Dusunen Adam The Journal of Psychiatry and Neurological Sciences 2018;31:115-124
DOI: 10.5350/DAJPN20183102001

Editorial / Editoryal

Comorbidity of Attention Deficit-Hyperactivity Disorder and Substance Use Disorder

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How to cite this article: Evren C. Comorbidity of attention deficit-hyperactivity disorder and substance use disorder. Dusunen Adam The Journal of Psychiatry and Neurological Sciences 2018;31:115-124. https://doi.org/10.5350/DAJPN20183102001

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Prevalence of Attention Deficit-Hyperactivity Disorder and Substance Use Disorder Comorbidity and Its Consequences

A number of studies with clinical as well as population samples show that attention deficit-hyperactivity disorder (ADHD) is found more frequently in individuals with substance use disorder (SUD) (1,2). Similarly, the probability of receiving a diagnosis of SUD is high in adolescents and adults with ADHD (2).

A recent meta-analysis and meta-regression study including 29 international studies reported that among mostly young adults seeking treatment for SUD, 23.1% were suffering from ADHD (3).

The cross-sectional International ADHD in Substance Use Disorders Prevalence (IASP) study (10 countries, n=3,558) reported a prevalence of 40.0% for ADHD in patients seeking treatment for SUD (4). The same team found the prevalence of ADHD to be lowest in Hungary and highest in Norway; according to DSM-IV criteria, the figures were 5.4% for Hungary and 31.3% for Norway, and according to DSM-5 the rates were 7.6% for Hungary and 32.6% for Norway, respectively (5).

In studies with patients in our clinic who had been admitted due to alcohol use disorder (AUD, n=190), the probable prevalence of ADHD was 18.4% (6), while a rate of 21.1% was found among cases suffering from heroin use disorder who were receiving opioid maintenance treatment as out- or inpatients (n=236) (7).

In a screening study carried out with 4,938 10th-grade students from 45 schools in 15 districts of Istanbul, the severity of ADHD symptoms was found to be higher in subjects with a lifetime history of smoking and alcohol/substance use; thus, lifetime alcohol use is one of the determinants of ADHD severity (8).

ADHD is a risk factor for smoking and SUD. Abuse of cannabis, alcohol, or a combination of both are the most common forms of substance abuse among adolescents with ADHD (9). In particular, a continuation of ADHD into adult life increases the risk of SUD. This increase is independent from comorbidities of conduct

disorder (CD) and antisocial personality disorder (ASPD). In the presence of both of these disorders, the risk for SUD increases further (10). SUD is found in 10-30% of adults with ADHD (11).

The symptoms of both disorders can mimic each other. SUD can present with symptoms in the areas of impulse, attention, and behavior similar to those of ADHD. For example, among cannabis users (even without ADHD), attention span difficulties, memory problems, and bursts of anger are common (10).

A study with cases of cocaine and/or opioid addiction reported that ADHD comorbidity is correlated with early onset of first substance use, increased substance addiction and psychiatric diagnoses, a high probability of suicide attempts, and more frequent hospitalization (12). In adults with ADHD with early onset substance use (smoking included), SUD, if present, generally progresses more severely. With additional psychiatric disorders, the course worsens even more (10). ADHD symptoms reduce compliance with psychosocial therapies for SUD and increase abandoning of treatment (1). Comorbidity of ADHD and SUD results not only in social and psychiatric inadequacy, but may also cause more severe substance use (13).

A number of studies undertaken at the AMATEM (Treatment and Training Center for Alcohol and Substance Dependence) clinic in Bakirkoy (Istanbul) with inpatients being treated for AUD found that the severity of ADHD symptoms (esp. the attention deficit subdimension) determined the intensity of unplanned impulsivity and problems of alcohol-addiction (14) as well as the severity of alcohol craving (15).

In a broad cohort study, the mortality rate (mainly through accidents) among individuals with ADHD was higher compared to those without ADHD, while SUD comorbidity further increased the mortality risk (16). SUD is among the most problematic conditions seen together with ADHD (9). Given that even each of these diagnoses on its own already causes numerous negative effects, even more so when occurring jointly, it is important to research the causes of these comorbidities and the effectiveness of therapy in these cases. However, while there are approved guidelines for this comorbidity, unfortunately these cases are neglected both in diagnosis and therapy. Thus a study with inpatients being treated for SUD found that 3.0% of them had received a diagnosis of ADHD previously, while a screening test carried out during the treatment found an ADHD rate of 44.0% (17).

