Chapter

Adult Attention-Deficit/Hyperactivity Disorder and Substance Use Disorder: A Systematic Review of the Literature

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Abstract

Attention-deficit and hyperactivity disorder (ADHD) often presents with comorbid substance use disorder (SUD). The extant literature on the comorbidity of adult ADHD and SUD was summarized on the etiology, prevalence, diagnosis, and treatment. ADHD is diagnosed in 15–20% of SUD patients, mostly as ADHD with a combined presentation. ADHD and SUD are believed to have shared pathophysiology. ADHD is associated with the majority of dependence diagnoses. A most used screening questionnaire for screening ADHD patients presenting with SUD is the Adult ADHD Self-report Scale (ARSR). Evidence on pharmacological treatment is limited, but new trials support the use of long-acting stimulants as also recommended with a combination of psychotherapy by expert opinion. Given the prevalence of both ADHD and SUD, more research is needed to understand the theoretical and clinical implications of this comorbidity.

Keywords: adult, attention-deficit hyperactivity disorder, comorbidity, substance use disorders, clinical implications

1. Introduction

Attention-deficit and hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by persistent symptoms of inattention and/or hyperactivity-impulsivity. There are three subtypes of ADHD, marked by predominantly inattentive symptoms, or by hyperactivity and impulsiveness, either a combination of inattentiveness and hyperactivity [1]. Studies suggest that the prevalence of ADHD among children may be as high as 15.5%, with approximately 20% of cases persisting into adulthood [2, 3]. A lower prevalence of ADHD in adults compared with children is consistent with the age-dependent decline of the disorder, which has been confirmed in a meta-analysis [4]. ADHD is diagnosed twice as often in boys as in girls. Boys with ADHD tend to present with more impulsivity, while girls with ADHD tend to have more inattentiveness [5].

The etiology and pathophysiology of ADHD are incompletely understood. There is evidence of a genetic basis for ADHD and secondary environmental risk factors.

Differences in the dimensions of the frontal lobes, caudate nucleus, and cerebellar vermis have been demonstrated. Neuropsychological studies have demonstrated deficits in executive functioning and alterations in the motivation and reward among individuals with ADHD [6]. There is both empirical and theoretical support for an association between ADHD and SUD. ADHD and SUD are believed to have shared pathophysiology. Dopaminergic dysregulation of the motivational and reward system of the midbrain the basal ganglia and the frontal cortical regions influence executive functions and response inhibition which are key characteristics in both disorders [6, 7].

The essential feature of a substance use disorder (SUD) is a cluster of cognitive, behavioral, and physiological symptoms. This indicates that the individual continues using the substance despite significant substance-related problems. An essential characteristic of SUD is an underlying change in brain circuits. These changes may persist beyond detoxification, particularly in individuals with severe disorders. The behavioral effects of these brain changes may be exhibited in the repeated relapses and intense drug craving when the individuals are exposed to drug-related stimuli. The diagnosis of a SUD is based on a pathological pattern of behaviors related to use of the substance, which includes impaired control over substance use, the consummation of substance in more significant amounts or over a longer period, persistent desire to cut down or regulate substance use, a great deal of time spent in using the substance, craving for the drug, social impairment, risky use of the substance, and pharmacological criteria including tolerance and withdrawal [1].

One of the most frequent co-occurring disorders with adult ADHD is SUD. A meta-analysis reported a prevalence of 15–20% of ADHD in adults diagnosed with SUD (nicotine excluded) [8, 9].

International consensus statement concluded that screening questionnaires such as the Adult ADHD Self-Report Scale (ASRS) are useful in screening patients presenting with SUD followed by in-depth diagnostic assessment if the screener is positive or if the clinician has a strong clinical feeling about the possible presence of ADHD. ADHD and SUD experts agreed that the simultaneous and integrated treatment of ADHD and SUD using a combination of pharmaco- and psychotherapy is recommended [10].

The aim of this study is to summarize extant scientific literature concerning the comorbidity of ADHD and SUD on the etiology, prevalence, diagnosis, and treatment.

