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## Взаимосвязи между синдромом дефицита внимания и гиперактивности и аддикциями

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### АННОТАЦИЯ

В статье группа молодых ученых приводит результаты дискуссии о взаимосвязях между синдромом дефицита внимания и гиперактивности (СДВГ) и аддикциями. Рассмотрены современные взгляды на общность возникновения этих состояний на генетическом, морфологическом и функциональном уровнях. Описаны возможные клинические проявления и частота коморбидности. Отдельно подробно обсуждены современные фармакологические и нефармакологические подходы к терапии этих коморбидных состояний. Выделены особенности терапии при сочетании СДВГ с различными аддикциями.

**Ключевые слова:** *СДВГ; аддикции; коморбидность*

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# The interactions between attention deficit hyperactivity syndrome and addictions

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## ABSTRACT

In the article, a group of early career psychiatrists presents the results of a discussion about the relationship between attention deficit and hyperactivity disorder (ADHD) and addictions. Modern views on the commonality of the occurrence of these conditions at the genetic, morphological and functional levels are considered. Possible clinical manifestations and the frequency of comorbidity are described. Modern pharmacological and non-pharmacological approaches to the treatment of these comorbid conditions are discussed in detail separately. The features of therapy in the combination of ADHD with various addictions are highlighted.

**Keywords:** *ADHD; addictions; comorbidity*

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## INTRODUCTION

Hyperactivity in children has remained a prominent area of research for scientists and researchers since last 50 years and more. It has been initially explained in multiple ways, with initial conceptualisation like behavioural problem of children and adolescents to finally shaping up to today's name of attention deficit hyperactivity syndrome (ADHD) as per Diagnostic and Statistical Manual of Mental Disorders IV (DSM-4) before having transient nosological status of a attention deficit disorder with or without hyperactivity in Diagnostic and Statistical Manual of Mental Disorders III (DSM-3). Also, substance abuse and modes of de addiction has evolved many steps with major paradigm shift, since the ancient ages with religious efforts to modern day psychotropics, very specific to treatment targets specific for addiction and related problems like acute withdrawal, craving management even up to partial agonist therapy. The simultaneous and combined understanding of both the disorders have turned important too which needs detailed discussion and further research as well.

### Prevalence of substance abuse in attention deficit and hyperactivity disorder

Various researches, both with clinical and population based samples, have shown that the high probability of receiving a diagnosis of substance use disorders (SUD) in adults with ADHD. Needless to say, this load of co morbidities puts extra burden of illness and caregiving as well, both on patients and their caregivers too. Many studies and reviews have documented that individuals with ADHD are at risk for increased substance intake and experimentation with newer ones [1–3].

One of the most comprehensive studies, by K. van Emmerik-van Oortmerssen, et al. (2012) which includes 29 international studies, has reported that 23.1% of young adults diagnosed with ADHD were also seeking treatment for SUD. Also, one of the most prominent and multi centred studies in the similar field, International ADHD in Substance Use Disorders Prevalence Study (IASP), on a sample of 3,558, among 10 countries, have reported a prevalence of 40.0% for ADHD in patients seeking treatment for substance abuse and related disorder [4]. In a screening study carried out in Istanbul with 4,938 10th-grade students from 45 schools in 15 districts by C. Evren, et al. (2015), the severity of ADHD symptoms were found to be higher in students with a lifetime history of smoking and alcohol/substance use [5].

### Behavioural addiction in attention deficit and hyperactivity disorder

Various researches indicate lower levels of Dopamine in people with ADHD which partially explains their more tendency towards behavioural addiction as well. While involving in risky behaviours increases the dopamine level,

therefore some individuals with ADHD are drawn towards risky behaviours and behaviours and risks associated behavioural addiction as well.

Risk behaviours ADHD and SUD both are correlated with high levels of drug-related and sexual risk-taking. However in a study by S. Darke, et al. (2006) it has been highlighted that likelihood of risky drug-related and sexual practices is similar and in higher number of screening positive for ADHD symptoms, than in case of SUD alone.

Some of the difficult or risky behaviours related to ADHD include:

- trouble getting motivated or finishing tasks (either at work or at home);
- being late or not following through on commitments, appointments, or responsibilities;
- impulsive spending or overspending;
- starting fights or arguing;
- trouble maintaining friendships and romantic relationships;
- speeding and dangerous driving;
- substance abuse;
- risky sexual behaviours, such as having unprotected sex [6].

### Cultural variations

Some brain regions which are definite and key to psychological well-being like language, feeling, connection, danger perception, risk takings, social desires and resilience, setting limits are certainly impacted by culture and are a perfect example of nature nurture interaction. Other than cultural impact both on hyperactivity and substance intake pattern, members of different cultural groups understand and respond differently to challenging behaviour in their children, based on their respective culturally appropriate and contextual factors. These factors could be many; like beliefs, values, perceptions, limited knowledge, fear of stigmatization, norms, medical approaches, language difficulties, limited insurance coverage, mistrust in school or health care institution, limited healthcare facilities, and higher threshold for behavioural tolerance before seeking assessment, etc.

