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Alcohol use disorders and ADHD

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ABSTRACT

Despite a growing literature on the complex bidirectional relationship of ADHD and substance use, reviews specifically focusing on alcohol are scarce. ADHD and AUD show a significant genetic overlap, including genes involved in gluatamatergic and catecholaminergic neurotransmission. ADHD drives risky behavior and negative experiences throughout the lifespan that subsequently enhance a genetically increased risk for Alcohol Use Disorders (AUD). Impulsive decisions and a maladaptive reward system make individuals with ADHD vulnerable for alcohol use and up to 43 % develop an AUD; in adults with AUD, ADHD occurs in about 20 %, but is vastly under-recognized and under-treated. Thus, routine screening and treatment procedures need to be implemented in AUD treatment. Long-acting stimulants or non-stimulants can be used to treat ADHD in individuals with AUD. However, it is crucial to combine medical treatment for ADHD with pharmacotherapy and psychotherapy for AUD, and other comorbid disorders. Identification of individuals at risk for AUD, especially those with ADHD and conduct disorder or oppositional defiant disorder, is a key factor to prevent negative outcomes.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most common neuropsychiatric disorders. The prevalence of ADHD in childhood and adolescence is estimated to be 7.1 % (Thomas et al., 2015), and 2.8 % in adults (Fayyad et al., 2017). However, since DSM-5 is the only official diagnostic manual that includes criteria for ADHD in adults and DSM-5 lowered the symptom threshold for adults, ADHD prevalence in adults according to DSM-5 is quite likely to be higher than estimated by studies using previous DSM or ICD-10 criteria (Thomas et al., 2015; Kooij et al., 2019a). The behavioral symptoms of ADHD include problems regarding attention, hyperactivity or restlessness, and impulsive decision making, but also emotional lability and dysregulation (Faraone et al., 2015). ADHD leads to an increased risk for a number of impairing outcomes, such as educational and vocational underachievement. The clinical picture of ADHD is heterogeneous and frequently affected by psychiatric co-morbidity, including substance use disorders (Faraone et al., 2015; Groenman et al., 2019; Dalsgaard et al., 2014). While ADHD is associated with an increased mortality, mostly due to accidents (Ruiz-Goikoetxea et al., 2018; Dalsgaard et al., 2015a; Sun et al., 2019), comorbid SUD further increases the risk for premature death among individuals with ADHD (Dalsgaard et al., 2015a; Sun et al., 2019). In line with this, patients in acute trauma care after an accident showed an increased ADHD prevalence, and those with ADHD were significantly more often under the influence of alcohol or other substances (Kittel-Schneider et al., 2019).

Pharmacotherapy of ADHD is effective and safe (De Crescenzo et al., 2017; Cortese, 2020), and also more effective than pharmacological treatment for most other psychiatric disorders and also for many common medical disorders (Fayyad et al., 2017; Leucht et al., 2012). The World Federation of ADHD International Consensus Statement states that ADHD medication reduces a large number of adverse outcomes typically associated with ADHD, such as "accidental injuries, traumatic brain injury, substance abuse, cigarette smoking, educational

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underachievement, bone fractures, sexually transmitted infections, depression, suicide, criminal activity and teenage pregnancy" (Faraone et al., 2021). Stimulants (amphetamines, methylphenidate) are more effective than non-stimulants (atomoxetine, guanfacine, clonidine) on a group level (Cortese et al., 2018), although the individual ADHD patient also needs an individualized and long-term treatment approach, also since severity of ADHD symptoms and their functional impact may vary over time (Caye et al., 2019). Placebo-controlled studies not only administer medication or placebo, but also "medical management" and psychoeducation, which both should not be underestimated in terms of improving treatment efficacy and treatment adherence. Other non-medical treatments such as cognitive behavioral therapy are effective but to a comparatively lesser degree than medication and thus represent an add-on to pharmacological treatment or are an option if medication is not tolerated or the patient is reluctant to medication. Other non-medical treatments such as neurofeedback showed no convincing results (Faraone et al., 2021). However, even though stimulants are more effective, there is concern regarding the misuse of prescribed stimulants (Faraone et al., 2020), especially in individuals with comorbid substance use disorder (Bjerkeli et al., 2018).

Substance use and substance use disorders (SUDs) are common worldwide (Anon., 2018). One of the most frequently used and abused substances is alcohol. Alcohol use is a leading risk factor for disease burden, causes a number of negative social, psychosocial and health consequences (e.g. suicides, traffic accidents, interpersonal violence, liver diseases) and is associated with increased mortality (Anon., 2018; Knox et al., 2019; Kraus et al., 2019). While there is no amount of alcohol consumption that can be considered safe, the risk for adverse outcomes increases with increased alcohol consumption (Anon., 2018). There are various definitions regarding risky alcohol use patterns, and some terms are defined slightly differently by different official authorities. Binge drinking is defined for example by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) in the US as a pattern of drinking alcohol that brings blood alcohol concentration (BAC) to 0.08 per cent - or 0.08 g of alcohol per deciliter - or higher. For a typical adult, this would be consuming at least 56 g of alcohol for women or 70 g for men within 2 h (National Institute on Alcohol Abuse and Alcoholism (NIAAA), 2004). Heavy drinking days are defined e.g. by the European Medicines Agency (EMA) as days with a total alcohol consumption of at least 40 g (women) or 60 g (men) (European Medicines Agency, 2010). Alcohol intake in the range of binge/heavy drinking is associated with increased risk for adverse outcome, although the use of this exact cut-off is under debate for some time (Pearson et al., 2016). Both definitions only describe drinking patterns that have possible negative psychosocial and physical impact and that increase the risk developing for an alcohol use disorder (AUD) or that can also occur as part of an AUD. In contrast, disorders such as AUD are defined by operational criteria in the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Disease (ICD). Moderate to severe substance use disorders (or "dependence" in the ICD) are characterized by craving, a pattern of compulsive substance use despite negative consequences, and a loss of control over substance use. Physically, increasing tolerance and subsequent withdrawal symptoms when substance intake is (suddenly) reduced can occur.

