Neurobiologija poremećaja pažnje i hiperaktivnosti

/ Neurobiology of Attention Deficit Hyperactivity Disorder

Ivana Stefanović[1], Marta Okružnik Želalić[1], Iris Žunić Išasegi[1], Dinko Horvat[1], Petra Visković[1], Ivan Begovac[1,2]

[1] Klinika za dječju i adolescentnu psihijatriju, Klinički bolnički centar Zagreb, Zagreb, Hrvatska, [2] Medicinski fakultet Sveučilišta u Zagrebu, Zagreb, Hrvatska

/ [1] *Department of Child and Adolescent Psychiatry, University Hospital Centre Zagreb, Zagreb, Croatia;* [2] *University of Zagreb School of Medicine, Zagreb, Croatia*

ORCID ID: https://orcid.org/0009-0006-8213-4652 (Ivana Stefanović)
ORCID ID: https://orcid.org/0009-0002-9067-5636 (Marta Okružnik Želalić)
ORCID ID: https://orcid.org/0000-0003-0282-003X (Iris Žunić Išasegi)
ORCID ID: https://orcid.org/0009-0004-4188-2457 (Dinko Horvat)
ORCID ID: https://orcid.org/0009-0003-0247-906X (Petra Visković)

Poremećaj pažnje i hiperaktivnosti (engl. *Attention deficit hyperactivity disorder,* ADHD) neurorazvojni je poremećaj karakteriziran poremećajem pažnje, prekomjernom motoričkom aktivnosti i impulzivnošću. Dijagnoza se postavlja na temelju kliničkog intervjua, opservacije ponašanja djeteta, heteroanamnestičkih podataka, važećih klasifikacija, odnosno različitim koracima u dijagnostičkom procesu. Ovaj pregledni rad ima za cilj prikazati aktuelno razumijevanje neurobioloških mehanizama koji doprinose mogućem nastanku i održavanju ADHD-a uključujući genetiku, moždane strukture i funkcije, kao i neurotransmitore. Ova tema je posebno interesantna s obzirom na etiopatogenetsku isprepletenost individualnih (biologijskih i psiholoških) i okolišnih čimbenika kod ADHD-a, a što je prikazano radovima u ovom pregledu. U liječenju ADHD-a koristimo psihosocijalne intervencije, kao i druge metode liječenja, a koje uključuju i farmakološko liječenje.

/ Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by attention deficits, excessive motor activity, and impulsivity. Diagnosis is based on a clinical interview, observation of the child's behavior, heteroanamnestic data, valid classifications, and various steps in the diagnostic process. This review aims to present the current understanding of neurobiological mechanisms that contribute to the possible emergence and maintenance of ADHD, including genetics, brain structure and function, as well as neurotransmitters. This topic is particularly interesting due to the interplay of individual (biological and psychological) and environmental factors in ADHD, which is demonstrated in this review. In the treatment of ADHD, we use psychosocial interventions, as well as other treatment methods, which include pharmacological treatment.

ADRESA ZA DOPISIVANJE / *CORRESPONDENCE*:
Ivana Stefanović, dr. med.
Klinika za dječju i adolescentnu psihijatriju, KBC Zagreb, Kišpatićeva 12, 10000 Zagreb, Hrvatska
E-pošta: ivana.stefanovic128@gmail.com

KLJUČNE RIJEČI / *KEY WORDS:*
Poremećaj pažnje i hiperaktivnosti / *Attention Deficit Hyperactivity Disorder*
Neurobiologija / *Neurobiology*

TO LINK TO THIS ARTICLE: https://doi.org/10.24869/spsih.2025.172

UVOD

Poremećaj pažnje i hiperaktivnosti (engl. *Attention Deficit Hyperactivity Disorder,* ADHD) neurorazvojni je poremećaj karakteriziran trijasom simptoma koji uključuju visok stupanj motoričkog nemira, impulzivno ponašanje i poremećaj pažnje (1). Međutim, kriteriji su različiti za ADHD prema jedanaestoj reviziji Međunarodne klasifikacije bolesti i srodnih stanja Svjetske zdravstvene organizacije (MKB-11/ICD-11) (2) u odnosu na ADHD prema petoj reviziji Dijagnostičkog i statističkog priručnika za duševne poremećaje (DSM-5) Američke psihijatrijske udruge (3).

Sveukupno, pojavljuju se tri glavne razlike u ove dvije klasifikacije:

1. Broj dijagnostičkih kriterija za simptome nepažnje (IA), hiperaktivnosti (HY) i impulzivnosti (IM) (tj. DSM-5 ima devet IA i devet HY/IM simptoma, dok ICD-11 ima 11 IA i 11 HY/IM simptoma);
2. Jasnoća i standardizacija dijagnostičkih pragova (tj. dijagnostički pragovi za broj simptoma u IA i HY/IM domenama su eksplicitno navedeni u DSM-5, dok u ICD-11 nisu; i
3. Podjela HY i IM simptoma u poddimenzije (tj. razlika u podjeli domena simptoma HY i IM povezana je s razlikama između trenutnog i prethodnih izdanja DSM-a i MKB/ICD-a , a to ima važne istraživačke implikacije) (4).

Prema MKB-11/ICD-11 klasifikaciji (6A05), poremećaj pažnje i hiperaktivnosti karakteriziran je trajnim obrascem (najmanje 6 mjeseci) nepažnje i/ili hiperaktivnosti-impulzivnosti koji ima izravan negativan utjecaj na akademsko, profesionalno ili socijalno funkcioniranje. Da bi se postavila dijagnoza, simptomi nepažnje i/ili hiperaktivnosti-impulzivnosti moraju biti prisutni u više situacija ili okruženja (npr. kod kuće, u školi, na poslu, s prijateljima ili rodbinom), ali vjerojatno će varirati ovisno o strukturi i zahtjevima okruženja. Simptomi variraju ovisno o kronološkoj dobi i težini poremećaja. Simptomi se ne mogu bolje objasniti drugim mentalnim

INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized by a triad of symptoms including high levels of motor restlessness, impulsive behavior, and inattention (1). However, the diagnostic criteria for ADHD differ between the 11th revision of the International Classification of Diseases (ICD-11) by the World Health Organization (2) and the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) by the American Psychiatric Association (3).

Overall, three main differences exist between these two classifications:

1. The number of diagnostic criteria for symptoms of inattention (IA), hyperactivity (HY), and impulsivity (IM) (i.e., DSM-5 includes nine IA and nine HY/IM symptoms, whereas ICD-11 includes 11 IA and 11 HY/IM symptoms);
2. The clarity and standardization of diagnostic thresholds (i.e., the DSM-5 explicitly defines thresholds for the number of symptoms required in the IA and HY/IM domains, while the ICD-11 does not); and
3. The separation of HY and IM symptoms into subdimensions (i.e., the differences in the subdivision of HY and IM domains are associated with changes between current and previous editions of DSM and ICD, which has important research implications) (4).

According to ICD-11 classification (code 6A05), ADHD is characterized by a persistent pattern (minimum 6 months) of inattention and/or hyperactivity-impulsivity that significantly impairs academic, occupational, or social functioning. For diagnosis, symptoms must be present across multiple settings (e.g., at home, school, work, with friends or relatives), although they may vary depending on the structure and demands of the environment.

(ili duševnim) poremećajem (npr. poremećajem povezanim s anksioznošću ili strahom, neurokognitivnim poremećajem poput delirija). Simptomi nisu posljedica učinaka tvari (npr. kokaina) ili lijekova (npr. bronhodilatatora, lijekova za nadomjestak štitnjače) na središnji živčani sustav, uključujući i simptome odvikavanja, te nisu posljedica bolesti živčanog sustava.

Simptomi nepažnje uključuju:

- Teškoće u održavanju pažnje na zadacima koji ne pružaju visoku razinu stimulacije ili nagrade ili zahtijevaju kontinuirani mentalni napor; nedostatak pažnje prema detaljima; pravljenje pogrešaka u školskim ili radnim zadacima; nedovršavanje zadataka.
- Lako se ometa stranim podražajima ili mislima koje nisu povezane sa zadatkom; često se čini da ne sluša kada mu se izravno govori; često se čini da sanjari ili da su mu misli negdje drugdje.
- Gubi stvari; zaboravan je u svakodnevnim aktivnostima; ima poteškoća s pamćenjem dovršetka nadolazećih dnevnih zadataka ili aktivnosti; teškoće u planiranju, upravljanju i organiziranju školskih aktivnosti, zadataka i drugih aktivnosti.

Napomena: Nepažnja možda neće biti vidljiva kada je pojedinac uključen u aktivnosti koje pružaju intenzivnu stimulaciju i česte nagrade.