Relation Between Attention Deficit-Hyperactivity Disorder and Substance Use Disorder

Individuals with ADHD in their childhood have a higher risk of developing SUD. In most studies, this risk is mediated at least partly by CD (2).

Some studies report ADHD as an independent risk factor for SUD even in the absence of comorbid psychiatric diagnoses (2). Among the factors further increasing the risk for SUD are comorbid disruptive behavior disorders (DBD) (e.g. ODD and CD) (2,18) and bipolar disorder (2).

One follow-up study monitored children and adolescents with and without ADHD for 10 years until young adulthood and found a 1.47 times greater risk to develop SUD in the ADHD cases (9). The risk increased 1.51 times for AUD, 2.74 times for SUD, and 2.38 times for smoking. Together with ADHD, initial CD (2.74 times) and ODD (2.21 times) determined SUD.

One meta-analysis assessed studies following individuals with ADHD longitudinally into adolescence or adulthood (19). Most of them found the likelihood of persons with ADHD to use nicotine and other substances, though not alcohol, being elevated. In these children, high probabilities were found for developing SUD for nicotine (almost 3 times), alcohol, cannabis, cocaine, and other substances (1.5 times).

Compared to their peers without ADHD, adolescents with ADHD were reported to have a higher SUD risk, including a tendency towards early onset and chronification (2). In a case-control study, adolescents with ADHD began to develop SUD early, the transition from first use to SUD was rapid, and they experienced a greater functional impairment and displayed more severe

substance abuse (20). In adolescents with CD comorbidity, most studies found correlations between strong smoking, SUD rates, and early onset.

A large epidemiological study in the US showed that ADHD subtypes are correlated with substance use and SUD, with the correlation being stronger for hyperactivity/impulsivity (21). These findings seem to be consistent with the knowledge that impulsivity is a precursor to substance use and SUD.

How does the Correlation Between Attention Deficit-Hyperactivity Disorder and Substance Use Disorder Develop?

Reasons for the correlation between ADHD and SUD are not well understood. Adolescents with active SUD often report an easing of their emotions and help in sleeping as reasons for their substance use (22). Adults with nicotine addictions identified an improvement of attention and executive functions, which is consistent with the recommendations in the literature to use nicotinic agents in the treatment of ADHD (23). Accordingly, and considering that ADHD is chronic and often correlated with demoralization and failure, the "self-medication" hypothesis gains importance (10).

While there are theories maintaining a neurobiological link between ADHD and SUD (24), these theories are contradicted by the results of a multicenter study showing that the neural circuits for each of the two disorders are completely different (25).

Theories trying to explain the link between the two disorders include family/genetic contributions (26,27) and familial exposure to SUD (28). Exposure to alcohol and nicotine during pregnancy has been related to an increased ADHD risk (29,30).

A recent large-scale population-based twin study found a strong correlation between ADHD and AUD with a 3.58 times increased risk (31). Twin analyses showed that shared genetic factors explain 64.0% of the overlap between ADHD and AUD, while the remaining 36.0% are explained by non-shared environmental factors; the contribution of shared environmental factors was found to be very small.

The Role of Comorbid Psychiatric Disorders

Among ADHD patients, those at greatest risk for SUD are the ones who are suffering from other psychiatric disorders frequently seen alongside ADHD, e.g. emotional disorders, antisocial personality disorder (ASPD), and anxiety. In 80.0% of ADHD and SUD comorbidity cases, at least one further comorbidity can be found, most commonly anxiety and emotional disorders (32).

When assessing the correlation between SUD and ADHD, other psychiatric comorbidities definitely need to be taken into consideration. Prospective data show an increased SUD risk in individuals with ADHD and concomitant CD or bipolar disorder (33,34). Population-based studies using a dimensional approach show a statistically significant and independent correlation between SUD and ADHD, even though sometimes being mediated by CD (35,36).

In an IASP study carried out in 47 centers in 10 countries enrolling SUD cases seeking treatment (n=1,205), a rate of 13.9% for ADHD according to DSM-IV have been found (37). In SUD cases with ADHD, compared to those without, the ASPD risk was 2.8 times higher, and for bipolar disorder 7.0 times (for alcohol) and 3.4 times (for substances); patients with alcohol as primary substance of abuse displayed a 4.1 times increased rate of major depression and a 4.3 times higher incidence of hypomanic episodes. These results show that patients using alcohol as primary substance had a higher rate of bipolar disorder and major depression. According to the subtypes, major depression was found increased in AD and compound subtype, hypomanic episodes and ASPD in the hyperactivity/impulsivity subtype, and bipolar disorder in all subtypes (compared to SUD cases without ADHD). Of the SUD patients with ADHD, 75.0% had at least one additional psychiatric disorder, as had 37.0% of patients without ADHD.