Treatment of alcohol use disorders is still mostly based on psychotherapeutic interventions to increase motivation to reduce consumption and – if possible – maintain abstinence. Pharmacological interventions differ depending on the phase of the treatment: physical withdrawal is usually treated with benzodiazepines to prevent possibly life-threatening complications such as delirium tremens or seizures, and to increase treatment adherence. After physical withdrawal or if withdrawal does not occur, pharmacotherapy can be used to reduce craving, to reduce alcohol intake (e.g. number of heavy drinking days) or to maintain abstinence. All of these treatment goals can be achieved by opioid-receptor antagonists such as naltrexone (or nalmefene, which is only approved in Europe). For naltrexone, a number needed to treat (NNT) of 12 has been reported by a Cochrane review for a reduction in heavy drinking and a NNT of 20 for abstinence (Rösner et al., 2010a). Acamprosate, which possibly acts via NMDA or GABA receptors, only increases the probability for maintaining abstinence with a NNT of 12 (Rösner et al., 2010b). Disulfiram has a different mode of action, as it blocks the metabolism of ethanol, leading to unpleasant to severe or even life-threatening side effects when alcohol is consumed while on medication. Other non-approved but possibly promising drugs include topiramate or varenicline, which also mainly reduce heavy drinking (Knox et al., 2019). Recently, ketamine has shown very promising results in AUD (Das et al., 2019; Dakwar et al., 2020). All drugs are under-utilized and thus it is not surprising that there are no publications on AUD medication in individuals with AUD and ADHD.

There are a number of well written reviews on the complex bidirectional relationship of ADHD and SUD (e.g. (Zulauf et al., 2014; Özgen et al., 2020; Crunelle et al., 2018)), but – to our knowledge – there has not been an extensive review specifically focusing on the substance alcohol. Most of the literature on ADHD and SUD is mainly concerned with cannabis, cocaine or stimulant use disorders. E.g., in cocaine use disorder, the prevalence of ADHD was estimated at 10 % (range 5–20%) in a recent systematic review (Oliva et al., 2020). Nevertheless, individuals with ADHD are also at increased risk for AUD (Lee et al., 2011; Groenman et al., 2017a; Vogel et al., 2016), and lifetime prevalence of any AUD in ADHD is up to 43 % (Tuithof et al., 2012a), while lifetime prevalence of alcohol dependence (corresponding to moderate to severe AUD) is around 3–11 % (Tuithof et al., 2012a; Molina et al., 2007), with adults showing higher rates compared to adolescents (Molina et al., 2007). Thus, ADHD co-occurs in up to 20 % of individuals with AUD (Luderer et al., 2018a), and the comorbidity of ADHD and AUD is associated with a number of other comorbidities as well as worse treatment outcome (Luderer et al., 2018a, 2020). Since AUD is the second the most prevalent SUD (after tobacco) worldwide and causes significant morbidity and mortality (Peacock et al., 2018), the high comorbidity of ADHD with AUD is of high relevance also on a population level.

To our knowledge, this is the first comprehensive review of ADHD and AUD that covers the common neurobiological and neuropsychological risk factors of both disorders and their interaction and self-reinforcing properties, and summarizes recent recommendations on identification and treatment of individuals with ADHD and AUD.

2. Methods

In this narrative review, we provide a broad description of the complex connections between ADHD and AUD, starting with an overview of the links between both disorders during adolescence and early adulthood, highlighting the bidirectionality from a clinical point of view. In the second section, we continue with a more detailed look at the various shared risk factors, from genetics and early development (e.g. pre-natal alcohol-exposure) over traumatic experiences and brain injuries to common neuropsychobiological findings and gender specific aspects. In the third and fourth section, we discuss the clinical impact of ADHD in patients with AUD and refer to recent international recommendations on diagnostic and treatment.

Although the aim of this review was to highlight the mechanisms that link ADHD and AUD throughout the lifespan, data on AUD are not always available for some aspects. In these cases, results from studies investigating the relationship between SUD and ADHD were used for indirect conclusions that have not been confirmed for AUD yet.

3. Overview of the bidirectional effects of ADHD and alcohol use during adolescence and early adulthood

The risk of developing an AUD increases through adolescence and early adulthood (Pedersen et al., 2014; Dalsgaard et al., 2020). Although children with ADHD often no longer fulfill all diagnostic criteria for

ADHD when they grow older, two-thirds continue to have impairing symptoms in young adulthood (Faraone et al., 2006) leading to enduring impairment in adulthood (Merrill et al., 2020; Franke et al., 2018). Persistent or partially remitted ADHD (Huntley and Young, 2014) or being diagnosed with ADHD in later adolescence or adulthood (Faraone et al., 2007) increases the risk for later AUD as well as faster developing AUD (Luderer et al., 2018a; Molina et al., 2018).

From a clinical perspective, ADHD is not only a risk factor for SUD, but also for many other psychiatric disorders (van Emmerik-van Oortmerssen et al., 2014; Hartmann et al., 2021). During childhood, conduct disorder (CD) and oppositional defiant disorder (ODD) are the most common comorbidities of ADHD. Both ODD and CD are associated with a higher risk for SUD in individuals both with ADHD (Dalsgaard et al., 2014; Molina and Pelham, 2003) and without (Groenman et al., 2017b; González et al., 2020). CD and ODD serve as a mediating factor in some studies (Tuithof et al., 2012b), while childhood ADHD remains an independent risk factor for early substance (mis-)use and the development of SUD (Groenman et al., 2017b; González et al., 2020; Groenman et al., 2013).

