning to belong was a key factor, with patients indicating that substances made them feel more 'normal' and accepted by others.<sup>24</sup> Other possible mechanisms which have been mentioned but still have to be studied in more detail, are the role of ADHD-related impairments such as social rejection which may lead to affiliation with substance-using peers in some cases, just as possible moderators of these trajectories (e.g. parenting strategies).<sup>15</sup>

### ***Possible role of ADHD medication in developing SUD***

Although initially concerns were raised by clinicians and researchers that stimulant treatment of children with ADHD might enhance the risk of developing SUD later in life, the opposite seems to be more likely. Some studies did not find an effect of ADHD medication on subsequent SUD development,<sup>25,26</sup> but most evidence points to a protective effect of stimulants if medication was started early and used consistently for a longer period.<sup>27-30</sup>

### ***Conclusion of research question 1:***

The prevalence of ADHD in SUD patients is generally high but varies between studies (10-30%). Country (Nordic versus non-Nordic), primary substance of abuse, setting and the diagnostic instrument for ADHD all have an influence on the prevalence of ADHD in SUD patients. In addition, we conclude from the relevant literature that children and adolescents with ADHD are at an increased risk to develop SUD in later life compared to normal controls, and that genetic factors, comorbid behavioral problems, and dysfunctional motivation-reward processing, among other factors, explain this finding. Finally, stimulant treatment of

ADHD starting at an early age may prevent the development of SUD.

## **2. Does the comorbidity profile of SUD patients with ADHD differ from SUD patients without ADHD?**

In **chapter 5**, we reported on the more complex comorbidity profile of SUD patients with ADHD compared to SUD patients without ADHD in the IASP study. SUD patients with ADHD had one or more additional comorbidities in 75% of cases, whereas this was true in “only” 37% of SUD patients without ADHD.

In the same IASP study, Konstenius and colleagues showed that childhood trauma exposure was more frequently reported in SUD patients with ADHD than in SUD patients without ADHD,<sup>31</sup> and Wapp et al. reported that ADHD had a higher prevalence in SUD patients with borderline personality disorder than in SUD patients without borderline personality disorder.<sup>32</sup> As the IASP study was cross-sectional, only associations between ADHD and comorbid disorders such as borderline personality disorder could be established, and no conclusions about the temporal relations or causality could be drawn. Other (prospective) studies, however, have reported that ADHD is a risk factor for the development of a wide variety of psychiatric disorders, such as mood disorders, anxiety disorders and personality disorders.<sup>33,34</sup> This is in line with our finding that SUD patients with ADHD had a more complex comorbidity profile than SUD patients without ADHD.

It should also be noted that some patients in our study met diagnostic criteria for no less than six disorders at the same time (SUD, ADHD, antisocial disorder, borderline personality disorder, depression and (hypo)mania). One could wonder if it is correct to endorse all these disorders as separate entities. It might be better to conclude that some ‘symptoms are better explained by some other disorder’ as DSM advocates.<sup>35</sup> Also, one could argue whether the combination of several disorders should be seen as the presence of distinct disorders or as a representation of some common and rather severe underlying psychopathology. In line with this, Kendler and colleagues identified two general genetic factors: one for internalizing disorders (such as depression and anxiety), and one for externalizing disorders (conduct disorder, antisocial personality disorder, SUD, ADHD).<sup>36</sup> These more fundamental questions on the concept of comorbidity do not alter the fact that in general, SUD patients with ADHD clearly suffer from more psychopathological symptoms than SUD patients without ADHD and that clinicians should assess different symptom domains in these patients at the start of and during treatment to provide optimal and tailored treatment.

The finding that SUD patients with ADHD are overall more complex than SUD patients without ADHD, implies that standard treatment for this patient group may not be sufficient, and underlines the need for research into tailored treatment interventions, such as integrated treatments in which not only substance use is targeted, but also ADHD and possibly other comorbid disorders.

### **Conclusion research question 2:**

The comorbidity profile of SUD patients with ADHD is much more complex than the comorbidity profile of SUD patients without ADHD.