Simptomi hiperaktivnosti/impulzivnosti najočitiji su u strukturiranim situacijama koje zahtijevaju samokontrolu ponašanja,a uključuju:

- prekomjernu motoričku aktivnost; napuštanje mjesta kada se očekuje da mirno sjedi; često trči okolo; ima poteškoća sa mirnim sjedenjem bez vrpoljenja (mlađa djeca); osjećaji fizičkog nemira, osjećaj nelagode zbog tišine ili mirnog sjedenja (adolescenti i odrasli). Previše govori, izbrblja kod odgovoranja u školi, komentira na poslu; teško čeka red u razgovoru, igrama ili aktivnostima; prekida ili se miješa u tuđe razgovore ili igre.

Symptoms vary depending on the individual's chronological age and the severity of the disorder. Symptoms must not be better explained by another mental disorder (e.g., anxiety-related disorders, neurocognitive disorders such as delirium), nor be due to the effects of substances (e.g., cocaine) or medications (e.g., bronchodilators, thyroid hormone replacements) on the central nervous system, including withdrawal effects, nor due to neurological diseases.

Symptoms of inattention include:

- Difficulty sustaining attention on tasks that do not provide high stimulation or reward, or that require sustained mental effort;lack of attention to detail; careless mistakes in school or work tasks; unfinished tasks;
- Easily distracted by external stimuli or unrelated thoughts; often appears not to listen when spoken to directly; seems to daydream or to have thoughts elsewhere;
- Frequently loses items; forgetful in daily activities; trouble remembering upcoming tasks; difficulty planning, managing, and organizing schoolwork or other responsibilities.

Note: Inattention may not be apparent when the individual is engaged in activities offering intense stimulation or frequent rewards.

Symptoms of hyperactivity/impulsivity are most evident in structured situations requiring self-control, and include:

- Excessive motor activity; leaving one's seat when expected to remain seated; frequent running; difficulty sitting still (younger children); physical restlessness and discomfort with silence or stillness (adolescents and adults). Excessive talking, blurting out answers in class, making comments at work; difficulty waiting for one's turn in conversations or games; interrupting or intruding in others' conversations or play.

- Prisutna je sklonost impulzivnom djelovanju kao odgovor na neposredne podražaje bez promišljanja ili razmatranja rizika i posljedica (npr. sudjelovanje u ponašanjima s potencijalom za tjelesne ozljede; impulzivne odluke; nepromišljena vožnja) (2).

Prema DSM-5 klasifikaciji, u jednoj su skupini (klasteru) sindrom prekomjerne aktivnosti i impulzivnosti, a dob početka simptoma je podignuta na 12 godina života. Traži se da bude zadovoljeno barem šest od devet kriterija u vezi s nepažnjom i/ili barem šest od devet kriterija u vezi s hiperaktivošću/ impulzivnošću. Iznimka je u osoba starijih od 17 godina kada je dovoljno barem pet simptoma iz područja nepažnje i / ili barem pet simptoma iz područja hiperaktivnosti/impulzivnosti (1). Longitudinalne studije sugeriraju mogućnost najmanje četiri razvojna pravca ADHD-a koje uključuju rani početak (predškolski ADHD 3-5 godina), početak u srednjem djetinjstvu (6-14 godina) s postojanim tijekom, početak u srednjem djetinjstvu s adolescentnim pomakom i početak u adolescenciji ili odrasloj dobi (16 godina i stariji) (5,6). ADHD rijetko utječe na samo jednu životnu domenu. On utječe na mnoge aspekte života pojedinca uključujući fizičko zdravlje te školsko, društveno i radno funkcioniranje (7). Simptomi su povezani sa funkcionalnim oštećenjem i povećanim rizikom od depresije, zlouporabe sredstava ovisnosti i antisocijalnim ponašanjem (8). Pojedinci s ADHD-om imaju poteškoće u nekoliko domena uključujući pažnju i kognitivne funkcije: rješavanje problema, planiranje, orijentacija, upozoravanje, kognitivna fleksibilnost, održavanje pažnje i radna memorija (9,10).

Ovaj poremećaj pogađa djecu i odrasle diljem svijeta,a početak simptoma ima u ranoj dječjoj dobi načelno prije 5. godine života (11). Prema svjetskim podacima procjenjuje se da je prevalencija ADHD-a kod djece između 2,6 i 4,5 % (12) dok je kod odraslih oko 2,9 % (13).

ADHD se češće javlja u dječaka u odnosu na djevojčice (14).

- Tendency toward impulsive actions in response to immediate stimuli without reflection or consideration of risks and consequences (e.g., engaging in potentially dangerous behaviors; impulsive decisions; reckless driving) (2).

According to DSM-5, hyperactivity and impulsivity are grouped together, and the age of onset was raised to 12 years. At least six out of nine criteria related to inattention and/or at least six out of nine criteria related to hyperactivity/impulsivity must be met. An exception applies to individuals over the age of 17, for whom at least five symptoms in the domain of inattention and/or at least five symptoms in the domain of hyperactivity/impulsivity are sufficient (1). Longitudinal studies suggest at least four developmental trajectories of ADHD: early onset (preschool ADHD, ages 3–5), onset in middle childhood (ages 6–14) with a persistent course, onset in middle childhood with adolescent remission, and onset in adolescence or adulthood (age 16 and older) (5,6). ADHD rarely affects only one domain of life. It impacts many aspects, including physical health, academic performance, social interactions, and work functioning (7). Symptoms are associated with functional impairment and increased risk of depression, substance abuse, and antisocial behavior (8). Individuals with ADHD show deficits in various domains, including attention and cognitive functions: problem-solving, planning, orientation, alertness, cognitive flexibility, sustained attention, and working memory (9,10).

This disorder affects children and adults worldwide, with symptom onset typically before the age of five (11). Global estimates suggest a prevalence of 2.6–4.5% in children (12) and about 2.9% in adults (13).

ADHD is more prevalent in boys than in girls (14).

Dijagnoza ADHD-a postavlja se na temelju kliničkog intervjua, opservacije ponašanja djeteta ili osobe,heteroanamnestičkih podataka i važećih klasifikacija DSM-5 i MKB-11, a koristi se dijagnostički proces koji se inače koristi u dječjoj psihijatriji (15). Postavljanje dijagnoze ADHD-a ponekad je izazovno zbog značajne heterogenosti poremećaja u smislu kliničkih i patofizioloških aspekata (16). Bitno je voditi računa o diferencijalnoj dijagnozi koja pomaže kliničarima da razlikuju ADHD od drugih potencijalnih medicinskih stanja koja uzrokuju slične simptome, osiguravajući time provedbu odgovarajućih i učinkovitih strategija liječenja. Visoke stope psihijatrijskih komorbiditeta uočenih u bolesnika s ADHD-om i značajan udio preklapanja simptoma i uzroka s drugim mentalnim poremećajima važni su čimbenici koje treba razmotriti. Više od 60 % osoba s dijagnozom ADHD-a ima barem jedan komorbiditetni psihijatrijski poremećaj uključujući depresiju, anksioznost i poremećaj ponašanja. Međutim, sukladno njemačkim autorima, treba voditi brigu o vodećoj dijagnozi, odnosno ne preporučuje se davanje više od tri dijagnoze (17). Najčešći komorbiditeti u djece uključuju eksternalizirajuće (opozicijsko i prkosno ponašanje) poremećaje i poremećaje učenja (18,19,20). Anksioznost i depresija česti su komorbiditeti među adolescentima s ADHD-om. Istraživanja pokazuju da više od jedne trećine adolescenata s ADHD-om ima komorbidne anksiozne poremećaje(21). Nacionalno istraživanje o zdravlju djece u Sjedinjenim Državama iz 2007. godine pokazalo je da su djeca i adolescenti s ADHD-om imali veću vjerojatnost da će imati depresiju od onih bez ADHD-a (14%:1%) (22). Lee i sur. proveli su meta-analizu longitudinalnih studija koje su prospektivno pratile djecu sa i bez ADHD-a u adolescenciji ili odrasloj dobi. Djeca s ADHD-om imala su značajno veću vjerojatnost da će razviti poremećaje zlouporabe/ovisnosti o nikotinu, alkoholu, marihuani, kokainu i drugim drogama (23).

Nedavna istraživanja su pokazala da drugi neurorazvojni poremećaji poput autizma,

Diagnosis is based on clinical interviews, behavioral observation, hetero-anamnestic information, and the use of current classification systems (DSM-5 and ICD-11), following standard diagnostic procedures in child psychiatry (15). Diagnosing ADHD can be challenging due to the disorder's considerable heterogeneity in clinical and pathophysiological presentation (16). Differential diagnosis is essential to distinguish ADHD from other medical conditions that may produce similar symptoms and to implement appropriate treatment strategies. High rates of psychiatric comorbidity and symptom overlap with other mental disorders must be considered. Over 60% of individuals with ADHD have at least one comorbid psychiatric disorder, including depression, anxiety, and conduct disorders. However, according to German authors, attention should be paid to the primary diagnosis, and it is not recommended to assign more than three diagnoses (17). In children, the most common comorbidities include externalizing disorders (oppositional defiant disorder) and learning disabilities (18,19,20). Anxiety and depression are common among adolescents with ADHD, with research indicating that more than one-third have comorbid anxiety disorders (21). A 2007 U.S. National Survey of Children's Health found that children and adolescents with ADHD were more likely to be diagnosed with depression than those without (14% vs. 1%) (22). A meta-analysis by Lee et al. tracked children with and without ADHD into adolescence or adulthood. Children with ADHD had significantly higher odds of developing substance abuse or dependency on nicotine, alcohol, cannabis, cocaine, and other drugs (23).