A systematic review and meta-analysis of 22 studies researching the correlation between ADHD and post-traumatic stress disorder (PTSD) showed that the relative risk (RR) for PTSD in ADHD cases was 2.9 (3.7 in healthy control samples, 1.6 in traumatized

control samples) (38). In cases with PTSD, the ADHD RR was 1.7 (2.1 in traumatized controls; it was not significant in a control group of inpatients receiving psychiatric treatment). The authors thus report a two-way relation between PTSD and ADHD. Earlier studies showed that childhood symptoms of ADHD are related with childhood dissociative disorder (39) as well as with adult dissociation (40).

A study carried out with inpatients receiving AUD therapy at the AMATEM clinic in Bakirkoy (Istanbul) found that childhood trauma (esp. emotional abuse) and the severity of ADHD symptoms (both in the attention deficit and the hyperactivity/impulsivity dimensions) were correlated with the intensity of PTSD (41). In another study with the same sample, even after control for the severity of depressive symptoms, the severity of ADHD symptoms (esp. in the attention deficit dimension) was correlated with the severity of dissociative symptoms, and physical abuse in childhood partly mediated this correlation (6). These two studies demonstrate an important effect of a childhood trauma history on ADHD and additional psychiatric symptoms. It has been reported that patients with opioid use disorder and ADHD patients under maintenance treatment show a high rate of obsessive-compulsive disorder (42). A study with out- and inpatients in Turkey being treated for opioid use disorder found that a probable ADHD diagnosis is correlated with the severity of the psychopathology, especially in the obsessive-compulsive dimension, and that the severity of impulsivity (esp. unplanned and motor impulsivity) may have a relevant effect on this correlation (7).

Effect of Attention Deficit-Hyperactivity Disorder Treatment on Comorbidity

Pharmacotherapy for ADHD is a well-researched field, but the misuse potential of the relevant drugs, esp. stimulants, and the possibility that they later begin to play a role in SUD are causing some concerns (43). However, in the available literature the situation is not portrayed in this way. One meta-analysis reported a reduction in substance issues, esp. in adolescents, after ADHD therapy using stimulants (44). A recent meta-analysis studying the impact of ADHD pharmacotherapy on the subsequent course of alcohol/substance problems came to a negative result (45). Studies published after this meta-analysis reported that pharmacotherapy either had no effect on the course of SUD or influenced it in a positive way. A prospective long-term open study with adolescents using extended-release methylphenidate for ADHD found a lower risk of smoking (46) and SUD (47) than in adolescents with ADHD not using the drug.

A multi-center study in Europe found that in the ADHD treatment group SUD was reduced (48). While findings regarding the reduction of risk are conflicting, some studies indicate that pharmacotherapy for ADHD does not increase the risk for SUD subsequently but may even reduce it. Actually, some studies report a reduction during adolescence but do not answer the question if the effect continues into adulthood, the reason being that in long-term studies very few cases remain in treatment, thus not allowing the establishment of a protective effect.

A study in Sweden monitoring young adults with an ADHD diagnosis for 5 years, about half of whom were receiving pharmacological treatment, reported that the crime rate was significantly lower (41.0% in females and 32.0% in males) (49). In addition, crime rates were lowest during the period of ADHD pharmacotherapy.

Effect of Pharmacotherapy

Stimulants, noradrenergic agents, and catecholaminergic antidepressants have been reported to be effective in reducing ADHD symptoms (24). Some review studies recommend the use of non-stimulant agents (atomoxetine), antidepressants (bupropion), and extended-release or long-acting stimulants with a low misuse risk in adolescents with ADHD and SUD comorbidity (50). It is believed that in comorbid patients the course of therapy should vary according to the starting time (e.g. considering if the patient has an active SUD or is in a short-term period of abstinence).

A 12-week multi-center randomized control trial with adult AUD patients who were not receiving

cognitive behavioral therapy (CBT) and had been abstinent for a short period found that atomoxetine reduced ADHD symptoms, alcohol craving scores, and heavy drinking but was not effective on time-to-relapse (51). The reliability of atomoxetine was examined in a different study with the same sample, and the completion rates in the atomoxetine group for heavy drinkers (60.9%) and patients without AUD (71.0%) were similar, while the rate for non-heavy drinkers was low (35.7%) (52). However, in heavy drinkers using atomoxetine, compared to light drinkers, neither increased side effects nor impaired liver function were established.