### **3. Can ADHD be diagnosed during active substance use?**

The findings of our test-retest study in **chapter 8** suggest that a diagnostic assessment of ADHD can reliably be performed during active substance use, because a positive diagnosis is likely to be confirmed after a period of reduced substance use or abstinence. It should be noted, however, that we did not test whether the absence of a diagnosis of ADHD during active substance use could also be confirmed after a period of abstinence. Findings from the IASP study, where the screening instrument was re-administered after a period of a few weeks, however, indicate that only a small minority of patients had a false negative screening result at intake. Therefore, we conclude that ADHD can indeed be diagnosed during active substance use.

Although our study was the first to directly examine the validity of a diagnosis of ADHD during active substance use, some other studies have studied the influence of substance use on ADHD symptoms from another angle. For example, one study reported an increase of ADHD symptoms (measured with the ADHD Investigator Symptom Rating Scale) related to relapse of alcohol abuse in a subgroup of 75 placebo-treated ADHD patients with alcohol use disorder.<sup>37</sup> This study suggests that ADHD symptoms can worsen under the influence of substance use, but nevertheless in these patients, ADHD symptoms were already high also during abstinence.

The relevance of our study results is illustrated by a recent international consensus paper on the diagnosis and treatment of SUD patients with comorbid ADHD<sup>38</sup> stating that the diagnostic process of ADHD should start as soon as possible, when there are no serious withdrawal or serious intoxication symptoms, that abstinence is not required, but that verification of the diagnosis in the course of SUD treatment is recommended. Our study contributes to the evidence-base of this expert consensus. The finding that a diagnostic assessment of ADHD is possible during active substance use directly impacts the feasibility of our newly developed integrated cognitive behavioral therapy for SUD and ADHD (**chapter 7**). Such a treatment can only be provided if a diagnosis can reliably be made in an early stage of treatment. For some patients, it is their only chance to receive a formal ADHD diagnosis and treatment advice, because they are very likely to drop out of addiction treatment in a later stage (i.e. on the way to abstinence) (**chapter 11**). Furthermore, they may also have received at least some psycho-education on ADHD if this is done timely.

### **Conclusion research question 3:**

In patients with SUD, a reliable diagnosis of comorbid ADHD can be made during the first days after admission when patients are still actively using substances, but verification of the diagnosis during the treatment process is recommended.

#### **4. What is the efficacy of adding a shortened CBT specifically focusing on ADHD symptoms to regular therapy for SUD in patients with both conditions?**

Over the last decade, research into different treatments for ADHD in SUD patients has emerged. Medication is an important treatment modality, but the literature on the effect of ADHD medication in SUD patients with comorbid ADHD is rather inconsistent. Most placebo-controlled studies found no or only a very small effect of stimulant medication on ADHD symptoms and generally no effect on substance use,<sup>39-43</sup> but recently two studies have shown promise for a treatment with high doses of stimulant medication in stimulant dependent patients with comorbid adult ADHD with positive effect on both ADHD symptom severity and drug use.<sup>44,45</sup> We decided to investigate the efficacy of another treatment modality, namely cognitive behavior therapy (CBT) for ADHD in patients with SUD (**chapter 8**). CBT had already been shown to be effective in adult ADHD patients without comorbid SUD,<sup>46-51</sup> although one study did not find a difference between group CBT and individual clinical management.<sup>52</sup> Also in adolescents, several studies demonstrated the effectiveness of CBT for reducing ADHD symptoms,<sup>53,54</sup> with sustained positive effects after one-year follow-up,<sup>55</sup> Recently, an open feasibility study was published in which a self-reported decline of ADHD symptoms was reported among the participants of a skills training for men with ADHD in compulsory care for SUD,<sup>56</sup> with training elements derived from Dialectical Behavioral Therapy. Our study was the first randomized controlled trial investigating the effect of CBT for ADHD in a double-diagnosis population of SUD patients with ADHD.

##### ***Primary outcome***

We found that patients who received integrated CBT reported significantly less ADHD symptoms after treatment than patients who received standard SUD treatment, i.e. treatment focusing on motivation, coping and the prevention of relapse in substance abuse. The between-groups effect size for ADHD symptoms at post-treatment was 0.34, which is lower than the effect size of the study by Safren et al.<sup>47</sup> who used the original ADHD intervention among adult ADHD patients without SUD, but which is nevertheless a clinically relevant effect. Moreover, one should bear in mind that the study by Safren et al. tested the intervention against placebo psychotherapy (relaxation therapy), whereas in our study evidence based CBT (for SUD) was the control condition. Furthermore, absolute effects (pre-post) were much larger and again showed a clear difference between the two treatment conditions.