Recent research suggests that other neurodevelopmental disorders such as autism, schizophrenia, and epilepsy share genetic variants with ADHD, indicating potential comorbidities (24). Individuals with ADHD also have higher

shizofrenije i epilepsije dijele genske varijante s ADHD-om, a što bi također upućivalo na moguće komorbiditete (24). Bolesnici s ADHD-om također imaju veću stopu pretilosti, poremećaja spavanja, astme, autoimunih i upalnih bolesti te drugih somatskih i metaboličkih problema (25,26,27). Aktualno razumijevanje neurobioloških mehanizama koji doprinose mogućem nastanku i održavanju ADHD-a, uključujući genetiku, moždane strukture i funkcije, i neurotransmitore čini nam se posebno interesantnom temom s obzirom na isprepletenost individualno-bioloških, individualno-psiholoških i okolišnih čimbenika kod ADHD-a.

U svrhu ovog preglednog rada pretražene su baze podataka *WOS*, *Medline*, *Scopus*, *PubMed* i *Google Scholar* pristupom koji koristi kombinacije ključnih riječi poremećaj pažnje i aktivnosti */attention deficit hyperactivity disorder* i neurobiologija */neurobiology*. Kriterij odabira referenci bili su pregledni radovi, meta-analiza i originalni istraživački radovi na engleskom ili hrvatskom jeziku u području neurobiologije ADHD-a.

ETIOPATOGENEZA ADHD-a

Općeniti aspekti

Etiopatogeneza poremećaja pažnje i hiperaktivnosti nije do kraja poznata, odnosno pretpostavlja se da je multifaktorijalna te se čini da u njoj ravnomjerno sudjeluju individualni (neuro/biološki i psihološki) i okolišni čimbenici. Od individualno-bioloških čimbenika treba spomenuti genetske čimbenike, epigenetske čimbenike, prenatalni čimbenici (alkohol, duhan) i perinatalne čimbenike (prematuritet, hipoksija tijekom poroda). U ovom modelu također su važni i individualno-psihološki čimbenici koji uključuju razvoj ličnosti, privrženost i adaptaciju (vulnerabilnost vs. otpornost) i drugi čimbenici. O ovim aspektima se u ovom radu neće detaljnije pisati, vidi o tome drugu dostupnu literaturu (1).

rates of obesity, sleep disorders, asthma, autoimmune and inflammatory diseases, and other somatic and metabolic conditions (25,26,27). The current understanding of the neurobiological mechanisms contributing to the possible development and maintenance of ADHD — including genetics, brain structures and functions, and neurotransmitters — appears to us to be a particularly interesting topic, given the interplay of individual-biological, individual-psychological, and environmental factors in ADHD.

For the purposes of this review, the databases WOS, Medline, Scopus, PubMed, and Google Scholar were searched using a keyword combination approach with terms such as attention deficit hyperactivity disorder and neurobiology. The selection criteria for references included review articles, meta-analyses, and original research papers in English or Croatian in the field of ADHD neurobiology.

ETIOPATHOGENESIS OF ADHD

General Aspects

The etiopathogenesis of Attention Deficit Hyperactivity Disorder (ADHD) is not yet fully understood. It is assumed to be multifactorial, involving both individual (neurobiological and psychological) and environmental factors in relatively equal measure. Among the individual-biological factors, it is important to mention genetic and epigenetic factors, prenatal influences (such as alcohol and tobacco exposure), and perinatal factors (such as prematurity and hypoxia during birth). This model also emphasizes the importance of individual-psychological factors, which include personality development, attachment, and adaptation (vulnerability vs. resilience), among others. These psychological aspects will not be discussed in detail in this paper—see other available literature on the topic (1).

Od okolišnih čimbenika mogu biti prisutni stresori, trauma, životni događaji, obiteljski čimbenici, škola, socijalni i ekološki uvjeti. Ako bi ADHD u dječjoj psihijatriji usporedili s drugim poremećajima kod djece i adolescenata, kod ovih poremećaja bi mogli zaista ustvrditi o ravnomjernoj isprepletenosti individualnih (neuro/bioloških i psiholoških) i okolišnih čimbenika, uz prevagu prema biološkim čimbenicima (28).

Individualno- biologijsko-genetski čimbenici

Genetski čimbenici uključeni su u etiopatogenezu ADHD-a, ali mehanizam djelovanja nije u potpunosti razjašnjen. ADHD ima moguću složenu poligensku pozadinu u kojoj više genetskih varijanti doprinosi etiologiji poremećaja kod većine pacijenata. Iako je veliki dio etiopatogeneze ADHD-a uzrokovan genima, mnogi okolišni čimbenici i potencijalne interakcije gena i okoliša također su povezane s povećanim rizikom za razvoj poremećaja (29,30). Studije blizanaca i obitelji poduprle su snažan genetski doprinos poremećaju s nasljednošću u rasponu od 60 do 90 % (31).

Za identifikaciju rizičnih gena ADHD-a provedena su višestruka molekularna genetička istraživanja. Zbog visoke prevalencije ADHD-a u populaciji, potraga za genetskim čimbenicima uglavnom je usmjerena na uobičajene genetske varijante (32,33).

Studija asocijacije na razini cijelog genoma (engl. genome-wide association study, GWAS) pomaže znanstvenicima identificirati gene povezane s određenom bolešću. GWAS studija ukazala je na postojanje gena koji igraju ulogu u nastanku ADHD-a, a koji bi se mogli povezati s mehanizmima neuronske plastičnosti (migracija neurona, adhezija stanica i proliferacija neurona) (34) ili s nedostacima u sintezi neurotransmitora (NT), uglavnom dopamina, ali također i serotonina i noradrenalina (35,36).

Environmental factors may include stressors, trauma, life events, family-related issues, school influences, and broader social and ecological conditions. Compared to other psychiatric disorders in childhood and adolescence, ADHD appears to involve a relatively balanced interplay of individual (neurobiological and psychological) and environmental contributors, with a predominance of biological factors (28).

Individual-Biological-Genetic Factors

Genetic factors are involved in the etiopathogenesis of ADHD, although the exact mechanisms remain unclear. ADHD may have a complex polygenic background, in which multiple genetic variants contribute to the disorder's etiology in most patients. Although genes account for a large part of ADHD's etiopathogenesis, numerous environmental factors and potential gene–environment interactions are also associated with increased risk (29,30). Twin and family studies have demonstrated a strong genetic contribution, with heritability estimates ranging from 60% to 90% (31).

To identify ADHD risk genes, numerous molecular genetic studies have been conducted. Given the high prevalence of ADHD, research has largely focused on common genetic variants (32,33).

Genome-wide association studies (GWAS) help researchers identify genes linked to specific disorders. GWAS studies have pointed to the existence of genes that play a role in the development of ADHD and may be linked to mechanisms of neuronal plasticity (such as neuron migration, cell adhesion, and neuronal proliferation) (34), or to deficiencies in neurotransmitter synthesis—primarily dopamine, but also serotonin and norepinephrine (35,36). Meta-analyses of these studies have revealed significant associations with common variants in several candidate genes. These include genes coding for

Meta-analize provedenih studija identificirale su moguće značajne povezanosti uobičajenih genskih varijanti u nekoliko gena kandidata.

To su geni koji kodiraju transportere dopamina i serotonina, SLC6A3/DATI i SLC6A4/5HTT, geni koji kodiraju D4 i D5 dopaminske receptore DRD4 i DRD 5, serotoninski receptor, HTRIB i gen za sinaptosomski-povezani protein 25, SNAP25. U provedenoj meta-analizi identificirani su dodatni geni koji kodiraju dopamin beta-hidroksilazu DBH, adenoreceptor alfa 2A (ADRA2A), tripotofan hidroksilazu 2 (TPH2) i monoamino oksidazu A (MAOA),a povezani su s ADHD-om (37,38,39). Studije skeniranja genoma o potencijalnim alelima za ADHD pokazale su povezanost na kromosomima 5p13, 6q12, 16p13, 17p11 i 11q 22-25 (40,41). U osoba s ADHD-om prijavljena je povećana stopa velikih, rijetkih kromosomskih delecija i duplikacija poznatih kao varijante broja kopija (24).