Various cross-cultural studies, from the U. S, Europe and Israel have shown that children from ethnic minority are less likely to be recognized and treated for ADHD than their counterparts. In some cultures, for example, the Muslim and Christian Lebanese, hyperactivity and/or impulsivity in boys can be recognized as characteristic by parents and viewed as gender specific behaviour [7].

According to the American National Institute of Mental Health, adults of an ethnic minority background are less likely to be diagnosed with ADHD than non-minority groups. However, the efficacy of ADHD treatment in reducing psychiatric morbidity, transport accidents and criminality emphasizes the academic and clinical imperative of studying ethnic diversity in ADHD care among various ethnic and cultural groups.

## Neurobiology

ADHD is believed to be a highly genetic condition with heritability up to 77% as seen in multiple twin studies [8]. Two approaches have been taken to see the genetic basis of ADHD: 1) the genome scan and 2) candidate gene approach. Among various genetic loci, Regions 16p13 and 17p11 have been linked persistently with ADHD [9]. ADHD is a heterogeneous and a lifespan disorder with roots in early childhood and extending up to adulthood.

### Difference between ICD-10 and ICD-11

ADHD is a clinical diagnosis requiring detailed evaluation of current and previous symptoms. The DSM-5 puts ADHD under the heading of neurodevelopmental disorder and defines ADHD in children (< 17 years) as the presence of 6 or more symptoms either in hyperactivity / impulsivity and inattention domain or both. Less than 5 symptoms are required for diagnosing adult ADHD. The age of onset of symptoms has been changed to before age of 12 years to increase the range and ease of diagnosis. In International Statistical Classification of Diseases and Related Health Problems (ICD) 10th Revision (ICD-10), ADHD was categorised under *hyperkinetic disorder* (F90), further categorized as *disturbance of activity and attention*, *hyperkinetic conduct disorder*. Now in ICD 11th Revision (ICD-11) ADHD is categorized under *neurodevelopmental disorder* and coded as 6A05, it is further categorised as *ADHD predominantly inattentive presentation*, *ADHD predominantly hyperactive-impulsive presentation*, *ADHD combined presentation*. ICD-11 describes the essential features of the disorder, without giving the precise age of onset, duration and number of symptoms [10].

### Attention deficit and hyperactivity disorder & addictions

There are 3 mechanisms for relationship between ADHD and SUD:

- impulsivity and sensation seeking, impaired executive functioning and poor judgment may lead the individual with ADHD to try new substances;
- ADHD subjects often have difficulty in modulating reward response, impaired self-control;
- increased exposure to psychosocial risk factors like educational failures, adverse peer groups and earlier exposure to addictive drugs [11].

### Etiology and recent changes in understanding the neuro-biology and radiological advances in attention deficit and hyperactivity disorder

I. Birth and development: prenatal and perinatal risk factors like pre-maturity, low birth weight.

Intrauterine exposure to tobacco, maternal stress, obesity during pregnancy increases the risk of development of ADHD [12].

II. Environmental: exposure to artificial colouring and flavouring [12].

III. Genetic changes in ADHD:

a) genes encoding for dopamine and serotonin transporters are associated with ADHD;

b) meta-analysis on 7 linkage studies showed that small arm of chromosome 16 might be associated with ADHD symptoms;

c) CDH13 might be a risk gene for ADHD as it modulates the interneurons of hippocampus;

d) gene variant in calcium channel activity may have pleiotropic effect in evolution of ADHD neuropsychobiology;

e) there are 24 hot genes (candidate genes) suspected in ADHD, e.g. D3 (DRD3), DDC, DRD2, HTR1B, DRD4, MAOB, COMT, MAOA, ADRA2 [13].

IV. The higher genetic liability of having ADHD as indexed by Polygenic risk score – ADHD (it represents the total number of genetic variants that an individual has to assess their heritable risk of developing a particular disease) is associated with higher risk of substance use disorder in individuals with ADHD [14].

V. Structural Brain Changes:

a) *grey matter and subcortical changes* in ADHD: Magnetic Resonance Imaging (MRI) studies in ADHD have shown lower overall brain grey matter volumes particularly in right caudate and lentiform nucleus in comparison to controls. Several studies have shown variability in cortical thickness in ADHD;

b) *white matter changes* in ADHD: several Diffuse Tensor Imaging (DTI) studies show white matter abnormalities. DTI is a MRI based technique which characterizes microstructure integrity and microfiber pathways using diffusion properties of water molecules. FA measures the directionality of water diffusion of the underlying tissue and MD measures the magnitude of water diffusion in tissue. High FA values mean better axonal integrity and high MD values mean poor myelination. Various meta-analysis reports microstructure abnormalities in fronto-striatal-cerebellar neurocircuitry. Decreased FA in corpus callosum area suggests poor myelination in patients. DTI studies have pointed out the role of Fronto-Accumbal circuit whose abnormalities may lead to increased aggression in individuals with ADHD [13].