##### ***Secondary outcomes***

For all the secondary outcomes (substance use, depressive and anxiety symptoms and quality of life), patients in both treatment groups improved equally. Although we hypothesized that treating ADHD would also have a favorable effect on substance use, a larger reduction of ADHD symptoms was not immediately translated into a larger reduction of substance use. Interestingly, symptoms of depression and anxiety improved in both conditions, even though the treatments were not specifically aimed at treating depression or anxiety. One

wonders whether these symptoms were partly drug-induced. CBT/Integrated also had no additional benefit in terms of quality of life (measured with the EQ-5D), compared to standard addiction treatment. Possibly, the 5-item EQ-5D was not sensitive enough to catch subtle differences in everyday functioning that might have occurred in the CBT/Integrated compared to the CBT/SUD condition as the EQ-5D comprised only one question on daily functioning at home, work and other activities, with 3 possible answers (normal functioning, some problems, or not able to function at all). On the other hand, it is also possible that CBT/Integrated did not result in a better quality of life compared to CBT/SUD, in which case the cost-effectiveness of CBT/integrated could be questioned (see also paragraph on cost-effectiveness below).

### *Effective elements in CBT/Integrated*

For the treatment of ADHD, CBT/Integrated applied elements that were described by Safren et al. in their treatment protocol for ADHD<sup>57</sup> but now in a more condensed version. Five ADHD-related elements were addressed in CBT/Integrated, but we do not know which of these elements contributed (most) to the treatment effect. The emphasis of the treatment was on implementing planning and organizing skills, which was the first element of the ADHD treatment and it was rehearsed in all subsequent sessions. In most other CBT treatment programs for ADHD,<sup>47,48,53</sup> planning and organizing skills are a key element as well, suggesting that this might be at least one of the effective elements. Indeed, secondary analyses using the inattention and hyperactivity/impulsivity subscales of the ARS as outcomes revealed a significant difference between treatment groups at post-treatment on the inattention subscale of the ARS ( $p=0.026$ ) but not on the hyperactivity/impulsivity subscale ( $p=0.059$ ) (data not shown in **chapter 9**), although the latter effect was borderline significant as well. In other studies on CBT for ADHD, data were not shown for the inattention and hyperactivity/impulsivity subscales, except for the study by Young et al. in which CBT resulted in a significant reduction of ADHD symptoms in both subscales.<sup>50</sup>

### **Conclusion research question 4:**

Integrated cognitive behavioral therapy (CBT/Integrated) aimed at the treatment of both SUD and ADHD is effective in further reducing ADHD symptoms, but not in further reduction of substance use, depressive and anxiety symptoms, and not in improving quality of life compared to CBT/SUD.

### **5. Which patient factors influence drop-out and efficacy of an integrated cognitive behavioral therapy for SUD and ADHD? Which patients factors are suitable for patient-treatment matching?**

Further analyses of the data of our RCT showed that drug use disorder (compared to alcohol use disorder) and reduced planning abilities (measured with the Tower of London) were associated with higher drop-out in the early phase of treatment, i.e. before starting the first ADHD element of the integrated treatment. The presence of more ADHD symptoms at post-

treatment and follow-up in the integrated treatment were predicted by higher depression and anxiety symptoms and by the use of ADHD medication at baseline, whereas higher levels of substance use at post-treatment and follow-up were (unexpectedly) predicted by higher planning abilities (measured with the Tower of London). There were no patient characteristics to guide patient-treatment matching (**chapter 11**). Our findings about early drop-out are in line with the existing literature on this topic, in which diminished cognitive functioning is consistently associated with low treatment adherence.<sup>58,59</sup> Other risk factors for drop-out that were found in a systematic review include low treatment alliance, comorbid personality disorder, and younger age.<sup>58</sup> The latter was not confirmed in our study and we had no data on treatment alliance and comorbid personality disorder.