2. Methods

Publications on adults with combined ADHD and SUD were included focusing on etiology, prevalence, diagnosis and treatment. PubMed search was performed for articles published between 2010 and 2020 using the terms: adult ADHD, drug abuse, substance use disorder, addiction, and dependence. Publications were limited to articles published in English and were discarded if: they did not include adults; ADHD or SUD was not the primary diagnosis; they were reviews before a meta-analysis; they were personal opinion papers; and they were study protocols. The search was conducted on August 17, 2020.

3. Results

A total of 143 articles were found on initial search and screened on title and abstract. Of these, 68 articles did not discuss a combination of ADHD and SUD

specifically. Articles focusing solely on children or discussing other topics were excluded (n = 9) and also those in other languages (n = 7) or they were too old (n = 13). A total of 46 peer-reviewed studies were included for full-text review. Additional five articles were found with cross-referencing cited by authors that had not been found by initial research.

All together 51 articles were focusing either on etiology (n = 6), prevalence and symptom severity (n = 28), screening (n = 4), and treatment (n = 13) of adult ADHD and SUD.

3.1 Etiology

A study exploring childhood trauma exposure in SUD patient with ADHD and control group found higher rates of childhood trauma in ADHD and SUD patients, but not with the persistence of childhood ADHD into adulthood [11]. A familial risk analysis of probands followed from childhood to young adulthood found that SUDs in probands increased the risk for SUDs in relatives irrespective of ADHD status [12].

A large trans-ancestral genome-wide association study (GWAS) of alcohol dependence revealed common genetic underpinnings with ADHD, which indicates shared etiology between the two disorders [13]. Shared genetic susceptibility ADHD and SUD is also reported in Spanish study with polygenic scores based on GWAS [14]. Study on shared genetic contribution of the ADHD and SUD showed significantly increased frequency of the dopamine beta-hydroxylase (DBH) rs2519152 and the opioid receptor mu-1 (OPRM1) risk genotypes rs1799971 [15]. Dutch International Multicenter ADHD Genetics study reported that the serotonin genetic risk score significantly predicted alcohol use severity, but no significant serotonin × dopamine risk score or effect of stimulant medication was found [16]. An Italian study reported that patients with ADHD showed a higher intensity of craving for heroin than patients without ADHD in the absence of withdrawal symptoms. We can conclude on shared neurobiological mechanisms that mutually influence the evolution of both disorders where dopamine dysfunction within various brain circuits may influence impulsivity levels, motivation, inhibitory control, executive functions, and behavior and, consequently, the intensity of craving [17].

A study which analyzed commercial health-care claims from adolescent and adult ADHD patients shows results that receiving ADHD medication is unlikely to be associated with a higher risk of substance-related problems in adolescence or adulthood. Instead, medication was associated with lower concurrent risk of substance-related events and, at least among men, with lower long-term risk of future substance-related events [18].

3.2 Prevalence and symptom severity

Existing evidence shows a prevalence of 15–20% of ADHD in adults diagnosed with SUD [8]. International European study exploring the prevalence of DSM-IV and DSM-5 adult ADHD varied from 5.4 to 32.6%. Prevalence estimates for DSM-5 were slightly higher than for DSM-IV [19]. Another study on inpatients with alcohol dependence showed that ADHD prevalence was 20.5% [20]. Nigerian study observed an ADHD prevalence of 21.5% with the combined subtype being the most prevalent [21].

Adult ADHD was reported to be associated with fewer years of education, earlier initiation of regular tobacco use and more extensive lifetime poly-drug [22], as also with a more severe pattern of cocaine consumption [23]. ADHD in the cocaine-dependent patient was associated with factors such as male gender, age at the start

of cocaine use and dependence, the amount of cocaine consumed weekly, increased occupational alteration, alcohol consumption, general psychological discomfort, depressive disorder, and antisocial personality disorder [24]. A large study reported that high rate of ADHD symptoms was found among heroin-dependent patients, particularly those affected by the most severe form of addiction. These individuals had higher rates of unemployment, other comorbid mental health conditions, and heavy tobacco smoking [25]. Another study reported that ADHD in long-term methadone maintenance treatment of patients is characterized by greater addiction severity and more comorbid psychopathology [26]. Mexican study reported that adolescents diagnosed with ADHD were more likely to have problems with use or abuse of or dependence on inhalants, and an elevated prevalence of parental SUDs was found in both the adolescent and adult groups [27].

