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CHAPTER 2

AN INTRODUCTION TO ADHD AND ADDICTION

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ABSTRACT

Attention deficit hyperactivity disorder (ADHD) is characterized by symptoms of inattention and/or hyperactivity and impulsivity. It is frequently present in substance use disorder (SUD) patients; estimates of the prevalence of ADHD vary between 14% and 23% in SUD populations. The high comorbidity is partly based on communal underlying neurobiological characteristics such as a shared genetic background of the two disorders. Neuropsychological correlates of both disorders include a dysfunction of the motivational/reward system and impulsivity. In general, patients with this type of comorbidity represent a more severe subgroup of SUD patients with more additional comorbidity and a more disadvantageous prognosis and higher treatment drop-out than SUD patients without ADHD. It is important to detect and treat ADHD in SUD patients, and substance use disorder treatment centers can play an important role in this by screening for ADHD. Treatment options may include medication, although convincing evidence of effect in SUD populations is yet lacking, and cognitive behavioral therapy. As problems of SUD and ADHD can be intertwined, it is appropriate to start ADHD treatment during SUD treatment, ideally after initial stabilization of substance use. As this patient group is characterized by high complexity, further research and development of integrated treatment programs are warranted.

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common psychiatric disorders in childhood, affecting approximately 4-8% of children in the general population.¹ Although symptoms wane in some patients in adulthood, the majority of patients continues to be impaired by their symptoms,² leading to a prevalence of 1-5% in adulthood.³

ADHD is characterized by symptoms of attention deficit and/ or hyperactivity and impulsivity. Three different subtypes exist: patients who exhibit mainly attention deficit symptoms have the attention deficit subtype, whereas patients experiencing mainly hyperactivity and impulsivity symptoms are diagnosed with the hyperactive/ impulsive subtype. The majority of the clinical population has symptoms in both domains, and is diagnosed with the combined subtype.⁴ In line with recent changes in the classification of psychiatric disorders in which axis I and II are no longer distinguished, the difference between ADHD and personality disorders in terms of its lifelong impact can be debated, as ADHD starts at young age and its symptoms often persist in adulthood. ADHD can lead to functional impairments in all domains of life. It is associated with lower level of education, higher level of unemployment, but also higher rates of unsuccessful marriages, criminality and road traffic accidents.^{5, 6} Altogether, these consequences are responsible for a reduced quality of life, which is also caused by the fact that ADHD is often accompanied by comorbid disorders. Antisocial personality disorder, borderline personality disorder, mood disorders and anxiety disorders are frequently present and have an impact on the prognosis.^{7, 8} Substance use disorders (SUDs) are also an important comorbid disorders in ADHD patients, affecting 15% of adult ADHD patients.⁹

Several treatment options for adult ADHD exist. Pharmacological treatment with stimulants such as methylphenidate is by far the most described treatment modality, resulting in symptom improvement in a majority of patients .¹⁰ Although symptoms of for example inattention can be improved by medication, medication offers no solution for the fact that planning and organization skills are often not developed to their full potential. Recently, therapists and researchers in the field have focused on developing a cognitive behavioral therapy (CBT) for ADHD patients, that addresses these functional skills.¹¹ More research is needed to corroborate their promising results, and also to investigate other treatment options.

In this chapter, we will provide an overview of the epidemiology of SUD patients with comorbid ADHD, and of the neurobiological correlates of this type of comorbidity. We will then focus on the clinical presentation, treatment and prognosis of these patients, and end with recommendations for future research.

EPIDEMIOLOGY OF ADHD IN SUD PATIENTS

Several studies have shown that children with ADHD have a greater risk of developing SUD later in life than children without ADHD.¹² Not surprisingly, the prevalence of ADHD in SUD patients is much higher than in the general population; a meta-analysis of predominantly American studies estimated the prevalence of ADHD in SUD patients to be 23.1%¹³ and in

the largest study so far in 3558 SUD patients in 10 mostly European countries, prevalence rates ranged from 5.4 to 31.3% depending on country.¹⁴ The latter study found significant differences between countries, with Scandinavian countries having a higher ADHD prevalence than for example southern European countries. Also, differences were found between patients with different types of SUD, as a lower ADHD prevalence was found among alcohol dependent patients compared to illicit drug dependent patients. Altogether, these findings suggest that ADHD is a frequently present comorbid disorder in SUD patients. Several factors contribute to this high co-occurrence of both disorders. In the next paragraph, genetic and neurobiological mechanisms explaining the high comorbidity are discussed.