VI. Functional brain changes in ADHD: Functional MRI (fMRI) quantifies the cerebral activity (using oxygen consumption) against a task *in vivo*. On task-based fMRI the working memory and inhibition control of ADHD patients show lower activation in fronto-striatal, parietal and attentional networks than healthy controls. The rs-fMRI shows abnormalities in DMN, cerebellum, anterior cingulate cortex in patients of ADHD [13].

## Types of addiction in attention deficit and hyperactivity disorder

Video game addiction and ADHD: studies report that gamers who have severe symptoms of ADHD have greater risk of developing video game addiction and its negative consequences regardless of what type of video game they play. These children can be benefitted from psychoeducation about the problematic play [15]. Internet addiction disorder (IAD), Mobile phone addiction (MPA) and Internet gaming disorder (IGD): study found that female gender is associated with MPA while male gender is associated with IGD hyperactive/impulsive type and combined presentation of ADHD are associated with IGD [16]. ADHD and Food Addiction (FA): ADHD symptom severity and general distress were significantly and independently associated. Emotional distress partly mediated the relationship between FA and ADHD symptoms severity [17].

Cocaine use disorder: use of high dose of Atomoxetine has shown benefit [18]. Alcohol use disorder: use of Atomoxetine seems to be safe in reduction of ADHD symptoms [18]. Cannabis use: ADHD and cannabis use are partly determined by genetic factors; the heritability of ADHD is estimated to be 70–80% and cannabis use to be 40–48%. Analysis done on meta-analysis of Genome Wide Association studies (GWAs) of ADHD and lifetime cannabis use. It was found that there is a temporal relationship between ADHD and future cannabis use [19].

## Management

In 2018 the International Collaboration on ADHD and Substance Abuse (ICASA) published a consensus statement on assessment and treatment of ADHD and SUD as a dual diagnosis. They advised prompt treatment of ADHD commencing with treatment of SUD. As the first line treatment of ADHD is medications and stimulants which have risk of potential misuse and diversion. They advocated the adoption of combined approach of pharmacotherapy with behavior therapy, psychoeducation and cognitive behavioral therapy (CBT) which includes confidence building, activity scheduling, removal of dysfunctional beliefs & negative thinking and positive social network [20].

Chronic use of alcohol and substance use has been associated with visuospatial and memory deficit along with deficit in memory and executive functioning of young adults. Drugs of abuse often modify ADHD and worsen the clinical picture and outcome; the efficacy of treatment and drug therapy also remains as a challenge as very few studies are conducted. In general, an active patient with SUD's should be treated before beginning of ADHD treatment. Pharmacological treatments usually target the patients self- medicating behavior to treat his ADHD symptoms, it doesn't reduce craving or withdrawal [21].

Long acting and extended release preparations of non- stimulants like Atomoxetine offer promising though not conclusive results in short term treatment of ADHD in patients with co-occurring SUD and ADHD [21].

Novel emerging drugs (not yet fully tested), repurposed emerging drugs (drugs that have been repurposed and systematically tested in clinical trials for ADHD) and drugs with a suspended clinical development [22] (Table 1).

**Table 1.** Novel options in pharmacological treatment [22]

Group	Medications
Monoamine reuptake inhibitors	1) Noradrenergic Reuptake Inhibitors: Viloxazine (Qelbree) approved by FDA in April 2021 2) BLI-100 derived from a Chinese herbal sedative under phase 2 development for Adult ADHD 3) Serotonin–norepinephrine reuptake inhibitors (SNRIs): Duloxetine 60mg/day effects start after 4 weeks
Other monoamine-based mechanisms	1) Titepidine (novel emerging) 2) Vortioxetine (repurposed)
GABAergic transmission	1) N-pantoyl-GABA (NPG, novel emerging) is a fusion analogue of GABA1 and pantothenic acid
Glutamatergic transmission	1) Amantadine (repurposed emerging) 2) Memantine (repurposed emerging) 3) Glutamatergic drugs on hold: Fasoracetam
Melatonergic transmission	1) Melatonin (repurposed emerging) 2) Agomelatine (repurposed emerging)
Dopaminergic transmission	D2 receptors and molindone
Cannabinoid transmission	Sativex (repurposed emerging) is an oromucosal spray
Histaminergic transmission	MK-0249, a H3 inverse agonist: Bavisant
Nicotinic cholinergic transmission (drugs on hold)	Pozanicline: $\alpha 4\beta 2$ partial agonist

Примечание: <sup>1</sup> GABA — gamma-aminobutyric acid



## Non-pharmacological management

Non-pharmacological approaches have either been adapted from other clinical areas or complementary medicine and they are now recommended as a part of multimodal treatment approach in cases of plain ADHD or with co-morbidities.