Strukturne i funkcionalne promjene mozga kod ADHD-a

Neuroslikovne studije dale su mogući uvid u etiopatogenezu i patofiziologiju ADHD-a prikazujući razlike u strukturnoj i funkcionalnoj arhitekturi mozga između pacijenata s ADHD-om i neurotipičnih pojedinaca, posebno djece (42). Te razlike primarno uključuju promjene u volumenu mozga, kortikalnoj debljini i površini (43). Specifične regije mozga uključene su u moguću patofiziologiju ADHD-a, a istraživanja ukazuju na smanjenje volumena u prefrontalnom korteksu, bazalnim ganglijima, *corpus callosumu* i malom mozgu (44,45). Prefrontalni korteks uključen je u izvršne funkcije poput pažnje, radne memorije i kontrole impulsa. Strukturne slikovne studije izvjestile su o mogućem smanjenom volumenu i kortikalnoj debljini prefrontalnog korteksa u pacijenata s ADHD-om, a osobito u dorzolateralnom i orbitofrontalnom prefrontalnom korteksu (46). Nadalje, bazalni gangliji

dopamine and serotonin transporters (SLC6A3/DAT1 and SLC6A4/5-HTT), dopamine receptors D4 and D5 (DRD4, DRD5), the serotonin receptor HTR1B, and the synaptosomal-associated protein SNAP25. In the conducted meta-analysis, additional genes were identified that encode dopamine beta-hydroxylase (DBH), the alpha-2A adrenergic receptor (ADRA2A), tryptophan hydroxylase 2 (TPH2), and monoamine oxidase A (MAOA), all of which have been linked to ADHD (37,38,39). Genome scanning studies have identified potential ADHD-related alleles on chromosomes 5p13, 6q12, 16p13, 17p11, and 11q22–25 (40,41). Individuals with ADHD have also shown increased rates of rare large chromosomal deletions and duplications—known as copy number variants (CNVs) (24).

Structural and Functional Brain Changes in ADHD

Neuroimaging studies have offered valuable insight into the etiopathogenesis and pathophysiology of ADHD by highlighting structural and functional differences in the brains of individuals with ADHD compared to neurotypical controls, particularly in children (42). These differences primarily involve alterations in brain volume, cortical thickness, and surface area (43). Specific brain regions implicated in ADHD pathophysiology include the prefrontal cortex, basal ganglia, corpus callosum, and cerebellum, all of which have been found to exhibit reduced volume in individuals with ADHD (44,45). The prefrontal cortex is responsible for executive functions such as attention, working memory, and impulse control. Structural imaging studies have reported reduced volume and cortical thickness in this region, particularly in the dorsolateral and orbitofrontal areas (46). Furthermore, the basal ganglia play a key role in motor control, learning, and executive functions. In patients with ADHD, possible volumetric reductions in the basal ganglia have been observed (44,45). Structural imaging studies have shown potential reductions

igraju ključnu ulogu u motoričkoj kontroli, učenju i izvršnim funkcijama. Kod pacijenata s ADHD-om uočena su moguća volumetrijska smanjenja bazalnih ganglija (44,45). Strukturalne slikovne studije pokazale su moguće smanjenje volumena i promijenjenu morfologiju korpusa kalozuma kod osoba s ADHD-om što može ukazivati na poremećaj u komunikaciji među moždanim hemisferama s obzirom da *corpus callosum* povezuje desnu i lijevu moždanu hemisferu (44,47). Mali mozak uključen je u koordinaciju motorike, održavanje ravnoteže i kognitivne funkcije koje uključuju pažnju i radnu memoriju. Strukturalne slikovne studije izvjestile su o mogućem smanjenom volumenu malog mozga u osoba s ADHD-om (46,47). Longitudinalne studije pružile su dokaze o mogućem odgođenom kortikalnom sazrijevanju kod osoba s ADHD-om, posebno u prefrontalnom korteksu (48). Velika meta-analiza ADHD radne skupine ENIGMA (*Enchancing Neuroimaging Genetics through Meta-Analysis*) izvjestila je da djeca s ADHD-om mogu imati manji volumen u različitim subkortikalnim regijama mozga (npr. *nucleus accumbens*, amigdala, kaudatus, hipokampus, putamen) i ukupni intrakranijski volumen (49) kao i smanjenu kortikalnu površinu (uglavnom u frontalnim, cingularnim i temporalnim regijama) i debljinu (u fuziformnom i temporalnom girusu)(50). Analizom morfometrijskih slika cijeloga mozga prijavljena je moguća povezanost ADHD-a sa smanjenim volumenom u frontalnim režnjevima i striatumu kod djece i kod odraslih (51). Studija *The Adolescent Brain and Cognitive Development* (ABCD) također sugerira moguće smanjenje strukturne mjere mozga u djece s ADHD-om (52). Potrebne su daljnje multimodalne studije kako bi se istražila povezanost između strukturnih i funkcionalnih promjena kod ADHD-a. Razvojne studije mogu dalje pomoći u rasvijetljavanju mehanizama koji bi objasnili evoluciju kliničke prezentacije ADHD-a tijekom životnog vijeka (53).

in volume and altered morphology of the corpus callosum in individuals with ADHD, which may suggest impaired interhemispheric communication, given that the corpus callosum connects the right and left cerebral hemispheres (44,47). The cerebellum is involved in motor coordination, balance maintenance, and cognitive functions such as attention and working memory. Structural imaging studies have reported a possible reduction in cerebellar volume in individuals with ADHD (46,47). Longitudinal studies have provided evidence of possible delayed cortical maturation in individuals with ADHD, particularly in the prefrontal cortex (48). The large ENIGMA (Enhancing NeuroImaging Genetics through Meta-Analysis) consortium meta-analysis reported smaller volumes in various subcortical regions (e.g., nucleus accumbens, amygdala, caudate nucleus, hippocampus, and putamen), as well as reduced total intracranial volume in children with ADHD (49). Reductions in cortical surface area (mainly in frontal, cingulate, and temporal regions) and cortical thickness (in fusiform and temporal gyri) have also been observed (50). Whole-brain morphometric imaging analysis has reported a possible association between ADHD and reduced volume in the frontal lobes and striatum in both children and adults (51). The Adolescent Brain and Cognitive Development (ABCD) study has also indicated reduced structural brain metrics in children with ADHD (52). Multimodal studies are needed to better understand the relationship between structural and functional brain alterations in ADHD. Developmental research may further clarify mechanisms underlying the evolution of ADHD's clinical presentation across the lifespan (53).

Dysfunction of Neurotransmitter Systems

The prefrontal cortex, *caudate nucleus*, and cerebellum are considered the primary brain regions responsible for the development of ADHD, as they are involved in regulating consciousness,

Disfunkcija neurotransmiterskih sustava

Prefrontalni korteks, *nucleus caudatus* i mali mozak moguća su glavna područja mozga odgovorna za razvoj ADHD-a s obzirom da su uključeni u kontrolu svjesnosti, osjećaja, impulsa i ponašanja (54,55). Funkcija puteva unutar ovih regija regulirana je neurotransmitorima kao što su dopamin (DA),noradenalin (NE), serotonin (5-HT), glutamat i gama-aminomaslačna kiselina (GABA) (54). Razvoj ADHD-a može se objasniti nedostatkom katekolamina kao što su DA i NE (54) ili disregulacijom ovih neurotransmitora koji su neophodni za normalnu funkciju mozga, uključujući izvršne funkcije i funkcije pažnje (16). Istraživanja ADHD-a tradicionalno su usmjerena na katekolaminergičnu neurotransmisiju (56). Dopamin i noradrenalin glavni su katekolamini u mozgu i imaju predominantno modulatorno djelovanje na druge neurotransmitore.

Postoje dvije obitelji dopaminskih receptora, D1 (uključujući D1 i D5) i D2 (uključujući D2,D3,D4) koji su različito raspoređeni u mozgu (57,58). Dopamin djeluje kroz visoko topografski organizirane projekcije kao što je nigrostrijatalni put koji je dobro poznat po svojoj ulozi u regulaciji kretanja. Nadalje, mezokortikalni i mezolimbički dopaminergični putevi uključeni su u izvršne funkcije (59). ADHD se čini da je povezan s difunkcijom u sva tri puta (60,61). Također se istraživala uloga frontostrijatalnih puteva u ADHD-u (62), a oni doprinose motoričkoj, kognitivnoj i afektivnoj regulaciji (63). Nadalje, ADHD se čini da je povezan s noradrenergičkom disfunkcijom (64). Tehnike nuklearne medicine PET i SPECT omogućile su istraživanje disfunkcije katekolaminergičkih puteva kod ADHD-a (65). Nedostatak dopamina igra ključnu ulogu u medijaciji regulacije kortikalnog sustava pamćenja, raspoloženja, anticipacije događaja, motivacije, inhibicije ponašanja, donošenja odluka i rješavanja problema (66-68). Disfunkcija DA receptora (DRD1-5) i DA transpotera (DAT-1)

emotions, impulses, and behavior (54,55). The functioning of neural pathways in these regions is regulated by neurotransmitters such as dopamine (DA), norepinephrine (NE), serotonin (5-HT), glutamate, and gamma-aminobutyric acid (GABA) (54). The development of ADHD may be explained by a deficiency of catecholamines such as DA and NE (54), or by dysregulation of these neurotransmitters, which are essential for normal brain functioning, including executive function and attentional processes (16). Research on ADHD has traditionally focused on catecholaminergic neurotransmission (56). Dopamine and norepinephrine are the primary catecholamines in the brain and exert predominantly modulatory effects on other neurotransmitters.