Data from the National Epidemiologic Survey of Alcohol and Related Conditions (NESARC) on ADHD symptoms (DSM-IV) for the period when they were 17 years old or younger showed that hyperactive-impulsive symptoms were more consistently associated with lifetime substance use and SUD compared to inattentive symptoms [28]. Large American study investigated associations of lifetime hyperactive-impulsive ADHD and inattention ADHD. Both hyperactive-impulsive and inattention group were associated with the majority of dependence diagnoses in a linear pattern, such that each additional symptom was associated with a proportional increase in odds of dependence. Both were uniquely associated with alcohol, nicotine, and polysubstance dependence, but only hyperactive-impulsive ADHD was uniquely associated with dependence on illicit substances [29].

Prospective outcome study reported that adults with childhood ADHD are more susceptible than peers to developing alcohol (adjusted OR 14.38, 95% CI 1.49–138.88) and drug dependence (adjusted OR: 3.48, 95% CI: 1.38–8.79) [30]. A recent Dutch study confirmed this, where results showed that individuals with persistent ADHD were at significantly higher risk of development of SUD relative to healthy controls (OR = 4.56, CI 1.17–17.81). In contrast, levels of SUD in those with remittent ADHD were not different from healthy controls (OR = 1.00, CI: 07–13.02). They concluded that SUD and nicotine dependence are associated with a negative ADHD outcome [31]. Similar results were reported in Italian study where patients with ADHD symptoms and high-dose benzodiazepine dependence showed a significantly larger prevalence of poly-drug abuse than ones without them [32].

A French study reported that a history of ADHD was associated with an earlier onset of addiction, poly-dependence, and borderline personality disorder [33]. An Australian study reported that conduct disorder, rather than ADHD, is the strongest predictor of differences in patterns of drug use severity. The extensive comorbidity of those two highlights the great potential for misattributing drug use risks to ADHD [34]. A Dutch study on opioid-dependent patients found that conduct disorder patients had significantly higher problem severity scores, more frequent comorbid SUD, and more severe psychiatric comorbidity. ADHD was found to increase the risk of psychiatric comorbidity [35]. Another study on British prisoners, on the contrary, show that combined ADHD type is significantly associated with the need for coping as a way of managing primary and comorbid symptoms, but not conduct disorder [36]. Brazilian study also found no difference in drug use or dependence prevalence between ADHD and non-ADHD patients but observed different addiction patterns such as earlier use of cocaine and more severe use of cocaine correlated to earlier contact with cannabis [37]. The longitudinal study followed participants with childhood-limited ADHD and persistent ADHD compared to controls and found that there were no significant group differences in change in rates of substance dependence over time. However, individuals whose ADHD persisted into adulthood were significantly more likely to meet DSM-IV criteria for

alcohol, marijuana, and nicotine dependence [38]. An Australian study conducted in drug and alcohol treatment centers reported increased drug dependence complexity and chronicity in treatment-seeking SUD patients who screen positively for ADHD, specifically for amphetamine, alcohol, opiates other than heroin or methadone, and benzodiazepines [39].

A recent large study reported that symptoms of hyperactivity/restlessness and problems with self-concept increased the odds of having a diagnosis of ADHD and that impulsivity mediated the relationship between adult ADHD symptoms and alcohol dependence severity [40]. A Dutch study showed higher levels of motor and cognitive impulsivity in ADHD patients with comorbid cocaine dependence compared to ADHD patients without cocaine dependence and controls [41]. Belgian study also reported higher impulsivity in cocaine-dependent individuals to controls, regardless of whether they have concomitant ADHD or not [42]. Similar was reported by Brazilian study where patients who had ADHD and cocaine dependence had impairments in both cognitive and affective regulation [43]. Another study on cocaine dependence reported that the Barkley's executive dysfunction items showed statistically significant differences between cocaine-dependent patients with ADHD and those patients without ADHD diagnosis [44].