Alcohol consumption in adolescence i) reduces gray matter volumes and attenuates white matter growth (Squeglia et al., 2015), ii) increases attentional deficits (Louth et al., 2016), and iii) leads to poorer cognition regarding verbal memory, visuospatial functioning, psychomotor speed, working memory, attention, or cognitive control (Squeglia and Gray, 2016). These domains are already affected by ADHD (Pievsky and McGrath, 2018), leading to a worse developmental and cognitive outcome for individuals with ADHD who frequently drink higher amounts of alcohol. Worsening of ADHD symptoms such as inattention or CD symptoms such as delinquency leads to a higher risk for alcohol binge drinking and marijuana use in adulthood (Howard et al., 2015). Therefore, alcohol consumption during adolescence further increases the risk for high alcohol intake in individuals with ADHD leading to a vicious circle and worse health and socioeconomic outcome.

4. Shared risk factors for ADHD and AUD

4.1. Genetics of ADHD and AUD

ADHD is a neurodevelopmental disorder with a high heritability (above 74 %) (Faraone and Larsson, 2019). ADHD is highly polygenic, and several genomic regions with small individual effects were identified in genome wide association studies (GWAS) to contribute to the etiology of ADHD (Demontis et al., 2019). Currently, only a small proportion of the heritability of ADHD is explained by the additive effects of common genetic variants; likely, ADHD's heritability is also due to rare variants, gene by environment interaction and epistasis (Demontis et al., 2019; Lee et al., 2013; Anttila et al., 2018).

AUD has a heritability of around 50 % (range 40–70 %) (Carvalho et al., 2019; Verhulst et al., 2015). GWAS and GWAS meta-analysis identified several risk genes to be associated with the score on a screening questionnaire (Alcohol Use Disorders Identification Test – AUDIT (Saunders et al., 1993)) for AUD; these were mainly related to the pharmacokinetics (ADH1B, ADH1C) or pharmacodynamics (KLB, GCKR) of alcohol (Carvalho et al., 2019; Sanchez-Roige et al., 2019a).

ADHD and substance use or SUD are linked by familial coaggregation and shared heritability (Skoglund et al., 2015; Elkins et al., 2018), and adult patients with AUD and ADHD have a higher rate of positive family history for SUD compared to AUD only (Luderer et al., 2018a). ADHD symptoms and problem drinking, not meeting AUD criteria, are genetically correlated in adults ($r_g = 0.39–0.50$) (Derks et al., 2014). A positive genetic correlation between ADHD and alcohol-related problems could be confirmed ($r_g = 0.23$, $p = 1.1 \times 10^{-5}$) (Sanchez-Roige et al., 2019b). The same study found a weak but significant *negative* genetic correlation ($r_g = -0.10$, $p = 1.8 \times 10^{-2}$) of ADHD with the amount or frequency of alcohol intake as measured by AUDIT-C (three items on alcohol consumption from the Alcohol Use Disorders Identification Test (Saunders et al., 1993)). However, the relevance of this finding is questionable, since the association was weak, and since another study showed that the polygenic risk score for alcohol related problems is associated with a number of alcohol-related phenotypes such as AUD, while the AUDIT-C appears to be less useful (Johnson et al., 2020).

In contrast to small and underpowered studies (Gurriarán et al., 2018; Rabinowitz et al., 2018), large studies demonstrate a substantial and significant positive genetic correlation between AUD and ADHD ($r_g = 0.44$, $p = 4.2 \times 10^{6}$) (Walters et al., 2018). The genetic risk for ADHD is associated with an increased risk for AUD in individuals with and without ADHD: in ADHD, higher polygenic risk scores for ADHD increase the risk for AUD (OR 1.26) (Wimberley et al., 2020). In adults *without* ADHD, the polygenic risk score for ADHD was associated with higher frequency of alcohol intake and with AUD (Du Rietz et al., 2018). This suggests that not only a full diagnosis of ADHD, but also genetic risk factors that contribute to ADHD traits (or more severe ADHD symptoms) increase the risk for AUD. Mendelian randomization analysis suggests that the genetic variants associated with ADHD are causal risk factors for AUD (Treur et al., 2019).

For a long time, the pathophysiology of ADHD as well as AUD was suggested to be due to catecholaminergic dysfunction (Carvalho et al., 2019; Nutt et al., 2015). However, some aspects of AUD, such as craving and executive dysfunction or withdrawal, have been linked to glutamatergic neurotransmission (Koob and Volkow, 2016). Recent genetic findings in ADHD suggest a genetic etiology that impairs neural growth, synaptic plasticity and glutamatergic neurotransmission (Grimm et al., 2020a; Elia et al., 2011). While smaller studies identified genes involved in the serotonergic neurotransmission to predict alcohol use severity (Groenman et al., 2016), this was not confirmed in a meta-analysis of 30 different GWAS including data from up to 1.2 million individuals. Here, a number of genetic risk factors for increased alcohol consumption including genes involved in the glutamatergic and dopaminergic neurotransmission (Liu et al., 2019) were identified. A number of genes involved in neural development are linked to the comorbidity of ADHD and SUD (Arcos-Burgos et al., 2012). One of these genes, the *ADGRL3* (Latrophilin 3, *LPHN3*) gene, is involved in glutamatergic synapse development (O'Sullivan et al., 2012). Single-nucleotide polymorphisms (SNPs) in this gene have been associated repeatedly with alcohol use (Martinez et al., 2016) and ADHD (Bruxel et al., 2020; Arcos-Burgos et al., 2010), as well as SUD in ADHD (Arcos-Burgos et al., 2019), and can predict the effectiveness of stimulant medication in ADHD (Arcos-Burgos et al., 2010). Thus, *ADGRL3* might represent a valuable target for future pharmacogenomic studies in individuals with ADHD and AUD.

A polymorphism in *PRKG1* (Protein Kinase cGMP-Dependent 1) was found to moderate the association between exposure to traumatic events and severity of alcohol misuse (Polimanti et al., 2018). Although there are no robust positive findings on *PRKG1* in ADHD (Neale et al., 2010), the close relation between ADHD, post-traumatic stress disorder (PTSD), and AUD (Luderer et al., 2020; Spencer et al., 2016) suggests further investigation of this gene and gene-by-environment effects.