To date, there are only very few data available on the prediction of treatment outcome in RCTs in SUD patients with comorbid ADHD. In an RCT with 299 adolescents receiving osmotic release methylphenidate or placebo with concurrent CBT for SUD, post hoc prediction analyses revealed that SUD severity was associated with poorer ADHD and SUD outcome, whereas ADHD severity was associated with better treatment outcome for ADHD and SUD.<sup>60</sup> Our finding that absence of ADHD medication at baseline is associated with better ADHD symptom outcome is probably explained by the fact that the patients with more severe ADHD symptoms have a higher probability of having received a diagnosis and medication treatment earlier in life.

Treatment matching has also been understudied in ADHD research. We only found data of an RCT comparing 2 CBT's for adolescents with ADHD (without SUD). In this study comparing a planning focused intervention with a solution focused intervention, post-hoc analyses revealed that in a subgroup of patients with comorbid anxiety symptoms but low depression symptoms the planning intervention was the preferred treatment.<sup>61</sup>

### **Conclusion research question 5:**

Drug use disorders (versus alcohol use disorder) and impaired planning are associated with early drop-out from treatment. More severe anxiety, depression and probably ADHD at baseline predicted worse ADHD outcomes. No patient or disorder characteristics were identified that could be used for the matching of certain patients to either CBT/Integrated or CBT/SUD.

## **METHODOLOGICAL CONSIDERATIONS**

In the consecutive chapters, we already discussed the methodological issues related to the specific studies. In this chapter, we will point out more general methodological aspects of our studies.

### **Studies in part II of this thesis (chapters 3-6)**

#### *Measurement*

According to guidelines and a consensus statements, information from an informant such



as a family member is highly recommended in the assessment of ADHD.<sup>38,62,63</sup> In the IASP prevalence study (**chapter 5**), however, this information was not required for the diagnostic process. The main reason for this was a practical one: many patients in addiction care have troubled relationships with their families and we did not want to exclude all these patients from our study, because it would result in reduced external validity. According to some researchers, the use of informants results in a better recognition of ADHD symptoms,<sup>64</sup> and at the same time, it may prevent the clinician from endorsing ADHD symptoms too easily.<sup>65</sup> Thus, it is unclear in which direction our results of the ADHD prevalence may have been influenced by the lack informant reports.

### *Power*

Although the studies described in part two of this thesis were based on large numbers of patients, the samples were still quite small for more differentiated subgroup analyses. For example, analyzing subgroups of patients with different primary substances of abuse was not possible except in the meta-analysis; in the other studies, subgroup analyses based on the primary substance of abuse were confined to the broad distinction between alcohol or drugs and no distinction could be made between the different drugs.

### *External validity/ generalizability*

Because information about the initial number of referred patients (i.e. potential inclusions) and the number of actual inclusions in the IASP were not provided by all study centers, sampling bias may have occurred. As a consequence, SUD patients with ADHD symptoms may have been overrepresented, leading to an overestimation of the prevalence of ADHD. After inclusion in the IASP, a considerable number of patients also dropped out from participation after completing the screener but before participating in the full assessment with the CAADID, which may also have led to an overrepresentation of patients with a positive result on the ADHD screener in the full assessment. However, this was accounted for in further analyses on the ADHD prevalence. Moreover, the prevalence estimates of the IASP study were well within the 95% CI of the prevalence of ADHD that we found in our meta-analysis, suggesting that the prevalence estimates of the IASP study were not seriously hampered by sampling bias.

The patients in the IASP study were recruited from a range of different addiction treatment services; inpatient and outpatient clinics, alcohol clinics, drug clinics, and mixed other clinics, short and longer treatment programs. This enhances the generalizability of the findings although it is not clear to what extent the sample was representative of all country-wide service attendees.

## ***Studies in part III of this thesis (chapters 7-11)***

### *Study design*

As our RCT was the first to assess the value of CBT/Integrated, we wanted to test if an extension of standard addiction care with 5 sessions of ADHD treatment had any benefit

over standard addiction care. This resulted in two interventions of different intensity: 15 sessions in CBT/Integrated and 10 sessions in CBT/SUD. This could mean that the benefit of CBT/Integrated over CBT/SUD was due to treatment dose rather than to specific treatment activities. However, as the difference between both treatments was only seen in ADHD symptoms and not in anxiety, depression and quality of life, we think that the difference in outcome was not merely a result of a higher treatment dose, but a specific effect of the intervention.