Swiss study reported that patients with probable adult ADHD showed higher craving, more withdrawal and psychiatric symptoms, and rated withdrawal symptoms as more severe than did patients without ADHD symptoms [45]. Hungary study of drug-dependent patients with and without ADHD symptoms reported the highest severity of aggression when the ADHD positive status co-occurred with heroin use, while the lowest severity of aggression was detected when ADHD negative status co-occurred with the use of marijuana. ADHD positive patients showed a marked increase in depression symptoms, suicidal ideation, suicidal attempts, as well as self-injuries associated with suicidal attempts [46]. Study on Scottish prisoners reported that ADHD symptoms were the strongest predictor, followed by alcohol dependence for violent offending. Hence, the authors pointed out the importance to treat drug addiction and ADHD symptoms in order to reduce offending among the most persistent offenders [47]. Taiwan study among heroin-dependent participants entering methadone maintenance treatment showed that ADHD-screened positive patients showed higher depression scores ($p = .003$), and more severe heroin dependence ($p = .006$) [48]. Childhood ADHD was associated with obsessive-compulsive disorder, and both conditions were highly prevalent among former heroin addicts on methadone maintenance treatment [49].

3.3 Screening and diagnosis of ADHD and SUD

ADHD is a common comorbid disorder that is frequently overlooked in adults with SUD. DIVA diagnostic interview is important tool to diagnose ADHD in adult patients. Since it is an interview, it has greater diagnostic power then screening questioners. DIVA-5 is the successor to DIVA 2.0, the structured Diagnostic Interview for Adult ADHD, and is based on the criteria for ADHD in DSM-5 [50]. A most used screening questionnaire for screening ADHD patients presenting with SUD is the ASRS followed by in-depth diagnostic assessment [10]. In a Norwegian study, 33% of patients on opioid maintenance therapy [51] and in the Italian study, 19.4% [25] were positive for ADHD using the ASRS. Among patients with benzodiazepine dependence, 32% of them screened positive on ADHD [32].

Brazilian study validated the translated version of the adult self-report The Brown Attention-Deficit Disorder Scale (BADDS) using the ASRS as the gold standard [52], but ASRS appears to be more appropriate screener that BADDS in SUD patients [53]. Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID)

proved to be a diagnostic tool that can also be used during active substance use [54]. Study investigating the clinical utility of two self-report screening instruments such as Conners' Adult ADHD Rating Scale screening Self-Rating (CAARS-S-SR) and the ASRS in alcohol use disorder showed many false-negative results (ASRS: 89.5%; CAARS-S-SR: 92.3%) which indicates underreporting of ADHD symptoms. Authors suggested that underreporting of ADHD symptoms in ASRS and CAARS-S-SR of alcohol use disorder patients requires lower cut-off values to detect the majority of ADHD [55].

In a recent study from international multi-center, the Mini-International Neuropsychiatric Interview (MINI-Plus) on patients with substance use disorders was validated for the screening of adult ADHD in treatment-seeking SUD patients [56]. Another tool in understanding the possible causes and motivations behind substance misuse and its dependency is Substance Transitions in Addiction Rating Scale (STARS) where the subscales produced meaningful and reliable factors that supported the self-medication and behavioral disinhibition hypotheses of substance use motivation [36].

3.4 Treatment

Comorbid ADHD and SUD represent a challenge for health-care providers as the pharmacological trials have found mix results for efficacy [8]. The reviews on ADHD medications for ADHD with SUD point out limited efficacy of treatment, but more recent trials using psychostimulants in robust dosing have demonstrated positive results [57–60].

Guidelines recommend that when ADHD coexists with other psychopathologies in adults, the most impairing condition should generally be treated first [58]. Another approach is to first achieve abstinence before treating ADHD, where the main goal is to reduce the risk of diversion of stimulant medication [57]. The international consensus statement recommends long-acting stimulant medication [10].

While previous concerns arose whether stimulant therapy would increase the ultimate risk for substance abuse, recent studies have indicated that pharmacologic treatment appears to reduce the risk of substance abuse in individuals with ADHD [61]. Findings from 19 large open studies and controlled clinical trials show that the use of atomoxetine or extended-release methylphenidate formulations, together with psychological therapy, yield promising though inconclusive results about short-term efficacy of these drugs in the treatment of adult ADHD in patients with SUD and no other severe mental disorders. However, the efficacy of these drugs is scant or lacking in treating concurrent SUD [62]. The concern is as indicated by American study that ADHD is prevalent among chronic methamphetamine users, who are at increased risk for persistence of childhood diagnoses of ADHD into their adult years. ADHD also appears to play an important role in methamphetamine-associated disability, indicating that targeted ADHD screening and treatment may help to improve real-world outcomes for individuals with methamphetamine use disorders [63].