Of note, the existing literature shows a large heterogeneity regarding the investigated phenotypic variables (e.g. ADHD symptoms, ADHD diagnosis, problematic alcohol use, AUD diagnosis) and also regarding the inclusion of control variables such as comorbid psychiatric disorders. Thus, the role of comorbid disorders or transdiagnostic psychopathology in the genetic link between ADHD and AUD warrants further investigation.

4.2. Shared early developmental risk factors for ADHD and AUD

Maternal alcohol or tobacco use during pregnancy as well as preterm birth or complications during birth (Faraone et al., 2015) have been linked to ADHD in the offspring (Han et al., 2015; Obel et al., 2016). However, since ADHD is underdiagnosed in adults (Libutzki et al., 2019), and females suffering from ADHD more often display risk

factors for adverse obstetric and perinatal outcomes (smoking during the third trimester, high or low body mass index, AUD, SUD) (Skoglund et al., 2019), a diagnosis of maternal ADHD might be an important moderator and genetic risk or parenting style might play an important role as well.

Alcohol use during pregnancy can lead to fetal alcohol spectrum disorder (FASD), which has a large symptomatic overlap with ADHD. Importantly, even low to moderate alcohol consumption during pregnancy can lead to anatomical and behavioral changes, although the results are mixed (Römer et al., 2020). However, since alcohol use during pregnancy is associated with higher socio-demographic status, discrete behavioral or intellectual deficits in the short term as well as longer term negative outcomes might easily be missed. It can be very difficult to distinguish ADHD from FASD in older patients, especially when alcohol exposure during pregnancy is unclear and facial anomalies are not present or discrete. Individuals with FASD typically have lower IQ scores and more severe ADHD symptoms (Mattson et al., 2019), and respond less to stimulant treatment (Petrenko and Alto, 2017). Thus, FASD should always be considered as a possible differential diagnosis to ADHD, especially if ADHD treatment appears not to be as effective as usual. Early identification is crucial to develop a therapeutic approach that meets the requirements of FASD.

4.3. Trauma exposure in ADHD and AUD

Early adverse life events are common in ADHD (Green et al., 2010), and trauma related disorders are more frequent in ADHD than in normal controls, but also than in controls with past traumatic experiences (Spencer et al., 2016). The familial coaggregation of these two disorders suggests that these disorders share familial risk factors and that their co-occurrence is not due to diagnostic errors (Antshel et al., 2013); likely, there is a bidirectional relationship between ADHD and traumatic life events, with ADHD genetic risk going along with increased likelihood for early adversity, and trauma exposure increasing the risk towards an ADHD diagnosis.

Trauma related disorders such as PTSD, on the other hand, are important and independent risk factors for AUD. In turn, AUD is a risk factor and complicating comorbidity for PTSD (McLean et al., 2014; Balachandran et al., 2019). Thus, it is not surprising that in adult patients with ADHD, being prone to accidents and traumatic experiences such as sexual abuse are both linked to SUD (Nogueira et al., 2014), and in adult patients with SUD, traumatic childhood experiences are more frequent in patients with ADHD (Konstenius et al., 2017). In adult patients with AUD, ADHD was associated with a significantly higher rate of PTSD (65 % vs. 88 %), and in patients with AUD and potentially traumatic experiences, those with ADHD had an OR of 8.9 for PTSD compared to those without ADHD (Luderer et al., 2020).

4.4. Traumatic brain injuries: a vicious circle for ADHD and AUD

Traumatic brain injury (TBI) can cause persisting ADHD symptoms, while individuals with ADHD have a higher risk for accidents and TBI (Franke et al., 2018; Adeyemo et al., 2014). Alcohol use on the other hand is a significant risk factor for TBI, alcohol use after TBI hampers recovery, and TBI itself is also a risk factor for developing AUD (Cannella et al., 2019). The combination of ADHD and alcohol use therefore represents a vicious circle that is further accelerated by (repetitive) traumatic brain injuries.

4.5. Neuropsychobiology of ADHD and AUD

4.5.1. Impulsivity

One core symptom of ADHD is increased impulsivity (Grimm et al., 2021, 2020b); impulsivity has been associated with increased alcohol use and increased risk for AUD and SUD (Adan et al., 2017; Kozak et al., 2019; de Wit, 2009). For example, higher impulsivity in a go/no-go task predicted alcohol binge use in young social drinkers (Henges and Marczinski, 2012), and lower working-memory capacity and higher impulsivity predicted current alcohol use and future increases in alcohol use (Khurana et al., 2013). Also, abnormal brain activation patterns during inhibition tasks predicted alcohol use in adolescents, even though the actual performance in the task was similar (Whelan et al., 2014). Contextual fluctuations in impulsivity, as they often occur in ADHD, are related to higher alcohol use and problems (Pedersen et al., 2019).

In addition to impulsivity increasing alcohol use and risk for AUD, alcohol consumption also increases impulsivity, and individuals with ADHD are more sensitive to the acute disinhibiting effect of alcohol (Weafer et al., 2009). Also, initiation of frequent alcohol consumption in adolescence disrupts the developmental changes in control of impulsive behavior (Ivanov et al., 2020). This becomes a vicious cycle, with high ADHD-related impulsivity leading to increased alcohol consumption, which leads to even higher impulsivity (acute and chronic) and ultimately to binge drinking and loss of control.

A functional imaging study assessing individuals with AUD and/or ADHD reported increased inhibitory network activation, and higher reward system activation in patients with higher ADHD and higher AUD scores during an inhibition task while alcohol related cues were presented (Vollstädt-Klein et al., 2020). Common alterations in resting state connectivity in ADHD and/or AUD compared to healthy controls showed that networks associated with impulse control and reward processing link both disorders (Farré-Colomés et al., 2021).