### ***Measurement***

As mentioned earlier, another limitation is that diagnostic information on ADHD criteria from a key informant was also not available in the studies in part 3 of this thesis.

The fact that many people were not fully abstinent at the second assessment limits the ability to draw firm conclusions in the test-retest study (**chapter 8**). However, sensitivity analyses in subgroups of fully abstinent patients yielded similar results as in the total group, which clearly supports our conclusion.

### ***Power***

With fewer randomized patients than originally planned and with more drop-outs at post-treatment and follow-up, our RCT was slightly underpowered to detect relatively small but clinically relevant differences. Especially at follow-up, it is likely that a difference in ADHD symptoms between both conditions was not statistically significant due to the reduced sample size, indicated by the fact that the absolute difference in ADHD symptoms between the groups at follow-up was similar to the difference at post-treatment.

### ***External validity/ generalizability***

The patients in the RCT with integrated cognitive behavioral therapy had different substances of abuse but were all outpatients (with the possibility of a one-week inpatient detoxification). The most complex SUD patients were allocated to a 3-month inpatient treatment program and thus not included in this study. It is unknown whether CBT/Integrated would have had similar benefits in this complex inpatient group. However, we do know that in general, the more complex outpatients included in the RCT had a higher probability of early treatment drop-out. We also do not know how the current findings relate to the group of patients who could be recruited from ADHD outpatient treatment clinics, i.e. ADHD patients with less severe SUD problems in general. Thus, our findings and our conclusions regarding CBT/Integrated are limited to SUD patients with comorbid ADHD recruited at an addiction treatment center and with moderately severe SUD.

## ***General methodological considerations***

### ***Implications of our findings for the changes from DSM-IV to DSM-5***

The studies in this thesis used DSM-IV criteria for ADHD, SUD, and additional comorbidities. However, these criteria were changed in DSM-5.<sup>35</sup> For ADHD, the symptom threshold

changed from 6 to 5 symptoms (in one category of inattention or hyperactivity/impulsivity) in adulthood, and the minimum age of onset criterion changed from 7 to 12 years. This lowering of the number of symptom criteria was a result of the finding that there is a decline in ADHD symptoms as patients age. The change in the maximum starting age in DSM-5 was made because it is often hard to remember the exact starting point of symptoms.<sup>35</sup> The new criteria were meant to reduce false negative diagnoses. Critics, however, have claimed that the prevalence of ADHD might rise to unreasonable high levels due to an increase of false positive diagnoses due to this change in criteria. For SUD, substance abuse and substance dependence were combined resulting in a single diagnosis of substance use disorder, for which a minimum number of two out of eleven symptoms is required. Craving was added to the list of symptoms, and recurrent legal problems stemming from substance use was removed as a criterion. Mild, moderate or severe forms were specified according to the number of criteria: mild 2-3 criteria, moderate 4-5 criteria, and severe  $\geq 6$  criteria. Changing the criteria for disorders may affect both the prevalence of disorders and the relationship between disorders under study. In the IASP study, however, the effect of the changed criteria on the ADHD prevalence was found to be very small (**Chapter 5**): the prevalence range of ADHD in SUD patients hardly changed: from 5.4-31.3% to 7.6-32.6%.<sup>66</sup> In a large population study, the DSM-5 prevalence of substance use disorders was also very similar to the DSM-IV prevalence, with a slightly higher prevalence for DSM-5 alcohol use disorder and a slightly lower prevalence for DSM-5 cannabis use disorder compared to DSM-IV.<sup>67</sup>