After 4-30 days of abstinence, 147 adults with ADHD and AUD received a 12-week course of atomoxetine 25-100mg (mean final dose=89.9mg) or placebo (53). While no difference in time-to-relapse was found in patients taking atomoxetine, the cumulative heavy drinking rate was 24.0% lower than in the placebo group. Improvements in ADHD symptoms were correlated with reduction in alcohol craving. Relapse to alcohol use in the placebo group correlated with deterioration in ADHD symptoms, while in the atomoxetine group no correlation was found. In the study, atomoxetine was well tolerated and no negative effect was reported.

In contrast to these findings, atomoxetine was not found more effective than placebo in adolescents still using substances (54) and in adults addicted to cannabis (55). In conformity with these two studies, another study administering 72mg/day methylphenidate orally in adults showed a minimal effect in active users of alcohol/substance with ADHD on either condition (56). The stimulants administered for therapy were not misused and showed a relatively low misuse tendency (57) and side effects were similar in a study assessing adolescents with ADHD who did not use substances (56).

Similar results have been reported for the adult population. Thus a randomized control study with patients under methadone maintenance therapy receiving either methylphenidate, bupropion, or placebo plus CBT once per week found a clinically significant reduction of ADHD symptoms in all groups (58). Furthermore, in adults with ADHD and cocaine addiction, methylphenidate in addition to CBT did not improve the course of the disease more than placebo (59).

A review assessing 19 open and controlled studies researching the efficacy and reliability of pharmacotherapy in patients with ADHD and SUD comorbidity without other serious psychiatric diseases reported that atomoxetine or long-acting methylphenidate forms used together with psychotherapies were encouraging but insufficient (60). Serious safety problems or side effects did not occur and the misuse risk was found to be low. A systematic review of studies done in adolescents with ADHD and SUD comorbidity reported that a limited number of studies demonstrated the potential effectiveness of stimulant or non-stimulant drugs (61). A recent systematic meta-analytic review of studies assessing the effectiveness of pharmacotherapy in ADHD and SUD comorbidity cases found a small to moderate reduction of ADHD symptoms but no useful effect on substance abstinence or treatment discontinuation. There was a positive correlation between the effects on ADHD and SUD, respectively (62).

It is not quite clear why no efficacy was observed, but a potential explanation is that the immediate toxic effect of the substances may modify the effect of methylphenidate on dopamine neurotransmission in a way that could not yet be demonstrated (63). It has also been reported that individuals with SUD may require high doses (59). This explanation is supported by a recent study with amphetamine addicts just released from prison: administration of up to 180mg methylphenidate (normal: 0.5-1.0mg/day) improved ADHD symptoms, reduced relapse, and increased continuation of therapy (49). Finally, while studies in adults with ADHD and SUD found a certain reduction of symptoms, they showed no advantage relative to placebo in cases receiving psychotherapy. This may also demonstrate that psychotherapies such as CBT are an effective treatment to improve ADHD symptoms.

Individualizing the clinical decision and balancing benefit and harm for each comorbid patient, the decision regarding pharmacotherapy of ADHD needs to be taken accordingly. Attention needs to be paid to indications of

drug abuse or misuse such as missing controls, repeated request of high doses, or "lost" prescriptions. High-risk situations such as ASPD comorbidity, ongoing judicial procedures, or the presence of SUD in spouse or family need to be excluded.

Effect of Psychotherapy

Studies show that CBT is effective in adolescents and adults with ADHD (10). Randomized studies found a significant effect of CBT in adult ADHD patients, and this effect lasted for 12 months (64). There are no studies yet to show if this treatment, which is known to be effective in SUD as well, is also effective in comorbidity of both disorders. However, a presentation of two cases suggests that integrated CBT may be an encouraging new therapy option in comorbid ADHD and SUD (65).

Approaching Adolescent or Young Adult Substance Users and Therapy Suggestions

Before diagnosing ADHD and SUD comorbidity, initially each disorder needs to be assessed in detail. In those conditions, both familial and individual support are important. In cases with active substance used, management of SUD and controlling the condition, if possible, are necessary before therapy (Figure 1).

Subsequently, reevaluation of the individual is required. It is necessary to establish if continuing symptoms are related to SUD or to comorbid ADHD or anxiety or mood disorders (10).

Next, structured psychotherapies (esp. motivational interviewing and CBT) can be applied as first-line treatment. In cases with active SUD, therapy effect is low. The first choice should be pharmacotherapy with atomoxetine (in the highest possible dose).