4.5.2. The reward system in AUD and ADHD

In adults with ADHD, dopaminergic activity is reduced (Volkow et al., 2007a). Methylphenidate blocks the dopamine transporter and increases dopamine in the synaptic cleft (Schrantee et al., 2016), and alleviates ADHD symptoms mainly via the ventral striatum (Martinez et al., 2020; Volkow et al., 2012a). Dopamine receptor availability is reduced in patients with AUD, who also showed a reduced dopamine release in limbic brain areas, indicating a reduced reward sensitivity in AUD (Volkow et al., 2007b). In patients with AUD, intravenous methylphenidate leads to a lower dopamine release in the ventral striatum and putamen in comparison to healthy controls (Volkow et al., 2007b), suggesting a common dopaminergic pathophysiology in both AUD and ADHD.

However, beyond dopamine there are other relevant neurotransmitter involved in the etiology of both disorders (Koob and Volkow, 2016). Dopaminergic and glutamatergic neurotransmission are interlinked, and glutamatergic neurotransmission in brain regions such as the anterior cingulate cortex (ACC) has been associated with ADHD symptoms, especially hyperactivity and impulsivity (Bauer et al., 2018; Huang et al., 2019). This is in line with results from recent genetic studies linking ADHD with genes involved in dopaminergic and glutamatergic neurotransmission (Grimm et al., 2020a; Elia et al., 2011). Dopaminergic or noradrenergic ADHD pharmacotherapy reduces glutamatergic over-activity (Huang et al., 2019) and glutamatergic medication can alleviate ADHD symptoms (Elia et al., 2018) and the executive dysfunction associated with ADHD (Biederman et al., 2017).

Maladaptive reward processing with a preference towards immediate rewards is characteristic for adolescents but occurs more often and to a larger extent in ADHD (Geier, 2013; Luo et al., 2019). In ADHD, dysfunctional processing of reward cues has been linked to prefrontal brain regions and the striatum. The connectivity between these regions is normalized by methylphenidate (Furukawa et al., 2020). This disrupted reward processing makes adolescents with ADHD, especially if untreated, more vulnerable to the immediate positive or negative (relief) reinforcing effects of alcohol (Koob and Volkow, 2016).

Changes in dopaminergic and opioidergic neurotransmission in the striatum are associated with the transmission from intermittent binge drinking to a drinking habit, where continuous rewarding alcohol use leads to less salience of other usually rewarding activities. The prefrontal

cortex and the glutamatergic system appear to be relevant for craving induced by alcohol-related cues and goal-oriented decision making (Koob and Volkow, 2016).

Longitudinal functional imaging studies in adolescents show that increased activity in frontal brain regions during a reward task are associated with initiation of alcohol use (Whelan et al., 2014), and a blunted activity of the medio-orbitofrontal cortex with escalating alcohol use (Ivanov et al., 2020). Accordingly, the modulating role of the orbitofrontal cortex on the value of rewards seems to be disrupted in adult patients with AUD (Volkow et al., 2007b), suggesting deficient frontal control of reward-related impulses linking both disorders.

Individuals with ADHD are at risk for stressful life events (e.g. school problems, conflicts in the family) over the life-span (Kooij et al., 2019a; Franke et al., 2018) and these events affect reward processing and increase the risk for problematic alcohol use (Casement et al., 2015). Perceived stress is moderated by the secretion of cortisol via the hypothalamic-pituitary-axis (HPA), and dysfunctional HPA has been linked to AUD (Clarke et al., 2008; von der Goltz et al., 2011). In ADHD, changes in the hormonal stress system are more evident in adults (Raz and Leykin, 2015) than in children (Angeli et al., 2018; Pesonen et al., 2011), suggesting an influence of negative life events over time that may be either a cause or effect of the persistence of the disorder into adulthood.

The mesolimbic reward system is also involved in excessive food intake in obesity (Harris et al., 2005; Volkow et al., 2012b). Hormones involved in regulating food craving and other appetitive behavior, such as ghrelin and leptin, have been linked with impulsive behavior (Sutin et al., 2013; Anderberg et al., 2016). Although smaller studies revealed no significant findings of leptin and ghrelin in ADHD (Özcan et al., 2018), orexin, a hormone associated with the regulation of sleep and wakefulness, but also with reward processing (Harris et al., 2005), is closely related to leptin and ghrelin (Soya and Sakurai, 2020; Lawrence et al., 2006), and there is preliminary data that orexin A serum levels are reduced in ADHD, and especially linked to attentional problems (Baykal et al., 2019). Leptin and ghrelin also significantly influence craving and relapse risk in AUD (Koopmann et al., 2018; Bach et al., 2020) by modifying dopaminergic activity in the Nucleus accumbens (NAc) (Bach et al., 2020).

4.6. Gender specific risk of ADHD and AUD

Females with ADHD are underrecognized and the impact of ADHD on girls and women is underestimated (Staller and Faraone, 2006). During childhood and adolescence, approximately 80 % of ADHD cases in the treatment setting are male, while in adults the gender distribution is almost equal (Kooij et al., 2019a). This is most likely because boys show more prominent psychopathology such as impulsivity and hyperactivity until adolescence and thus are more often referred to treatment. In adults, hyperactivity generally wanes, disproportionally so in males, and as a result both genders approximate in terms of impulsivity and hyperactivity. This likely leads to a comparable pattern of ADHD symptoms in adults in the clinical setting, and an almost equal gender distribution (Larsson et al., 2011) of current ADHD and associated risky behavior. Reflecting the pattern in non-ADHD patients, women with ADHD experience significantly more anxiety, affective disorders and perceived mental health impairment than men (Cortese et al., 2016). Emotional lability and emotion dysregulation problems (irritability, low frustration tolerance, mood changes) are common in ADHD (Lenzi et al., 2018). However, these symptoms are more common or more severe in females who are then are more likely to be diagnosed with borderline personality disorder (Stepp et al., 2012). While both males and females with ADHD are at increased risk for suicide (Faraone, 2020), underdiagnosis of ADHD in females raised the concern of a pronounced risk for suicidal and non-suicidal self-harm (Meza et al., 2020), which has been found to be a genetic risk factor for AUD (Rosenström et al., 2018). Furthermore, experience of rejection and social isolation due to ADHD symptoms might be a gateway to increased alcohol and drug use especially in girls and women (Young et al., 2020).