There are two families of dopamine receptors: D1 (which includes D1 and D5) and D2 (which includes D2, D3, and D4), and these receptors are differently distributed throughout the brain (57,58). Dopamine acts via highly topographically organized projections such as the nigrostriatal pathway, which plays a well-established role in motor regulation. Additionally, the mesocortical and mesolimbic dopaminergic pathways are involved in executive functions (59). ADHD appears to be associated with dysfunction across all three of these pathways (60,61). Research has also explored the role of the frontostriatal pathways in ADHD (62), which contribute to motor, cognitive, and emotional regulation (63). Furthermore, ADHD is associated with noradrenergic dysfunction (64). Nuclear medicine techniques such as PET and SPECT have enabled the investigation of catecholaminergic pathway dysfunction in ADHD (65). Dopamine deficiency plays a key role in regulating cortical systems responsible for memory, mood, event anticipation, motivation, behavioral inhibition, decision-making, and problem-solving (66-68). Dysfunction of dopamine receptors (DRD1–5) and the dopamine transporter (DAT-1) are believed to be major contributors to altered dopaminergic

se čine da su glavni razlozi za promijenjenu aktivnost u dopaminergičnom sustavu igrajući značajnu ulogu u patogenezi ADHD-a (69). Metilfenidat i spojevi izvedeni iz amfetamina djeluju na DAT-1 receptore inhibirajući njegovu prijenosnu funkciju i time povećavajući razine izvanstaničnog DA (70).

Noradrenalin (NE) je važan neurotransmitor u kontroli ponašanja i igra važnu ulogu u kognitivnim procesima kao što su radna memorija i inhibicijski odgovor a za koje se čini da su poremećeni kod ADHD-a (71). NE je također uključen u regulaciju pažnje (72). Protein prijenosnik NE (NET) uključen je u ponovnu pohranu NE, a abnormalnosti u funkciji NET-a pridonose razvoju ADHD-a smanjenjem razina izvanstaničnog noradrenalina. Lijekovi za liječenje ADHD-a kao što su metilfenidat i amfetamin povećavaju razine noradrenalina i time smanjuju simptome hiperaktivnosti i impulzivnosti (71).

Neravnoteža ekscitatorne funkcije serotonina (5-HT) također može biti povezana s razvojem ADHD-a. (73,74). Disfunkcija serotonina može igrati ulogu u hiperaktivnom i impulzivnom ponašanju povezanim sa ADHD-om (75). Serotonin regulira aktivnost dopamina putem svojih receptora 5-hidroksitriptaminskog receptora 1B (5-HTR1B) ili 5-hidroksitriptaminskog receptora 2A (5-HTR2A). Disfunkcija ovih receptora može narušiti dinamiku serotonin-dopamin što rezultira simptomima ADHD-a (73,74). Nadalje, promjena ravnoteže glutamat/GABA povezana je sa smanjenom sposobnošću fokusiranja na zahtjevne zadatke i rezultira disregulacijom dopamina (76).

Okolišni čimbenici

Procijenjeni utjecaj okolišnih čimbenika u patogenezi ADHD-a iznosi oko 20 do 30 %. Prenatalni, perinatalni i postnatalni čimbenici igraju važnu ulogu u nastanku ovog poremećaja. Prenatalni čimbenici povezani su s majčinim načinom života tijekom trudnoće, npr. prena-

system activity and play a significant role in the pathogenesis of ADHD (69). Methylphenidate and amphetamine-derived compounds act on DAT-1 receptors by inhibiting their transport function, which leads to elevated levels of extracellular dopamine (DA) (70).

Norepinephrine (NE) is another crucial neurotransmitter in behavioral control and plays an important role in cognitive processes such as working memory and inhibitory control, which are often impaired in ADHD (71). NE is also involved in attentional regulation (72). The norepinephrine transporter protein (NET) is involved in the reuptake of NE, and abnormalities in NET function contribute to the development of ADHD by reducing extracellular norepinephrine levels. Medications such as methylphenidate and amphetamines raise NE levels and consequently reduce hyperactivity and impulsivity symptoms (71).

Imbalance in the excitatory function of serotonin (5-HT) may also be associated with ADHD development (73,74). Serotonergic dysfunction may play a role in the hyperactive and impulsive behaviors linked to ADHD (75). Serotonin regulates dopamine activity through its receptors, specifically the 5-hydroxytryptamine receptor 1B (5-HTR1B) and the 5-hydroxytryptamine receptor 2A (5-HTR2A). Dysfunction of these receptors may disrupt serotonin-dopamine dynamics, resulting in ADHD symptoms (73,74). Furthermore, glutamate/GABA imbalance has been linked to reduced ability to focus on demanding tasks and to dysregulation of dopamine activity (76).

Environmental Factors

The estimated contribution of environmental factors to the pathogenesis of ADHD ranges between 20% and 30%. Prenatal, perinatal, and postnatal influences play important roles in the development of this disorder. Prenatal factors are associated with maternal lifestyle during

talna izloženost alkoholu uzrokuje strukturne anomalije mozga, osobito malog mozga (77). Pušenje majke tijekom trudnoće dovodi do 2,7 puta većeg rizika za razvoj ADHD-a (78,79). Istraživanja su pokazala da značajan učinak ima i izloženost majke stresnim događajima, zdravstvenim problemima (80), lijekovima (79,81,82) i drugim tvarima kao što su olovo i mangan (83). Uočeno je da je izloženost acetaminofenu tijekom trudnoće povezana s visokom učestalošću ADHD-a u djece (84). Neki od perinatalnih čimbenika uključuju smanjenu porođajnu masu djeteta i komplikacije pri porodu (inducirani porod i hitni carski rez) (51,52). Postnatalni čimbenici uključuju pothranjenost, neravnotežu unosa esencijalnih masnih kiselina (omega 3 i omega 6) iako su potrebni dodatni dokazi kako bi se potvrdile ove tvrdnje (85).

Okolišni čimbenici povezani s razvojem ADHD-a uključuju nadalje lošiji socioekonomski status, nasilje u obitelji, narušen odnos roditelj-dijete, psihičku bolest majke, udomiteljstvo (86).

Nadalje, važno je spomenuti traumu i traumatski stres u djetinjstvu koji su prema sve većem broju istraživanja usko povezani s ADHD-om. Trauma može promijeniti arhitekturu mozga, posebno kod djece, što djelomično može objasniti njihovu vezu s razvojem ADHD-a. Klinička slika ADHD-a i traume također mogu pokazivati slične simptome, što može otežati procjenu (87). Istraživanja su pokazala da bi disregulacija osi HPA (hipotalamus-hipofiza-nadbubrežna žlijezda) mogla biti povezana s ADHD-om, a neke studije ukazuju na korelaciju između razine hormona HPA osi i težine simptoma ADHD-a, posebno nepažnje (88,89).

LIJEČENJE ADHD-a

Liječenje ADHD-a uključuje načelno psihosocijalne terapije (nefarmakološke) i farmakološke strategije. Osnova liječenja, kao i kod drugih

pregnancy. For example, prenatal exposure to alcohol can lead to structural brain abnormalities, especially in the cerebellum (77). Maternal smoking during pregnancy increases the risk of developing ADHD by 2.7 times (78,79). Research has also shown a significant impact of maternal exposure to stressful life events, health issues (80), medications (79,81,82), and toxins such as lead and manganese (83). Exposure to acetaminophen during pregnancy has been associated with a higher prevalence of ADHD in children (84). Perinatal factors include low birth weight and complications during delivery (e.g., induced labor and emergency cesarean section) (51,52). Postnatal factors may include malnutrition and imbalanced intake of essential fatty acids (omega-3 and omega-6), although further evidence is required to confirm these associations (85).

Environmental risk factors also include low socioeconomic status, domestic violence, disrupted parent-child relationships, maternal mental illness, and foster care placement (86).

Moreover, it is important to emphasize the role of trauma and traumatic stress in childhood, which, according to increasing research, are closely linked to ADHD. Trauma can alter brain architecture, particularly in children, which may partly explain its relationship to ADHD development. The clinical presentations of trauma and ADHD may overlap, which may complicate accurate assessment(87). Studies have also shown that dysregulation of the HPA (hypothalamic–pituitary–adrenal) axis may be associated with ADHD, while some findings point to a correlation between levels of HPA-axis hormones and the severity of ADHD symptoms, particularly inattention (88,89).

TREATMENT OF ADHD

The treatment of ADHD generally includes both psychosocial (non-pharmacological) and pharmacological strategies. As with other dis-

poremećaja u dječjoj psihijatriji jesu psihosocijalne intervencije (1).