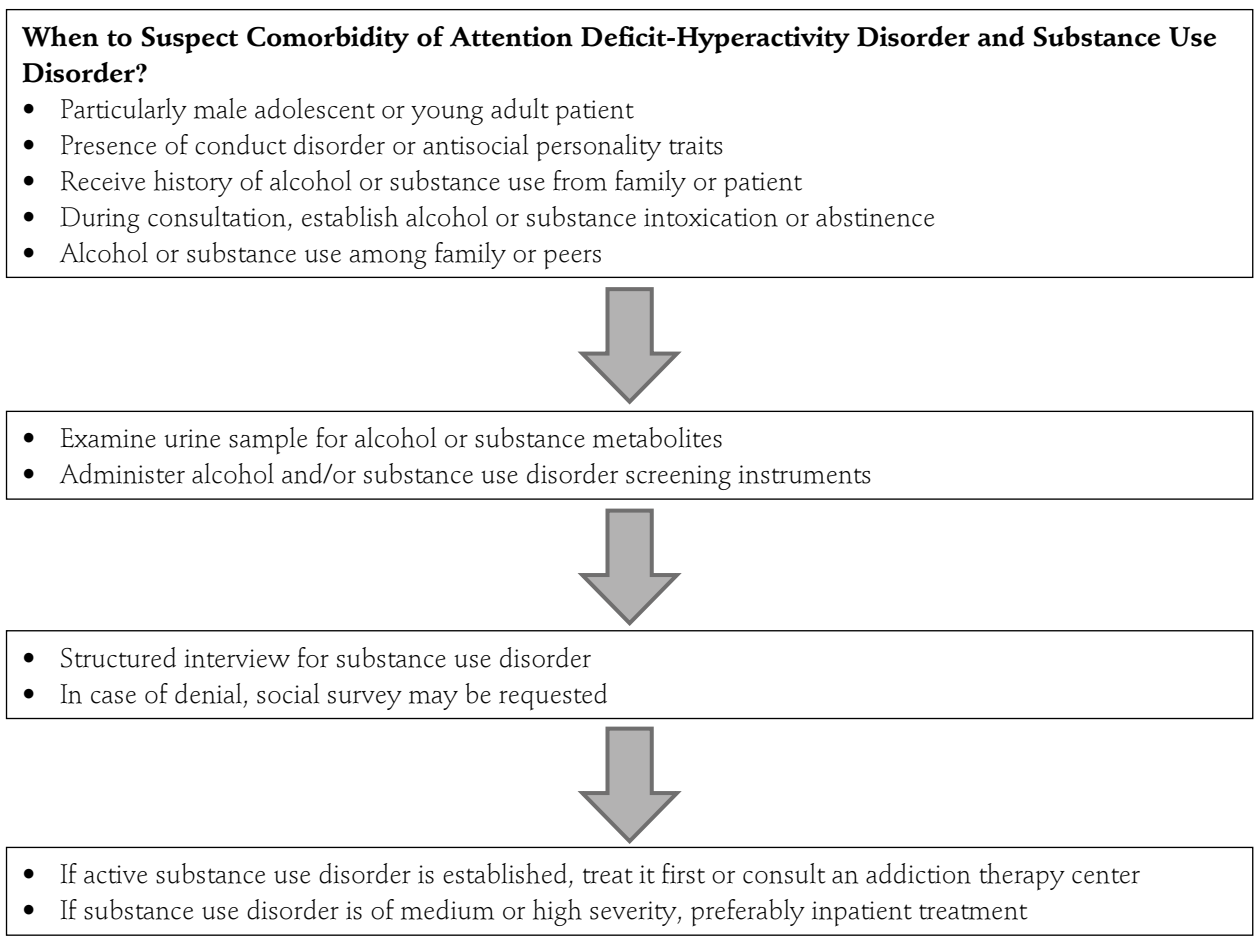

Figure 1: Assessment of attention deficit-hyperactivity disorder patients for alcohol/substance use disorder

In appropriate cases, bupropion can be tried. If treatment with stimulants is necessary, for patients addicted to substances other than alcohol (esp. stimulants), doses higher than normal are required. Among users of illegal substances, the incidence of ADHD is nine times higher than normal (66). In the presence of conduct disorder/ASPD, drug abuse risk is elevated (10). In case of active SUD, it is appropriate to wait for a 3-month remission (not required). The chosen drug has to be in extended-release form. The patient needs to be reminded that the drug has to be used regularly, and the other family members should be informed to keep track of the amount of drugs prescribed (10).

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