Although sex differences can mediate vulnerability for AUD in both directions, AUD and binge drinking are more prevalent in men than in women (Flores-Bonilla and Richardson, 2020). Psychological stress (Bekman et al., 2013) as well as hyperactivity and impulsivity (Elkins et al., 2018) are more strongly related to heavy drinking in adolescent girls than in boys. In two Danish register-based studies, females with ADHD had a higher rate of teenage pregnancies compared to non-ADHD females, and higher rates of alcohol and cannabis abuse compared to males with ADHD (Ottosen et al., 2016, 2019). Likewise, a longitudinal clinical study of ADHD youth found that, compared with boys with ADHD, girls with ADHD have a larger relative risk for SUDs (Elkins et al., 2020). In a population-based study, individuals with ADHD showed a gender distribution of comorbid disorders comparable to individuals without ADHD, but the rate of these comorbidities was approximately six times higher in both sexes when ADHD was present (Solberg et al., 2018).

5. ADHD in adult patients with AUD

5.1. Prevalence and impact of ADHD in adult patients with AUD

A meta-analysis (van Emmerik-van Oortmerssen et al., 2012) found a 23 % prevalence of ADHD in treatment seeking patients with SUD. However, most studies of ADHD in patients with SUD either focused on stimulant or cocaine abuse or were conducted on a sample with mixed substances of abuse. Only a few studies specifically focused on ADHD and AUD.

The available literature shows a broad span of ADHD prevalence rates in patients with AUD, ranging from 6.6% to 21.3%, depending on the setting and sample (Luderer et al., 2018a; Daigre et al., 2015; Johann et al., 2003; Ohlmeier et al., 2008; Reyes et al., 2016; Roncero et al., 2015; van de Glind et al., 2014). The largest study so far was the multicentric International ADHD in Substance Use Disorders Prevalence (IASP) study, which included 3558 patients with SUD, amongst them 690 patients with AUD as primary diagnosis (van de Glind et al., 2014). The prevalence of ADHD in AUD patients was 7.5 % (6% for inpatients, 9% for outpatients), with a high variability depending on the country and setting (e.g. inpatient prevalence rates between 5% and 22 %). The perception, recognition and therefore treatment rates of mental health disorders including ADHD, and also other socio-cultural risk factors for developing and maintaining substance misuse or SUD, differ between countries. Thus, the aforementioned rather broad prevalence range could be explained by socio-cultural influences (Slobodin and Crunelle, 2019).

One explanation for this range of prevalence rates could be that ADHD is associated with higher rates of relapse and treatment discontinuation. Since treatment dropout often also means study dropout in prevalence studies with a formalized diagnostic approach (as opposed to those relying on simple self-report questionnaires), this might well have an impact on prevalence rates. Only two studies reported their dropout rates. The IASP study had around 50 % dropout (van de Glind et al., 2014), but did not differentiate dropout by main substance of abuse. The largest study on inpatients with AUD managed to keep the dropout rate as low as 12.5 % (N = 415; ADHD prevalence 20.5 %) (Luderer et al., 2018a).

Another reason for the differences in prevalence rates could be that an ADHD diagnosis is often overshadowed by AUD. Acute effects of alcohol or withdrawal can imitate, mask or amplify ADHD symptoms (Crunelle et al., 2018; Luderer et al., 2019). In one study, only 6% of the adult patients with AUD and ADHD had previously been diagnosed with ADHD, and only 2% had received ADHD medication at the time of admission (Luderer et al., 2018a). This finding is supported by the fact that the highest prevalence rates (16–21 %) were reported in studies with the most comprehensive diagnostic approach (Luderer et al.,

2018a; Daigre et al., 2015; Roncero et al., 2015), and when abstinence was ensured for a period of at least 4 weeks while maintaining low dropout rates at the same time(Luderer et al., 2018a).

As mentioned above, the comorbidity of ADHD and SUD is associated with a number of adverse outcomes, including premature death (Dalsgaard et al., 2015a; Sun et al., 2019). In AUD, ADHD leads to a higher relapse risk even in a highly structured inpatient setting with low relapse rates (Luderer et al., 2018a). Comorbid patients are younger when entering treatment, but their dependence begins at an earlier age. AUD is also more severe and is more often associated with other SUDs when ADHD is also present (Luderer et al., 2018a).

5.2. Identification of ADHD in adult patients with AUD

Two recent international Consensus Statements on ADHD and SUD emphasize that the diagnosis as well as treatment of ADHD in patients with SUD is often sub-optimal (Özgen et al., 2020; Crunelle et al., 2018). This is of concern since AUD starts around 8 years earlier in patients with ADHD (Luderer et al., 2018a), the course of the disorder is less favorable, and the severity of the AUD is worse (Luderer et al., 2018a; Seitz et al., 2013).

Because of the high prevalence rate, the high rate of unrecognized cases and the detrimental effect on clinical outcome, routine screening for ADHD in patients in substance use treatment is highly recommended in pertinent guidelines, as well as screening for SUD in patients with ADHD (Özgen et al., 2020; Crunelle et al., 2018; Kooij et al., 2019b; Luderer et al., 2018b). In patients with AUD, the Adult ADHD Self Report Scale (ASRS) (Kessler et al., 2007; Ustun et al., 2017) is easy to administer in a routine setting and has been proven to be useful in patients with AUD (Daigre et al., 2015; Reyes et al., 2016; Luderer et al., 2018b; van de Glind et al., 2013), but misses up to one third of ADHD cases when using the cut-off of ≥ 14; thus, a higher detection rate can be achieved by using the cut-off of ≥ 12 (Luderer et al., 2018b).

The Conners' ADHD Adult Rating Scale in a self-report screening version (CAARS-S-SR) (Conners et al., 1999) showed a better sensitivity than the ASRS at a low threshold (ADHD Index $\geq$60) with still good specificity (Luderer et al., 2018b). A combination of ASRS and CAARS-S-SR led to even better results (Luderer et al., 2018b). However, the clinical application of the CAARS-S-SR is less convenient than the ASRS since the results for each item need to be converted into normalized t-values, adjusted for age and gender.