NEUROBIOLOGY OF ADHD

Pathophysiology underlying ADHD has been extensively investigated in the past two decades and the field is growing rapidly. Along with technical advances, exciting results from both genetic and brain imaging studies are emerging. This section briefly presents important findings regarding the neurobiological underpinnings in ADHD.

Genetic factors

ADHD has a strong heritable component. The mean estimated heritability is 76 % in twin studies.¹⁵ In familial studies, parents and siblings of ADHD patients show increased risk of ADHD. This risk is more strongly associated in index patients with persisting ADHD compared to remitted ADHD.¹⁶ A number of risk genes for ADHD have been identified but results have yet been inconsistent. The most replicated findings involve dopamine (DA) and serotonin transmission.¹⁷

To date research has shown that ADHD involves multiple genes of moderate effect in complex interaction with environmental factors. For example health complications early in life may modulate the genetic risk for ADHD.¹⁸

ADHD subtypes based solely on DSM-IV symptom criteria have been criticized as providing too heterogeneous samples for the purpose of genetic studies. Identifying endophenotypes based on neuropsychological deficits is suggested to offer more well-defined subtypes of ADHD¹⁶ (for definition of endophenotypes see Castellanos and Proal).¹⁹

Neuropsychological functioning

Over the years, several theories about core cognitive deficits in ADHD have been formulated based on results from neuropsychological studies and behavioural observations; focussing for example on deficits in executive functioning²⁰ or a dual pathway model of executive function deficits and reward deficiency.²¹ Barkley proposed that executive function deficits seen in children with ADHD are secondary to failure in inhibition.²²

Meta-analysis of studies investigating neuropsychological functioning in ADHD show that, compared to controls, individuals with ADHD most consistently display differences in

response inhibition, vigilance, spatial working memory, signal detection (arousal), set shifting and some measures of planning.²³

Results from imaging studies

Results from both structural²⁴ and functional imaging studies²⁵ have repeatedly shown involvement of fronto-striatal-cerebellar networks in the neurobiology of ADHD, implicating neurotransmission involving DA and noradrenaline (NA). Prefrontal cortex (PFC) is rich in DA and NA receptors and has a vital role in cognitive control by regulating information received from sensory cortices and attention based on the relevance of incoming information. PFC is also important for sustaining attention over delay and shifting attention based to task demands. In addition, it has an important role in regulating behaviour and emotion.²⁶

Functional brain imaging studies have initially investigated subjects performing cognitive tasks challenging e.g. attention, working memory and response inhibition thus activating brain areas of interest, comparing individuals with ADHD to controls or medicated individuals to non-medicated. Recently, interesting results are emerging from imaging studies investigating brain activity during resting state suggesting a more diffuse connectivity between functional networks in individuals with ADHD.²⁷

Few imaging studies have been able to prospectively follow up individuals, who were diagnosed with ADHD as children, from childhood to adulthood. In a prospective study of 59 boys (aged 6 – 12 when diagnosed with ADHD) and 80 comparisons who underwent MRI after approximately 33 years of initial diagnosis, a reduction in brain gray matter was found in areas involved in attention, emotion regulation and motivation.²⁸ These results were independent of current diagnosis and the authors suggest that remission in ADHD is linked to compensatory maturation of prefrontal, cerebellar and thalamic circuitry.

Recently, based on findings from brain imaging studies, involvement of several large-scale brain systems in ADHD has been proposed instead of focusing mainly on the influence of prefrontal brain regions.¹⁹ The suggested brain systems include: 1) the fronto-parietal network, also referred to as an executive control circuit involved in goal directed behaviour, 2) the dorsal and ventral attentional networks, which form the key components of the attention regulatory system; especially the dorsal attentional network is implicated in ADHD, 3) the visual network, which is important in sustained attention and interacts with the dorsal attentional network, 4) the motor network; ADHD children often exhibit motoric hyperactivity, and 5) the default network, the activity of which is diminished during a task and increased during rest. Diminished suppression of the default network during tasks is related to lapses in attention (for a detailed account see Castellanos and Proal).¹⁹

Disruptive externalizing disorders (CD, ODD, SUD and ADHD) that commonly co-exist share behavioural symptoms and neuropsychological dysfunctions and it has been suggested that they involve common genetic networks.²⁹ Brain circuits involved in addiction vulnerability include those of reward, memory, executive function, and motivation, all of which play a role in ADHD as well. Deficient DA transmission reported in ADHD is also implicated in

vulnerability to addiction.³⁰

To conclude, ADHD is a highly heritable disorder and its pathophysiology involves fronto-striatal-cerebellar networks and DA and NA neurotransmission (while not excluding other potential neurophysiological mechanisms). Results from imaging studies also support the notion that ADHD and SUD share some common neurobiological underpinnings.