Psihosocijalno liječenje ADHD-a uključuje načelno bihevioralne, kognitivne i psihodinamske terapije, a koriste se i drugi oblici liječenja (npr. *neurofeedback*).

Bihevioralne terapije koriste metode treninga, modifikaciju ponašanja i operantne metode, a u terapiju su uključena djeca, kao i njihovi roditelji (90).

Kognitivne terapije se zasnivaju na samoinstrukcijama, odnosno dijete uči samostalno regulirati vlastite impulse, kako definirati problem, istraživati načine rješavanja problema I kako postupati kod pogrešaka, a s ciljem razvoja samokontrole (91)

Psihodinamske terapije orijentirat će se na povećanje simbolizacijskih i mentalizacijskih mogućnosti djeteta putem sadržavajuće funkcije terapeuta (92).

Kao druge moguće terapije unutar multimodalnoga pristupa mogu biti motorički treninzi, odnosno fizičko vježbanje (aerobik, joga i dr.) (93), senzorički trening, radna terapija, *neurofeedback*, muzikoterapija, metode relaksacije, terapijsko jahanje konja (94).

Prva linija u farmakološkom liječenju su tzv. „stimulansi"- metilfenidat (MPH). Druga linija farmakološkog liječenja uključuje tzv. „nestimulativne" lijekove - atomoksetin. Stimulansi su korišteni kao prva linija farmakološkog liječenja zahvaljujući većoj učinkovitosti u smanjenju simptoma u usporedbi s nestimulirajućim lijekovima u svim dobnim skupinama (djeca, adolescenti i odrasli) (95,96). Nestimulativni lijekovi se primjenjuju kada su stimulansi kontraindicirani ili zbog nedostatnog odgovora na liječenje stimulansima ili u slučaju intolerancije na lijek (96). Također je moguća primjena lijekova iz drugih skupina: npr. antipsihotici, guanfacin, klonidin itd. (1).

U svijetu postoje različite smjernice liječenja ADHD-a (97,98).

orders in child psychiatry, psychosocial interventions form the foundation of treatment (1).

Psychosocial treatment of ADHD primarily involves behavioral, cognitive, and psychodynamic therapies, as well as other approaches (e.g., neurofeedback).

Behavioral therapies apply training methods, behavior modification techniques, and operant conditioning strategies, involving both the child and their parents (90).

Cognitive therapies focus on self-instruction, teaching the child to independently regulate impulses, define problems, explore problem-solving strategies, and manage mistakes, with the goal of developing self-control (91).

Psychodynamic therapies focus on strengthening the child's ability to symbolize and mentalize through the therapist's containing function (92).

Other possible therapies within a multimodal approach include motor training or physical exercise (e.g., aerobics, yoga) (93), sensory integration therapy, occupational therapy, neurofeedback, music therapy, relaxation techniques, and equine-assisted therapy (94).

The first-line pharmacological treatment consists of so-called stimulants, particularly methylphenidate (MPH). The second-line pharmacological treatment includes non-stimulant medications, such as atomoxetine. Stimulants are preferred as first-line agents due to their greater effectiveness in reducing symptoms compared to non-stimulants across all age groups (95,96). Non-stimulants are prescribed when stimulants are contraindicated, when there is insufficient response to stimulants, or when stimulants are not well tolerated (96). Other medication classes may also be considered, including antipsychotics, guanfacine, clonidine, etc. (1).

Various treatment guidelines exist worldwide (97,98).

Terapijske smjernice europskog stručnog društva (ESCAP *European Society for Child and Adolescent Psychiatry*) (97) ne preporučavaju davanje lijekova predškolskoj djeci, dok prema smjernicama Američke akademije za dječju i adolescentnu psihijatriju (*American Academy of Child and Adolescent Psychiatry*) to ne isključuju (98).

Liječenje treba biti individualno prilagođeno svakom pojedinom djetetu, s ravnomjernom procjenom problema, ali i određenih snaga i sposobnosti djeteta (1).

Terapijske smjernice Britanskog društva za psihofarmakologiju (*British Assosiation of Psychofarmacology*) (99) i Nacionalnog instituta za zdravlje i izvrsnost usluge (*National Institute for Health and Care Excellence*) (100) preporučuju tzv. „stimulanse" kao farmakološki tretman prvog izbora za umjerene do teške slučajeve ADHD-a kod pacijenata u dobi od 6 godina i starije. Druga linija liječenja su tzv. „nestimulativni" lijekovi (npr. atomoksetin), nakon čega slijede adrenergični lijekovi (npr. klonidin, guanfacin) ili alternativni nestimulansi kao što su triciklički antidepresivi i bupropion (99-102). Premda niti jedan antipsihotik nije odobren za primjenu kod ADHD-a, relativno se često propisuju kod izostanka učinka psihostimulansa također i za poremećaj ponašanja u komorbiditetu s ADHD-om. Pri tome se najviše propisuje risperidon zbog dobro utvrđenog učinka na agresivno ponašanje (103). Dvostruko slijepo, placebom kontrolirano kliničko ispitivanje Aman i sur. pokazalo je da risperidon može značajno smanjiti simptome ADHD-a, te navode da su kombinacija risperidona i psihostimulansa bolja u kontroli hiperaktivnosti od one kod koje se postiže samo liječenjem stimulansima (104), te se može reći da je ovo inovativno područje, jer se sugerira kombinacija dvije vrsta lijekova.

Pojedine studije su pokazale da risperidon daje jednako dobre ili čak i bolje rezultate u liječenju ADHD-a u usporedbi s onim što se postiže primjenom metilfenidata (105,106). Studija Correia i sur. uključivala je djecu s umjerenim intelek-

The European Society for Child and Adolescent Psychiatry (ESCAP) does not recommend pharmacological treatment for preschool-aged children (97), whereas guidelines from the American Academy of Child and Adolescent Psychiatry do not exclude such use (98).

Treatment should be individually tailored, considering both the child's difficulties and their strengths and capabilities (1).

Guidelines from the British Association for Psychopharmacology (99) and the National Institute for Health and Care Excellence (100) recommend stimulants as the first-line pharmacological treatment for moderate to severe ADHD in patients aged 6 and older. The second-line treatment includes non-stimulant medications (e.g., atomoxetine), followed by adrenergic agents (e.g., clonidine, guanfacine), or alternative non-stimulants such as tricyclic antidepressants and bupropion (99-102). Although no antipsychotic medication is officially approved for the treatment of ADHD, antipsychotics are frequently prescribed in cases where psychostimulants are ineffective, especially in comorbid conduct disorders. The most commonly prescribed antipsychotic is risperidone, due to its well-established effect on aggressive behavior (103). A double-blind, placebo-controlled clinical trial by Aman et al. showed that risperidone significantly reduces ADHD symptoms, and that the combination of risperidone and a stimulant is more effective for managing hyperactivity than stimulant treatment alone (104). This suggests a potentially innovative therapeutic approach by combining two different medication classes.

Some studies indicate that risperidone is as effective, or even more effective, than methylphenidate in treating ADHD symptoms (105,106). For instance, a study by Correia et al. involving children with moderate intellectual disability and ADHD found that risperidone led to greater symptom reduction than methylphenidate. Comorbidity and side effect

tualnim teškoćama i ADHD-om. Rezultati studije su pokazali da je risperidon povezan s većim smanjenjem ukupnog rezultata ADHD-a nego metilfenidat kod djece s umjerenim intelektualnim teškoćama i ADHD-om. Komorbiditet i profil nuspojava mogu biti važni pri odabiru između lijekova, iako je obično razumno isprobati stimulanse prije antipsihotika kod ove djece (106).

Upotreba antipsihotika novije generacije u djece i adolescenata povezana je s mogućim debljanjem i kardiometaboličkim nuspojavama poput dislipidemije, inzulinske rezistencije i povišenog krvnog tlaka kod neke djece (107) i hiperprolaktinemijom (108).

Sigurnost i učinkovitost često korištenih lijekova za liječenje ADHD-a podupiru meta-analize (Cortese i sur. 2018) (62). Metilfenidat se dobiva iz piperidina i strukturno je sličan amfetaminu (109). Liječenje metilfenidatom uzrokuje povećanje dopaminske signalizacije kroz višestruke radnje koje uključuju blokadu ponovne pohrane dopamina, pojačanje trajanja odgovora dopamina i dezinhibiciju dopaminskog D2 receptora (110). Metilfenidat je također inhibitor ponovne pohrane noradrenalina (111). Dakle, farmakološka aktivnost metilfenidata uglavnom je rezultat blokiranja DAT-a i NET-a čime se inhibira ponovna pohrana ovih neurotransmitora u presinaptičke neurone. Regulacija ovog procesa može uključivati modulaciju funkcija kao što su pažnja, zadovoljstvo i motorička aktivnost (95). Stimulansi također poboljšavaju izvršne funkcije koje su često poremećene kod osoba s ADHD-om (112,113,114). Amfetamini i metilfenidat imaju sličan profil nuspojava koje su obično blage i prolazne, a najčešće uključuju smanjeni apetit, suha usta, razdražljivost, poremećaj spavanja, tahikardiju i glavobolju. Povezani su i s višom stopom nuspojava kao što su gubitak na tjelesnoj masi i nesanica (115). Učinkovitost psihostimulansa u smanjenju simptoma ADHD-a prikazana je u brojnim kliničkim studijama u djece i odraslih s ADHD-om (116). Meta-analiza koja je uključila više od 10000 djece i adolescenata u trajanju od tri mjeseca, otkrila je da su i metilfenidat i amfetamin imali umjerene

profiles should be considered when selecting medication, although it is generally advisable to try stimulants before antipsychotics in such population (106).