## IMPLICATIONS FOR CLINICAL PRACTICE:

### *Service delivery*

The identification and treatment of ADHD in SUD patients, described in this thesis, are an example of how general psychiatry and addiction care can be integrated and how patients may benefit from it. In The Netherlands, mental health and addiction treatment services are still largely separate with limited collaboration, but the need to collaborate is more and more recognized by both sides. As we discussed in **chapter 7**, treating SUD and ADHD separately seems suboptimal. Careful diagnostic evaluation of comorbid disorders in patients with SUD also fits the growing interest in personalized medicine, rather than applying a one-size-fits-all approach. The high prevalence of additional comorbidities (such as depression or personality disorders) in SUD patients with ADHD that was demonstrated in **chapter 6**, underlines this finding. The ASRS, a screening instrument for ADHD, was found to have good psychometric qualities in a SUD population<sup>68</sup> which - together with the high prevalence of ADHD in SUD patients - makes routine screening of ADHD in SUD populations not only possible but also necessary.

### *Implementation of CBT/Integrated*

The high prevalence of ADHD in SUD patients (**chapter 3**), the possibility to diagnose ADHD in an early stage (**chapter 8**), and the development of an integrated treatment which has

now been shown to further reduce ADHD symptoms in SUD patients with ADHD (**chapter 9**) all seem to be in favor of a broad implementation of CBT/Integrated in clinical practice. Furthermore, its benefits are not restricted to specific patient subgroups according to our treatment matching analyses (**chapter 11**). However, there are some caveats when considering this treatment for widespread use, because data on the cost-effectiveness and long-term efficacy are not available yet, and no effect was found on quality of life (compared to CBT/SUD). Also, direct comparisons with other treatment modalities such as (high dose) stimulant medication are not available yet. Furthermore, integrated treatment did not improve treatment retention, with drop-out still being an important clinical problem, especially early in treatment. As we showed in **chapter 11**, lower cognitive functioning was one of the drivers of non-adherence. This finding is consistent with other studies on drop out from addiction treatment, and suggests that patients with lower cognitive functioning might need other interventions to prevent them from dropping out and enabling them to benefit from treatment. These are all important issues for further research, and will be discussed in the last paragraph.

## **RECOMMENDATIONS FOR FUTURE RESEARCH**

### ***Cost-effectiveness***

Now we know that CBT/Integrated is effective in reducing ADHD symptoms, a cost-effectiveness analysis is warranted to investigate whether CBT/Integrated is not only effective but also cost-effective. CBT/Integrated consists of more sessions than CBT/SUD which implies higher costs, and both treatments were equally effective in enhancing quality of life, although this was measured in a rather broad way with the EQ-5D. We have not shown whether CBT/Integrated may still be more cost-effective due to, for example, higher productivity at work. Data on this subject have been collected in the RCT and will be analyzed later.

### ***Long-term effects of CBT/Integrated***

CBT/Integrated outperformed CBT/SUD at post-treatment in terms of reduction of ADHD symptoms. At 2-months follow-up, the difference was still the same but no longer statistically significant probably due to study drop-out and the related reduced power. However, we currently have no data on long-term efficacy of CBT/Integrated. In the study by Safren et al. on CBT for ADHD though, a significant benefit for the intervention was shown up to 12-months follow-up.<sup>47</sup> More research into the long-term efficacy of CBT/Integrated is important to better understand its value over time.

### ***Value of CBT/Integrated compared to other treatment modalities***

CBT/Integrated was tested in patients who predominantly did not use ADHD medication and we do not know what the effects of CBT/Integrated will be when it is applied in conjunction with medication or when it is tested against medication only, nor do we know whether

different treatment modalities may work for different patients (patient-treatment matching/personalized medicine). Moreover, only very few studies have explored potential relevant factors that predict treatment outcome in SUD+ADHD patients. These are important research questions to address. The international collaboration for ADHD and substance Abuse (ICASA) is currently conducting a naturalistic study to address these questions: International Naturalistic Cohort Study of ADHD and Substance Use Disorders (INCAS).

### ***Integrated therapy for multiple disorders***

As was shown in **chapter 5**, SUD patients with ADHD often suffer from additional comorbidities. CBT/Integrated addresses only SUD and ADHD and leaves additional comorbidities untreated. Perhaps future treatments could adapt to specific symptoms of a patient in a more flexible way, by using modular treatment components for clusters of symptoms and tailoring interventions from them. Positive results with this approach have been shown in CBT-E for eating disorders, where a range of co-existing problems are targeted as well, depending on individual needs.<sup>69</sup> Research into such symptom-driven treatments in addiction is warranted.