I. **Neurostimulation in treating ADHD.** The traditional treatment and medications come with number of side-effects, and the effect lasts till the time is therapy continued, no long term modulation is observed with the medications. To counter this novel neurostimulation treatment has emerged. Neurostimulation involves the electrical or magnetic stimulation of the brain to cause long term changes in excitability or neurochemical activity.

- **Transcranial magnetic stimulation (TMS):** non-invasive method which depolarise or hyperpolarise cortical neurons.

- **Repetitive TMS (rTMS):** it involves placement of electromagnetic coil over scalp which delivers magnetic pulse which induces electrical activity in neuronal membranes. A low frequency (1 Hz) 1200 pulse/day given over 1 on dorsolateral prefrontal cortex (DLPFC) for 4 months has reported reduction in hyperactivity. Similar protocols were followed using DLPFC stimulation in reduction of ADHD symptoms.

- **Transcranial Direct Current Stimulation (tDCS):** current is passed through electrodes placed on the scalp, current is flown from anodal to cathodal electrode to stimulate brain area.

- **Vagal Nerve stimulation (VNS):** it involves the electrical stimulation of the vagus nerve via a surgically implanted electrode, delivering pulses at a set frequency, charge and duration. Chronic stimulation of VNS increases Locus ceruleus (LC) activity in rats as measured by c-fos level in LC. There is increase in Noradrenaline level in hippocampus and prefrontal cortex.

- **Trigeminal nerve stimulation:** FDA has approved Monarch external trigeminal nerve stimulation in ages 7 to 12 years. It is connected via a wire to a small patch that adheres to a patient's forehead, just above the eyebrow. It delivers low-level electrical stimulation to the branches of trigeminal nerve.

- **Ultrasound stimulation:** lacking research [23].

II. **Neurofeedback and ADHD.** Neurofeedback is a therapeutic technique that tries to modulates and re-train brain function to address neurological or psychological symptoms [24].

- **Theta/Beta Neurofeedback;**
- **Slow cortical potential neurofeedback;**
- **Z-score neurofeedback and heart rate variability training** [25].

III. **Mindfulness meditation:** Studies have shown that mindfulness improves information processing, cognitive flexibility, attention regulations has shown positive result on

cognitive, attentional and emotional functions. Mindfulness is defined as the awareness that emerges through paying attention on purpose, in the present moment, and non-judgmentally to the unfolding of experience moment by moment. Interventions including Mindfulness workshops which consist of sitting meditation, mindful walking and eating, yoga and body scan. The RESPeRATE device allows the person to practice slow breathing for 15 mins daily by monitoring. It was observed that mindfulness practice decrease hyperactivity and inattention and device guided breathing was associated with reduced stress [26].

IV. **Massage Therapy:** massage includes number of techniques pressing, grasping, kneading, pinching. There are many types of massage therapy like Swedish massage, Thai massage, Traditional Chinese massage (TCM). TCM aka tuina is based on TCM meridian theory, from its perspective ADHD occurs due to abnormal exuberance of yang which can be relieved by specific massage therapy. Few RCT reports benefit of TCM on ADHD [27].

V. **Technology and ADHD.** Cognitive training using technology in today's youth can be engaging. With combination of augmented reality, neurofeedback and virtual reality the new intervention which is designed is called 'serious games' which aims to improve attention control and set shifting in children with ADHD [25].

- **APPS and ADHD:** around 109 ADHD apps are available on virtual stores which are developed for patients, caregivers and healthcare professional. Most of the app are designed for assessment and treatment of ADHD. 3 apps were most downloaded namely ADHD test, ADHD adults, ADHD test lite which are freely available [28].

- **Technology assisted delivery of standard treatment.** Telepsychiatry can provide care for the patients, text message to remind to refill medicine [28].

- **Computer games:** these games improves attentional and executive training and improves performance in training task e.g. [28].

## CONCLUSION

Neurodevelopmental disorders often progresses and turns into spectrum and interactions of multiple disorders. In the future which can be explained by its early onset, definite and strong biological propensity, high genetic loading along with more effect of difficulties in social interaction and social learning too. Addiction biology, which itself has a huge genetic basis, and with research showing its neurodevelopmental origin needs further exploration too. Overall, attention deficit hyperactivity syndrome and substance abuse has been kept as an independent research interest since long but considering nature of commodity and its coexistence and most importantly one affecting others course, progress and prognosis, its a relatively new research interest for the entire world.

## ДОПОЛНИТЕЛЬНО

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