Use of second-generation antipsychotics in children and adolescents has been associated with potential side effects, including weight gain, cardiometabolic risks (e.g., dyslipidemia, insulin resistance, hypertension) (107), and hyperprolactinemia (108).

The safety and efficacy of commonly used ADHD medications is supported by meta-analyses (62). Methylphenidate is a piperidine derivative and structurally similar to amphetamine (109). It increases dopaminergic signaling via multiple mechanisms, including blocking dopamine reuptake, prolonging dopamine response, and disinhibiting dopamine D2 receptors (110). Methylphenidate is also a norepinephrine reuptake inhibitor (111). Thus, its pharmacological activity is primarily due to blocking DAT and NET, thereby inhibiting the reuptake of these neurotransmitters into presynaptic neurons. Regulation of this process may affect functions such as attention, reward, and motor activity (95). Stimulants also enhance executive functions, which are frequently impaired in individuals with ADHD (112,113,114). Amphetamines and methylphenidate have similar side effect profiles, typically mild and transient, most commonly appetite suppression, dry mouth, irritability, sleep disturbances, tachycardia, and headache. They are also associated with higher rates of weight loss and insomnia (115). The efficacy of psychostimulants in reducing ADHD symptoms has been demonstrated in numerous clinical trials involving both children and adults (116). A meta-analysis involving over 10,000 children and adolescents over a three-month period found that both methylphenidate and amphetamines produced moderate to large improvements in ADHD symptoms (25). Another meta-analysis of 18 studies confirmed the effectiveness of methylphenidate in adults with ADHD (117).

do visoke učinke na simptome ADHD-a (25). Meta-analiza 18 studija pokazala je da je metilfenidat također učinkovit kod odraslih (117).

Atomoksetin je snažan i selektivni inhibitor ponovne pohrane noradrenalina koji djeluje putem bolkade NET-a. Takva presinaptička inhibicija NET-a dovodi do povećanja izvanstanične razine noradrenalina uglavnom u prefrontalnom korteksu, ali ne i u mezolimbičkim i mezokortikalnim putevima do nukleusa akumbensa zbog čega nema potencijal za moguću zloupotrebu ili stvaranje ovisnosti (118). Atomoksetin ima smanjeni afinitet za DAT, ali također potiče povećanje koncentracije dopamina u prefrontalnom korteksu što može biti posljedica nespecifične modulacije ponovne pohrane dopamina putem NET-a (119). Atomoksetin je pokazao učinkovitost u liječenju simptoma ADHD-a u komorbiditetu s anksioznim poremećajem ili tikovima (120,121). Guanfacin je selektivni agonist alfa-2 adrenergičkih receptora i moguće je da poboljšava radnu memoriju stimulacijom postsinaptičkih alfa-2 receptora jačajući funkcionalnu povezanost mreža prefronatalnog korteksa (122) i pokazao je moguću učinkovitost u smanjenju simptoma ADHD-a (123). Meta-analiza 25 ispitivanja atomoksetina u djece s ADHD-om pokazala je umjerenu veličinu učinka međutim veliki dio pacijenata (otprilike 40%) imao je trajne simptome koji su zahtijevali dodatnu kliničku intervenciju (124). Malo se zna o dugoročnim učincima stimulansa na funkcionalnu organizaciju mozga u razvoju, što iziskuje također klinički i znanstveni oprez (125) te daljnja istraživanja. Nedavna dvogodišnja longitudinalna studija (ADDUCE study) pokazala je da je metilfenidat siguran za dugotrajnu upotrebu (do dvije godine) kod djece i adolescenata s ADHD-om (126).

ZAKLJUČAK

Etiopatogeneza poremećaja pažnje i aktivnosti je kompleksna i još uvijek nije u potpunosti razjašnjena. Istraživanja su ukazala na moguću

Atomoxetine is a potent and selective norepinephrine reuptake inhibitor that acts by blocking NET. This presynaptic inhibition raises extracellular norepinephrine levels, especially in the prefrontal cortex, but not in the mesolimbic and mesocortical pathways leading to the nucleus accumbens, which may explain its lack of abuse or addiction potential (118). Atomoxetine has a low affinity for DAT but also increases dopamine concentrations in the prefrontal cortex, likely via nonspecific modulation of dopamine reuptake through NET (119). Atomoxetine has shown effectiveness in treating ADHD symptoms comorbid with anxiety disorders or tics (120,121). Guanfacine is a selective alpha-2 adrenergic receptor agonist that may enhance working memory by stimulating postsynaptic alpha-2 receptors, strengthening functional connectivity within prefrontal cortex networks (122). It has demonstrated potential efficacy in reducing ADHD symptoms (123). A meta-analysis of 25 atomoxetine trials in children with ADHD found a moderate effect size, but approximately 40% of patients had persistent symptoms requiring further clinical intervention (124). Little is known about the long-term effects of stimulants on the functional organization of the developing brain, which calls for both clinical and scientific caution (125), as well as further research. A recent two-year longitudinal study (the ADDUCE study) demonstrated that methylphenidate is safe for long-term use (up to two years) in children and adolescents with ADHD (126).

CONCLUSION

The etiopathogenesis of Attention Deficit Hyperactivity Disorder (ADHD) is complex and not yet fully understood. Research has pointed to the potential involvement of genetic factors, brain structures and functions, and several neurotransmitter systems in the development

uključenost gena, moždanih struktura i funkcija, te nekoliko neurotransmitorskih sustava u nastanku i održavanju ovog poremećaja. Razumijevanje ovih mehanizama može biti važno za razvoj i identificiranje specifičnijih i ciljanijih metoda liječenja.

Daljnja istraživanja su potrebna za potpunije razumijevanje interakcije gena i okoline u razvoju ADHD-a kao i za razvoj novih i inovativnih metoda liječenja. Posebna pažnja treba biti posvećena personaliziranoj medicini, koja uzima u obzir individualne i okolišne faktore prilikom odabira optimalnog tretmana.

Napredak u neuroimaging tehnikama i genetičkim istraživanjima će vjerojatno dovesti do daljnjeg napretka u razumijevanju neurobiologije ADHD-a i poboljšanju kvalitete života osoba s ovim poremećajem.

and maintenance of the disorder. Understanding these mechanisms may be crucial for the development and identification of more specific and targeted treatment methods.

Further studies are needed to gain a more comprehensive understanding of gene–environment interactions in ADHD, as well as to develop new and innovative therapeutic approaches. Special attention should be given to personalized medicine, which takes into account individual and environmental factors in selecting the optimal treatment strategy.

Advancements in neuroimaging techniques and genetic research are likely to contribute significantly to further progress in understanding the neurobiology of ADHD and improving the quality of life for individuals affected by this disorder.