CLINICAL PRESENTATION OF ADHD

Table 1 lists the ADHD symptoms of inattention and hyperactivity/ impulsivity. A DSM5 ADHD diagnosis in adulthood can be established if a patient (retrospectively) meets all criteria in childhood as well as in adulthood. These criteria are: symptom criterion (i.e. at least 6 symptoms of inattention and /or 6 symptoms of hyperactivity and impulsivity in childhood, and 5 symptoms of inattention and/ or hyperactivity/ impulsivity in adulthood); age criterion (age of onset before 12); pervasiveness criterion (symptoms are present in at least two domains of life); impairment criterion (symptoms lead to a significant impairment); and diagnostic category (symptoms are not better explained for by the presence of another disorder).

While the core symptoms of inattention, hyperactivity and impulsivity are well pronounced in children, the presentation is generally more subtle in adults. Hyperactivity at an adult age for instance is not expressed in running and climbing excessively, but rather as inner restlessness, inability to relax, over talkativeness, or avoiding going to theatres etc. This makes it more difficult to recognize the symptoms, especially since the description of symptoms in the DSM is sometimes more suitable for a childhood situation than for adults.

As mentioned before, ADHD is often accompanied by comorbid disorders. This is also true for SUD patients with ADHD: in comparison to SUD patients without ADHD they even suffer more often from additional psychiatric disorders, such as antisocial personality disorder, borderline personality disorder, depression or anxiety disorders. In fact, the majority of SUD patients with ADHD have at least one more comorbid disorder³¹ which contributes to the fact that this is a subgroup of SUD patients with more severity.

Although in childhood, ADHD is more often recognized in boys, the rates of ADHD for men and women are more equal in adult populations and are equal in adult SUD populations as well.

SCREENING AND DIAGNOSTIC ASSESSMENT OF ADHD

Typically, in many SUD patients with ADHD the disorder has not been identified by health care workers, so substance abuse treatment centers may often be the first to recognize the ADHD symptoms and perform diagnostic assessment. Screening and diagnostic assessment is however hampered by a number of important difficulties. As an example, ongoing substance use can mask ADHD symptoms, but it may also mimic ADHD symptoms that are no longer present when the effects of substance use have faded. The same holds

Table 1: ADHD symptoms of inattention and hyperactivity/impulsivity.

	<i>Inattention symptoms</i>
1	Often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities.
2	Often has difficulty sustaining attention in tasks or play activities.
3	Often does not seem to listen when spoken to directly.
4	Often does not follow through on instructions and fails to finish schoolwork or duties in the workplace (not due to oppositional behavior or failure to understand).
5	Often has difficulty organizing tasks or activities.
6	Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (like schoolwork or homework).
7	Often loses things necessary for tasks or activities (e.g. toys, school assignments, pencils, books, or tools).
8	Is often easily distracted by extraneous stimuli.
9	Is often forgetful in daily activities.
	<i>Hyperactivity/impulsivity symptoms</i>
1	Often fidgets with hands or feet or squirms in seat.
2	Often leaves seat in classroom or in other situations in which remaining in seat is expected.
3	Often runs about or climbs excessively in situations in which it is not appropriate (in adolescents and adults, may be limited to subjective feelings of restlessness).
4	Often has difficulty playing or engaging in leisure activities quietly.
5	Is often “on the go” or often acts as if “driven by a motor”.
6	Often talks excessively.
7	Often blurts out answers before the questions have been completed.
8	Often has difficulty awaiting turn.
9	Often interrupts or intrudes on others (e.g., butts into conversations and games).

for withdrawal symptoms such as restlessness and concentration problems. Several ADHD screening instruments exist, of which the ASRS-v1.1 has been validated in a population of SUD patients.³² It is important to remember that a diagnosis cannot be based on a simple screening, so in case of a positive result of the screening instrument, diagnostic assessment is indicated. This is usually postponed until after a period of several weeks of abstinence when interfering intoxication/ withdrawal symptoms have been minimized. However, valuable information can also be obtained if careful attention is given to childhood ADHD symptoms, and to ADHD symptoms in past periods of abstinence, even if a patient is not abstinent at the time of assessment. It is generally recommended to involve an informant,

such as a parent, to collect additional information on childhood symptoms; similarly, a partner or other significant person can shed light on adulthood symptoms. Structured interviews such as the Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID)³³ and DIVA³⁴ are helpful in obtaining all necessary diagnostic information in a standardized way.