A recent study compared the Mini-International Neuropsychiatric Interview (MINI-Plus) with the Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID) (Epstein et al., 2021) as a gold standard in a sample of patients with mixed SUDs, including approximately more than 50 % with AUD. The authors reported a high specificity (96 %) and a moderate sensitivity (75 %) and since it is much shorter than the more detailed CAADID, it might be used as a screening interview followed by a more detailed diagnostic assessment (Palma-Álvarez et al., 2020).

Psychiatric comorbidities, such as depression (Warden et al., 2012), are common in ADHD and/or SUD, and depression in ADHD increases the risk for binge drinking (Wang et al., 2019). Also, the rate of traumatic experiences and the rate of PTSD is increased in individuals with ADHD. PTSD is common in patients with AUD, and even more common in patients with AUD and ADHD (65 % vs. 88 %) (Luderer et al., 2020). Thus, special attention should be given to patients with AUD and comorbid disorders such as (treatment resistant) depression or PTSD, as they are common in patients with ADHD.

The diagnostic process should start as early as possible, when substance use is stabilized, e.g. there are no severe withdrawal or intoxication symptoms (Özgen et al., 2020; Crunelle et al., 2018). If detoxification is necessary (e.g. in patients with continuous heavy drinking), final diagnosis should be postponed until the pharmacological treatment of the withdrawal syndrome can be terminated. ADHD is a clinical diagnosis. However, structured interviews can help in the process and can formalize the diagnosis for research purposes. The CAADID and the Diagnostic Interview for Adult ADHD 2.0 (DIVA) (Kooij, 2012) have been applied frequently in patients with AUD (Luderer et al., 2018a; van de Glind et al., 2014; Huntley et al., 2012). Only DIVA has been validated in adults with AUD. The study used the diagnoses of two experts in ADHD / AUD as gold standard and found the best agreement of DIVA with experts' diagnoses, if the criteria for adult ADHD according to DSM-5 were used together with some retrospective childhood symptoms before the age of 12 (Luderer et al., 2018a).

As CAADID and DIVA show comparable results (Ramos-Quiroga et al., 2016), these structured interviews can be used to diagnose ADHD in patients with AUD, but the validity depends on the experience of the person conducting the interview.

6. Treatment of ADHD with AUD and AUD with ADHD

Treatment of ADHD can prevent or attenuate some of the negative consequences associated with ADHD. Stimulants such as methylphenidate or amphetamines are most commonly used and reduce the otherwise increased risk for accidents (Dalsgaard et al., 2015b) or suicide (Chang et al., 2020).

Of note, treatment of ADHD with stimulants does not increase the risk for later SUD or AUD, as emphasized by the International Consensus Statement of The World Federation of ADHD (Faraone et al., 2021). Quite the contrary, as outlined above, stimulant treatment during childhood might reduce the risk for developing a SUD, especially when the treatment is initiated early and intense (Groenman et al., 2019; Dalsgaard et al., 2014; Groenman et al., 2013; Mannuzza et al., 2008; Steinhausen and Bisgaard, 2014). Albeit many individuals with a SUD abuse more than one substance, there is only one study that investigated the effects of ADHD treatment in patients with ADHD and AUD on alcohol-related outcomes (Wilens et al., 2008).

6.1. Psychotherapy for ADHD with comorbid AUD/SUD

Only one randomized controlled trial (RCT) investigated an integrated psychotherapy (iCBT) for both ADHD and SUD in comparison to standard addiction treatment (CBT). iCBT showed a significantly greater reduction in ADHD symptoms, however the effect size was small ($d = 0.34$), the effect did not last, substance use was not different between both groups at any time and dropout rate was over 40 % (van Emmerik-van Oortmerssen et al., 2019). Importantly, almost none of the participants received pharmacological treatment for ADHD underscoring that medication might be an essential prerequisite for the efficacy of psychotherapy in ADHD (Philipsen et al., 2015).

6.2. Pharmacotherapy for ADHD and AUD/SUD

Register-based studies show that treatment with stimulants is associated with a risk reduction of about one third for SUD (Quinn et al., 2017; Chang et al., 2014). However, the design of the studies does not allow an answer to the question whether the treatment was initiated because the SUD was more stable, or the SUD was more stable because the treatment was initiated.

Earlier prospective and controlled studies on stimulant treatment in patients with ADHD and comorbid SUD failed to show an effect regarding substance use (Schubiner et al., 2002; Levin et al., 2006; Konstenius et al., 2010). A more recent randomized placebo-controlled study in individuals with amphetamine use disorder and ADHD used higher doses of OROS-methylphenidate (up to 180 mg/day). Both methylphenidate and placebo were accompanied by weekly cognitive behavioral therapy (CBT) focusing on relapse prevention. Methylphenidate led to a significant reduction of ADHD symptoms and drug use and to better treatment adherence (Konstenius et al., 2014). Another recent RCT conducted on patients with cocaine use disorder and ADHD used robust dosages of long acting mixed amphetamine salts (60 and 80 mg/d) also in combination with CBT based on relapse prevention.

Both groups showed a significant and clinically meaningful reduction in ADHD symptoms and cocaine use compared to placebo (Levin et al., 2015).

Only one RCT in individuals with ADHD and AUD has been published. In this study with about 50 % participants with alcohol dependence, the non-stimulant atomoxetine was compared to placebo. The rate of patients who relapsed to heavy drinking during treatment did not differ between treatment groups. Compared to placebo, cumulative heavy drinking days were significantly reduced by 26 % in the atomoxetine group while differences between treatment groups were significant approximately at 7–8 weeks of treatment. Additionally, ADHD symptoms and craving were also significantly reduced in the atomoxetine group (Wilens et al., 2008). These results are notable, since atomoxetine treatment might need several weeks before a sufficient effect is found (Upadhyaya et al., 2015), and most alcohol relapses occur during the first two months of treatment (Mann et al., 2013; Anton et al., 2006).