### ***Diminishing drop-out***

The high drop-out rates in SUD treatment are another major challenge in clinical practice. As described earlier, cognitive problems are a well-known predictor of drop out. Partly as a result of alcohol or substance use, but often pre-existing to substance use problems, cognitive impairments are frequently observed in SUD patients (especially in those with comorbid ADHD) and tend to improve only minimally.<sup>70</sup> Patients with lower cognitive functioning might benefit more from other interventions than traditional CBT, such as contingency management which has lower drop-out rates than more traditional therapies.<sup>71</sup> Alternatively, they might need additional interventions such as cognitive training or cognitive rehabilitation to improve the effectiveness of traditional therapies.<sup>72-74</sup> Apart from a combination with traditional therapies, research has also focused on the question if cognitive training is an effective SUD treatment on its own. In patients with problematic alcohol use, who were mixed with regard to educational level, working memory training improved working memory and reduced alcohol abuse in a study by Houben et al, in which working memory training was the sole intervention.<sup>75</sup> Finally, research into cognitive enhancers suggests that cognitive functioning can be improved through medication, such as stimulants, which could be combined with CBT.<sup>76</sup> These findings call for further development, study and implementation of alternative strategies to improve treatment retention and outcome for this group.

### ***Prevention***

Maybe one of the most important topics for future research is the prevention of SUD in children and adolescents with ADHD. Knowing that many ADHD patients develop SUD, we obviously want to find out how we can prevent adolescents with ADHD from developing SUD. Until now, studies have focused on the question whether the early initiation of

stimulant medication increases or decreases the risk to develop SUD with most data suggesting that (early initiation of) stimulant treatment at least does not increase the risk of SUD<sup>25,26</sup> and with an increasing number of studies showing that early treatment of ADHD with stimulant medication substantially reduces the risk of developing SUD.<sup>27-30</sup> However, the Multimodal Treatment of ADHD (MTA) trial, which compared medication management, behavioral treatment and a combination of these in 7-9 year old children, found that after a 6-8 years follow-up period, no differences existed between study groups, including on substance use outcomes.<sup>77</sup> Possibly, no effects of medication on substance use outcomes were found because medication exposure was too low in this study; after the initial 14-month treatment period, this study became an uncontrolled naturalistic study, with the majority of patients in the medication treatment arm stopping medication use some time during follow-up. With regard to behavioral treatment, this study suggested that behavioral treatment of ADHD in childhood did not moderate the risk of SUD development later in life. Studies which examine the effect of cognitive therapies in adolescents with ADHD on SUD development are lacking. Since the development of SUD in ADHD patients is the result of a complex interplay between multiple risk factors, prevention should target different factors simultaneously. Given the large numbers of ADHD patients with SUD, and the detrimental effects of SUD,<sup>78</sup> more insight into preventive strategies could make an enormous public health contribution.

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## EPILOGUE

At the start of this thesis (see prologue), we presented the case of John. Bearing the results of this thesis in mind, we now have more knowledge and tools when patients like John seek treatment for their substance use problem at the Jellinek Addiction Treatment Centre:

- John has a substantial risk of having a comorbid diagnosis of ADHD: overall, an average 23.1% of SUD patients have ADHD (chapter 3) and at the outpatient Jellinek Addiction Treatment Centre, 10% of the SUD patients have ADHD (chapter 5, table 2).
- If John has comorbid ADHD, he is very likely to also have other comorbid disorders (chapter 6), such as mood disorders and personality problems.
- Screening and diagnostic assessment of ADHD can be performed directly at intake (chapter 8) instead of waiting for full substance use stabilization or abstinence for 2-4 weeks or even more (and with a serious risk of drop-out).
- In the case of comorbid ADHD, we can offer John an integrated treatment of SUD and ADHD with cognitive behavioral therapy. This is effective in reducing both SUD and ADHD symptoms, and it also decreases depressive and anxiety symptoms and improves quality of life (chapter 9).
- Since alcohol is his primary substance of abuse, the odds that John will complete treatment and benefit from it is rather good (chapter 11).



# **PART V:**

## APPENDIX