A meta-analysis on the efficacy of atomoxetine in treating adult ADHD showed atomoxetine is efficacious in treating adult ADHD compared to placebo, though the efficacy is significantly superior for inattention than hyperactivity/impulsivity [64]. Study on alcohol-dependent patients with and without a diagnosis of ADHD hypothesized that atomoxetine could reduce the impulsivity trait [65]. A small study reported that atomoxetine may improve some ADHD symptoms but does not reduce marijuana use in marijuana-dependent adults with ADHD [66].

A small study on ADHD patient with cocaine use disorder showed that behaviors reflecting cocaine addiction were sharply reduced during the stimulant

treatment of adult ADHD, and were not correlated with age, gender, familiarity, length of treatment, or medication used. Cocaine use disorder improvement was closely correlated with adult ADHD improvement [67]. Earlier data show that patients with ADHD and comorbid cocaine dependence do not benefit significantly from treatment with methylphenidate, where Dutch study showed that low dopamine transporter occupancy is not the reason for that. Authors also suggest that higher dosages of methylphenidate in these patients are probably not the solution and that medications directed at other pharmacological targets should be considered in these comorbid ADHD patients [68]. ADHD patients with cocaine dependence are a distinctly more impulsive subpopulation compared to ADHD patients without cocaine dependence on objective measures of impulsivity. These findings are relevant for optimizing psycho-education and treatment of ADHD patients with comorbid SUD [41].

Sweden placebo-controlled double-blind study reported that methylphenidate treatment reduces ADHD symptoms and the risk for relapse to substance use in criminal offenders with ADHD and substance dependence [69]. Norway study reported about the safety and utility of central stimulant medications for patients with ADHD who are receiving opioid maintenance treatment [70]. Sustained-release methylphenidate in a double-blind, placebo-controlled trial for the treatment of ADHD in amphetamine abusers found no difference with regards to the craving for amphetamine or in retention in treatment [71]. Another double-blind, placebo-controlled study in adults with ADHD reported that extended-release methylphenidate was statistically superior to placebo in reducing emotional symptoms and a decline of obsessive-compulsive symptoms and those of problems with self-concept. Symptoms of anxiety, depression, anger and hostility, phobia, paranoid ideations and psychoticism were not improved [72]. A study that examined if stimulants would decrease marijuana use in a randomized controlled trial of extended-release mixed amphetamine salts for the treatment of co-occurring ADHD and cocaine use disorders found no significant baseline differences in marijuana use frequency and quantity [73].

A recent Dutch randomized clinical trial among SUD and ADHD patients reported that integrated cognitive behavioral therapy resulted in a significant improvement in ADHD symptoms in comorbid SUD and ADHD patients [74]. This finding leads to the conclusion that nonpharmacological interventions can contribute to ADHD symptom reduction in patients with comorbid ADHD and SUD. ADHD and SUD experts recommend that simultaneous and integrated treatment of ADHD and SUD, using a combination of pharmaco- and psychotherapy, is effective [10].

4. Conclusions

ADHD is highly comorbid with SUD, being diagnosed up to 20% in SUD patients. ADHD and SUD are believed to have shared pathophysiology. ADHD is associated with the majority of dependence diagnoses. A most used screening questionnaire for screening ADHD patients presenting with SUD is the ASRS. Evidence on pharmacological treatment is limited, but new trials support the use of a higher dose of long-acting stimulants as also recommended with a combination of psychotherapy by expert opinion. Finally, the decision to treat adult ADHD in the context of SUD depends on various factors, so clinical decisions should be individualized and based on a careful analysis of the advantages and disadvantages of pharmacological treatment for ADHD in the context of SUD. Given the prevalence of both ADHD and SUD, more research is needed to understand the theoretical and clinical implications of this comorbidity.

Conflict of interest

The authors declare no conflict of interest.

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