ADHD symptoms need not only be differentiated from substance use disorders, but also from bipolar disorders, depressive and anxiety disorders, and borderline personality disorder, all of which share overlapping symptoms with ADHD. For example, adults with ADHD often exhibit low self-esteem, low mood, affective lability and irritability, which may be confused with dysthymia, bipolar disorder or borderline personality disorder.³⁵ Diagnosing ADHD is further complicated by the fact that these differential diagnoses can also be present as comorbidities.

Although ADHD is associated with deviations in neuropsychological functions when groups of ADHD patients and normal controls are compared, these deviations are relatively unspecific and neuropsychological tests are not sensitive enough as diagnostic tools on an individual level. They may, however, provide useful information about a person's cognitive functioning that is important for treatment planning. This is apparent for example in patients with severe learning difficulties.

TREATMENT OF ADHD IN SUD PATIENTS

An important first step in the treatment of ADHD in SUD patients is psycho-education about the disorder. For patients who have experienced ADHD-related problems from childhood on, it is a relief to learn that there is a condition explaining these problems. Often they have been told that they are lazy and they may have developed a low self-esteem because of failing tasks. Realizing that ADHD is involved in the origin of these difficulties is very valuable information for many patients. It is important to explain that ADHD is a lifelong condition, and treatment is aimed at reducing symptoms and learning how to cope with symptoms. In this paragraph, treatment options for ADHD are described, as well as their efficacy in SUD patients with ADHD.

Pharmacological treatment

Stimulant medications such as methylphenidate are an effective treatment option for adults with ADHD.¹⁰ Methylphenidate blocks the dopamine transporters in the brain, which leads to enhanced dopamine levels and reduced ADHD symptoms. Dextroamphetamine, which is also a stimulant, exerts its effect through increased synaptic dopamine release. Although stimulant medication is effective in 70% of adult ADHD patients,³⁵ the effect of stimulant medication is not as clear in SUD patients with ADHD. Most randomized controlled trials to date did not find a convincing effect of methylphenidate on ADHD symptoms or SUD problems (e.g. Levin et al., Konstenius et al.).^{36, 37} The reasons for this putative lack of effect are not yet clear, but a possible explanation could be that direct toxic effects of drugs have altered dopamine neurotransmission in such a way that methylphenidate is not able to exert

its effect anymore.³⁸ It has also been suggested that higher doses may be warranted in a SUD population.³⁶ This is supported by results from a recent study showing that methylphenidate in doses up to 180 mg improved ADHD-symptoms, reduced relapse and improved retention to treatment in amphetamine dependent men recently released from prison.³⁹ Thus, although the first choice pharmacological therapy for ADHD is methylphenidate, it is important to realize that this medication may not be effective in many SUD patients with ADHD. Still a treatment with methylphenidate can be considered if a patient wants to try the option. In that case, it is important that a patient first becomes abstinent of substances, so the effect of medication is not disturbed by intoxication or withdrawal from substances, and that agreements are made in advance on how long the effect is monitored before deciding if there is any effect or not.

The regular treatment dose of methylphenidate is 0.5-1.0 mg/kg/day. Before starting treatment, a somatic check-up is required with specific attention for cardiac problems, epilepsy, thyroid problems, and registration of blood pressure and heart frequency, which is repeated during treatment. Methylphenidate is available as immediate-release and several forms of sustained release. Immediate release preparations have a short effect span and should be administered four to five times a day. One of the side effects of this type of stimulants is the rebound effect: ADHD symptoms worsen as the medication effect declines. The sustained-release formula is prescribed once or twice daily, which is more convenient and feasible for most patients. Rebound effects occur less frequent and less pronounced. Another advantage of this medication formula is the lower abuse liability, in contrast to the immediate release form which can be inhaled through the nose or injected. Compared to oral administration, sniffing or injecting methylphenidate results in a faster increase of extracellular dopamine, which evokes a reinforcing 'high'. In patients where abuse is a particular concern, it is probably wiser to prescribe the sustained release form.