Opiate receptor antagonists such as naltrexone or nalmefene reduce craving, heavy drinking and relapse risk in AUD (Knox et al., 2019) and might help to reduce the abuse potential of stimulants in individuals with ADHD (Spencer et al., 2018). However, no studies investigated the use of relapse-preventing or anti-craving medications in individuals with AUD and comorbid ADHD.

6.3. *Treatment recommendations for ADHD and AUD*

In a typical outpatient setting, improvement of ADHD usually occurs first before achieving abstinence (Levin et al., 2018). Thus, management of ADHD symptoms does play a role in SUD with comorbid ADHD. ADHD should be addressed in the treatment approach, but it will require more effort to improve substance use than to simply prescribe an ADHD medication (Levin et al., 2018). This is also emphasized by the international consensus statements on the comorbidity of SUD and ADHD in adults and adolescents that both recommend a combined psychotherapeutic and pharmacotherapeutic approach for both disorders (ADHD and SUD), as well as for further comorbid disorders (Özgen et al., 2020; Crunelle et al., 2018).

For AUD, psychotherapeutic interventions such as motivational interviewing are effective to reduce drinking and achieve abstinence (Knox et al., 2019). Also, a growing number of approved or promising pharmacological treatments for AUD are available but remain infrequently used (Knox et al., 2019). For ADHD in patients with SUD, long-acting stimulants, atomoxetine or extended release guanfacine are recommended (Özgen et al., 2020; Crunelle et al., 2018). Although not mentioned in recommendations based on international consensus, extended-release clonidine might as well be a valuable option (Jain et al., 2011; Vanderkam et al., 2020). Especially when another SUD is present, the risk for non-medical use (NMU) or the selling of prescribed stimulants should be considered. Although most NMU of prescribed stimulants is oral (Faraone et al., 2020), insufflation and injecting occur and lead to serious medical outcomes and death (Faraone et al., 2019; Vosburg et al., 2020). Although the abuse potential of long-acting stimulants is lower compared to immediate-release stimulants, NMU still is of concern especially in younger adults with SUDs (Faraone et al., 2020). For this group of patients, a careful approach balancing the risk of under-treatment and stigmatization with the risk of diversion and misuse of stimulants is highly important. If NMU is of concern, non-stimulants are the better option (Faraone et al., 2020).

7. Future directions

Although the scientific knowledge on ADHD and AUD has been increasing over the last years, a number of topics are still under-investigated, given the high prevalence of about 20 % ADHD in individuals with AUD (Luderer et al., 2018a) and up to 11 % individuals with ADHD that develop a moderate to severe AUD in early adulthood (Tuithof et al., 2012a; Molina et al., 2007).

Treatment recommendations have been deduced from the treatment of ADHD in other SUDs, since treatment studies of ADHD in AUD are more than scarce. Thus, studies on treatment with stimulants as well as non-stimulants such as atomoxetine or guanfacine, or novel glutamatergic agents including ketamine, are necessary. Future treatment studies might focus on harm reduction as a primary outcome, instead of abstinence. Since reduced alcohol consumption reduces negative health consequences, especially in the highest levels of alcohol use (Nutt et al., 2019), reduced alcohol intake is a valid outcome goal. Other more distal factors such as suicidal behavior or quality of life should also be studied. Hypotheses for controlled studies can be derived from larger naturalistic studies (Van de Glind et al., 2020). While there is an urgent need to generate more evidence about the treatment of ADHD in individuals with AUD, it would be even better to prevent AUD in individuals with ADHD. However, data on this topic is lacking (Özgen et al., 2020). Although advanced strategies such as machine learning might be of help to identify patients with ADHD who are at risk for developing a later SUD, more research is needed to improve their accuracy for clinical use (Zhang-James et al., 2020).

Since the rate of undetected ADHD in adults with AUD is high, many basic research and clinical studies on AUD probably included an uncertain number of ADHD cases, possibly explaining heterogeneous results regarding domains closely related to ADHD or treatment efficacy. Therefore, ADHD should be taken into account as a common comorbid disorder not only by clinicians, but also by basic researchers investigating alcohol use and AUD. Future research will improve our understanding of the etiology and pathophysiology of ADHD and AUD, especially when transdiagnostic and continuous measures of both ADHD symptoms and alcohol use and their social and health related consequences are taken into account. (Faraone and Larsson, 2019; Sanislow et al., 2010).

A growing literature has examined sex specific aspects in studies of ADHD or AUD, regarding different symptom profiles in females and males, different challenges over the life span, different etiologies, as well as different treatment outcomes (Young et al., 2020; Schick et al., 2020). Sex effects should also be incorporated in studies of the comorbidity of ADHD and AUD, as well as in preventive strategies for individuals at risk for AUD, e.g. with ADHD.

Although there is convincing evidence of a common neurobiological basis of ADHD and AUD as outlined above, only a small number of studies so far have investigated the two disorders together. Thus, studies aiming at pathophysiological mechanisms using e.g. functional imaging or neuropsychological profiling on individuals with both disorders (AUD and ADHD) compared to either one disorder are needed to strengthen previous findings.

We also found that the terminology on alcohol-consumption patterns used in different clinical and pre-clinical studies is quite heterogenous, which hampers the comparability of the results. Thus, there is an urgent need for clearly defined alcohol related outcomes that are clinically relevant and can be assessed reliably even in larger cohorts, both in basic and clinical research.

ADHD is a valid and reliable clinical diagnosis. However, the diagnostic process in patients with AUD can be labor intensive and the diagnosis of ADHD can sometimes remain uncertain, especially in those patients who are most severely affected by (additional) comorbid disorders. Also, strict categorical diagnoses do not cover the spectrum of ADHD and its interaction with alcohol use and AUD. Therefore, transdiagnostic neuropsychological and neurobiological phenotyping might help to identify a sub-population of individuals that benefit from treatment, e.g. with stimulants, more than others.

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Y.Z.J. has no competing interests to declare

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