Other medication options for the treatment of ADHD include atomoxetine and bupropion. Atomoxetine inhibits noradrenaline re-uptake and is considered an appropriate second-line alternative for stimulants. There is only limited information on the effects of atomoxetine in SUD patients with ADHD, but the scarce studies to date showed disappointing effects on ADHD symptoms. Only one double-blind RCT found that atomoxetine treatment was superior to placebo in improving ADHD symptoms in recently abstinent alcohol-dependent adults with ADHD.⁴⁰ The usual dosage for atomoxetine is 80-100 mg/day, and it is prescribed once daily. Bupropion is an inhibitor of catecholamines re uptake. It has antidepressive effects but it is also used in the treatment of ADHD. However, its use has hardly been studied in double-diagnosis patients with SUD and ADHD. Bupropion is dosed 300-450 mg/day, divided over 1 or 2 doses.

Cognitive behavioral therapy and coaching

Only recently, research has focused on Cognitive Behavioral Therapy (CBT) as treatment option for adults with ADHD. Even if medication is effective in a patient, for example by improving attention, many patients have never been able to learn basic planning and

organizing skills. Moreover, the accumulation of failure experiences in the past may still have an impact on patient's functioning. CBT addresses these issues, by training planning and organization skills on one hand, and teaching the patient to tackle automatic negative thoughts on the other hand. Several randomized trials have studied the effect of CBT in adult ADHD patients, and found a remarkable effect which also lasted at follow-up (e.g. Safren et al.).¹¹ Unfortunately, CBT for ADHD has not yet been studied in SUD patients with ADHD. At the present an integrated CBT treatment which addresses both SUD and ADHD is being investigated in a randomized controlled design in the Netherlands.⁴¹ SUD and ADHD symptoms can exacerbate one another, for example substances are sometimes used to alleviate ADHD symptoms (e.g. of restlessness), and at the same time substance use can worsen ADHD symptoms (e.g. concentration problems or impulsivity). The authors hypothesize that treating SUD and ADHD at the same time may result in better treatment outcomes for both SUD and ADHD. The integrated treatment incorporates both protocolized addiction treatment and elements of the CBT protocol for ADHD treatment by Safren and colleagues.⁴² After initial stabilization of substance use, sessions on addiction treatment alternate with sessions ADHD treatment. Basic planning skills are trained by instructing patients to use a calendar and task list, and ample attention is paid to prioritizing tasks and managing overwhelming tasks by cutting them into small parts. Reducing distractibility and coping with negative automatic thoughts are also part of the treatment protocol. Results of the study are not yet available at the moment of writing this chapter, but are expected in 2016.

Order of treatments

In treating SUD patients with ADHD, it is important to start with ADHD treatment as soon as possible. Symptoms of ADHD and addiction exacerbate each other and treatment of both disorders is therefore required. After initial stabilization of substance use, ADHD treatment in the form of psycho education and CBT or coaching can be taken up. In case of medication treatment, treatment should only be started once the patient is abstinent from substances. Investing in a stable work alliance between patient and therapist is of extra importance in order to prevent patients from dropping out of treatment. Apart from this, extra efforts could be useful to help these, generally chaotic, patients to remember their treatment appointments. Scheduling appointments on a fixed day and time, and sending a reminder text message before the appointment for example, can be very helpful.

PROGNOSIS

As stated earlier, SUD patients with ADHD represent a more severe subgroup of patients than patients with SUD only. They more often suffer from additional psychiatric comorbidities, and in general their SUD problems are more severe compared to SUD patients without ADHD. Furthermore, SUD patients with comorbid ADHD start abusing substances at a younger age, use more substances and are hospitalized more often than SUD patients without ADHD.⁴³ ADHD is also associated with higher relapse rates after SUD treatments.⁴⁴

On top of that, pharmacological treatment of ADHD symptoms has limited effect,⁴⁵ and results of CBT approaches have not yet been described in this patient group.

All in all, treatment of these double diagnosis patients should include not only addiction care, but also diagnostic assessment and treatment for ADHD symptoms to optimize the prognosis. Still, treatment of SUD patients with ADHD is challenging because these patients are often struggling with many long-existing problems, and developing tailored treatment programs should be a focus of future research. A more extensive treatment is generally necessary in comparison to patients with uncomplicated SUD, and can offer these patients a chance to overcome SUD problems and ADHD related problems in their lives. Successful treatment may result in better quality of life and large health gains for these patients.

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PART II:

PREVALENCE OF ADHD AND
ADDITIONAL COMORBIDITIES
IN SUD PATIENTS