LITERATURA / *REFERENCES*

1. Begovac I. Hiperkinetski poremećaj. Dječja i adolescentna psihijatrija. Zagreb: Sveučilište u Zagrebu: Medicinski fakultet, 2021. str. 493-506.
2. International classification of diseases.11.izd. Dostupno na: https://icd.who.int/en.
3. Američka psihijatrijska udruga. Dijagnostički i statistički priručnik za duševne poremećaje, peto izdanje. Jastrebarsko: Naklada Slap, 2014.
4. Gomez R, Chen W, Houghton S. Differences between DSM-5-TR and ICD-11 revisions of attention deficit/hyperactivity disorder: A commentary on implications and opportunities. World J Psychiatry 2023;13(5):138-43.
5. Moffitt TE, Houts R, Asherson P, Belsky DW, Corcoran DL, Hammerle M i sur. Is Adult ADHD a Childhood-Onset Neurodevelopmental Disorder? Evidence From a Four-Decade Longitudinal Cohort Study. Am J Psychiatry 2015;172(10):967-77.
6. Krasner AJ, Turner JJ, Feldman JF, Silberman AE, Fisher PW, Workman CC i sur. ADHD Symptoms in a Non-Referred Low Birthweight/Preterm Cohort: Longitudinal Profiles, Outcomes, and Associated Features. J Attention Disorders 2018;22(9):827-38.
7. Wright N, Moldavsky M, Schneider J, Chakrabarti I, Coates J, Daley D i sur. Practitioner Review: Pathways to care for ADHD -a systematic review of barriers and facilitators. J Child Psychol Psychiatry 2015;56(6):598-617.
8. Purper-Ouakil D, Ramoz N, Lepagnol-Bestel AM, Gorwood P, Simonneau M. Neurobiology of Attention Deficit/Hyperactivity Disorder. Pediatr Res 2011;69(5 Part 2):69R76R.
9. Sergeant JA, Geurts H, Huijbregts S, Scheres A, Oosterlaan J. The top and the bottom of ADHD: a neuropsychological perspective. Neurosci Biobehav Rev 2003;27(7):583-92.
10. Pasini A, Paloscia C, Alessandrelli R, Porfirio MC, Curatolo P. Attention and executive functions profile in drug naive ADHD subtypes. Brain and Development. 2007;29(7):400-8.
11. Lempp T. Kinder und Jugendpsychiatrie BASIC. 2nd Munchen: Urban & Fischer, 2014.
12. Polanczyk GV, Salum GA, Sugaya LS, Caye A, Rohde LA. Annual Research Review: A meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. J Child Psychol Psychiatry 2015;56(3):345-65.
13. Faraone SV, Biederman J. What Is the Prevalence of Adult ADHD? Results of a Population Screen of 966 Adults. J Attention Disord 2005;9(2):384-91.
14. Cabral MDI, Liu S, Soares N. Attention-deficit/hyperactivity disorder: diagnostic criteria, epidemiology, risk factors and evaluation in youth. Translational Pediatrics 2020;9(S1)S104-13.
15. Begovac I. Dijagnostički proces, plan liječenja. Dječja i adolescentna psihijatrija. Zagreb: Sveučilište u Zagrebu: Medicinski fakultet, 2021, 182-9.
16. Faraone SV, Bellgrove MA, Brikell I, Cortese S, Hartman CA, Hollis C i sur. Attention-deficit/hyperactivity disorder. Nat Rev Dis Primers 2024;10(1):11.
17. Begovac I. Klasifikacija psihičkih poremećaja. Dječja i adolescentna psihijatrija. Zagreb: Sveučilište u Zagrebu: Medicinski fakultet, 2021, 358-64.

18. Seo JC, Jon DI, Shim SH, Sung HM, Woo YS, Hong J i sur. Prevalence and Comorbidities of Attention Deficit Hyperactivity Disorder Among Adults and Children/Adolescents in Korea. Clin Psychopharmacol Neurosci 2022 28;20(1):126-34.
19. Gnanavel S, Sharma P, Kaushal P, Hussain S. Attention deficit hyperactivity disorder and comorbidity: A review of literature. World Journal of Clinical Cases [Internet]. 2019;7(17):2420-6.
20. Spencer TJ, Biederman J, Mick E. Attention-deficit/hyperactivity disorder: diagnosis, lifespan, comorbidities, and neurobiology. Ambul Pediatr 2007;7(1 Suppl):73–81.
21. Biederman J, Faraone SV, Spencer T, Wilens T, Mick E, Lapey KA. Gender differences in a sample of adults with attention deficit hyperactivity disorder. Psychiatry Res 1994;53(1):13-29.
22. Larson K, Russ SA, Kahn RS, Halfon N. Patterns of Comorbidity, Functioning, and Service Use for US Children With ADHD, 2007. Pediatrics 2011;127(3):462-70.
23. Lee SS, Humphreys KL, Flory K, Liu R, Glass K. Prospective association of childhood attention-deficit/hyperactivity disorder (ADHD) and substance use and abuse/dependence: A meta-analytic review. Clin Psychol Rev 2011;31(3):328–41.
24. Williams NM, Zaharieva I, Martin A, Langley K, Mantripragada K, Fossdal R i sur. Rare chromosomal deletions and duplications in attention-deficit hyperactivity disorder: a genome-wide analysis. Lancet 2010;376(9750):1401–8.
25. Akmatov MK, Ermakova T, Bätzing J. Psychiatric and Nonpsychiatric Comorbidities Among Children With ADHD: An Exploratory Analysis of Nationwide Claims Data in Germany. J Attention Disord 2019;108705471986577.
26. Chen Q, Hartman CA, Haavik J, Harro J, Klungsøyr K, Hegvik TA i sur. Common psychiatric and metabolic comorbidity of adult attention-deficit/hyperactivity disorder: A population-based cross-sectional study. PLoS ONE. 2018;13(9):0204516.
27. Instanes JT, Klungsøyr K, Halmøy A, Fasmer OB, Haavik J. Adult ADHD and Comorbid Somatic Disease: A Systematic Literature Review. J Attention Disord 2016;22(3):203-28.
28. Begovac I. Definicija psihičkog poremećaja, razvojna psihopatologija i etiopatogenetski modeli. Dječja i adolescentna psihijatrija. Zagreb: Sveučilište u Zagrebu: Medicinski fakultet, 2021. 148-60.
29. Banerjee TD, Middleton F, Faraone SV. Environmental risk factors for attention-deficit hyperactivity disorder. Acta Paediatrica [Internet]. 2007;96(9):1269-74.
30. Han JY, Kwon HJ, Ha M, Paik KC, Lim MH, Gyu Lee S, i sur. The effects of prenatal exposure to alcohol and environmental tobacco smoke on risk for ADHD: A large population-based study. Psychiatry Res 2015;225(1-2):164-8.
31. Curatolo P, D'Agati E, Moavero R. The neurobiological basis of ADHD. Italian Journal of Pediatrics [Internet]. 2010;36(1):79.
32. Li Z, Chang S, Zhang L, Gao L, Wang J. Molecular genetic studies of ADHD and its candidate genes: A review. Psychiatry Res 2014;219(1):10-24.
33. Neale BM, Medland SE, Ripke S, Asherson P, Franke B, Lesch KP i sur. Meta-Analysis of Genome-Wide Association Studies of Attention-Deficit/Hyperactivity Disorder. J Am Acad Child Adolesc Psychiatry 2010;49(9):884-97.
34. Ribasés M, Ramos-Quiroga JA, Sánchez-Mora C, Bosch R, Richarte V, Palomar G i sur. Contribution of LPHN3 to the genetic susceptibility to ADHD in adulthood: a replication study. Genes, Brain and Behavior 2010;10(2):149-57.
35. Faraone SV, Larsson H. Genetics of attention deficit hyperactivity disorder. Molecular Psychiatry 2018;24(4):562-75.
36. Lange M, Norton W, Coolen M, Chaminade M, Merker S, Proft F i sur. The ADHD-susceptibility gene lphn3.1 modulates dopaminergic neuron formation and locomotor activity during zebrafish development. Molecular Psychiatry 2012;17(9):946-54.
37. Gizer IR, Ficks C, Waldman ID. Candidate gene studies of ADHD: a meta-analytic review. Human Genetics 2009;126(1):51-90.
38. Faraone SV, Perlis RH, Doyle AE, Smoller JW, Goralnick JJ, Holmgren MA i sur. Molecular Genetics of Attention-Deficit/Hyperactivity Disorder. Biological Psychiatry. 2005;57(11):1313-23.
39. Li D, Sham PC, Owen MJ, He L. Meta-analysis shows significant association between dopamine system genes and attention deficit hyperactivity disorder (ADHD). Human Molecular Genetics 2006;15(14):2276-84.
40. Ogdie MN, Fisher SE, Yang M, Ishii J, Francks C, Loo SK i sur. Attention Deficit Hyperactivity Disorder: Fine Mapping Supports Linkage to 5p13, 6q12, 16p13, and 17p11. Am J Human Gen 2004;75(4):661-8.
41. Coghill D, Banaschewski T. The genetics of attention-deficit/hyperactivity disorder. Expert Review of Neurotherapeutics 2009;9(10):1547-65.
42. da Silva BS, Grevet EH, Silva LCF, Ramos JKN, Rovaris DL, Bau CHD. An overview on neurobiology and therapeutics of attention-deficit/hyperactivity disorder. Discover Mental Health 2023;3(1). Available from: https://link.springer.com/article/10.1007/s44192-022-00030-1
43. Cortese S. The neurobiology and genetics of Attention-Deficit/Hyperactivity Disorder (ADHD): What every clinician should know. Eur J Paediatric Neurol 2012;16(5):422-33.
44. Valera EM, Faraone SV, Murray KE, Seidman LJ. Meta-Analysis of Structural Imaging Findings in Attention-Deficit/Hyperactivity Disorder. Biological Psychiatry. 2007;61(12):1361-9.
45. Nakao T, Radua J, Rubia K, Mataix-Cols D. Gray Matter Volume Abnormalities in ADHD: Voxel-Based Meta-Analysis Exploring the Effects of Age and Stimulant Medication. Am J Psychiatry 2011;168(11):1154-63.
46. Shaw P, Lerch J, Greenstein D, Sharp W, Clasen L, Evans A i sur. Longitudinal Mapping of Cortical Thickness and Clinical Outcome in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder. Arch Gen Psychiatry 2006;63(5):540.
47. Hutchinson AD, Mathias JL, Banich MT. Corpus callosum morphology in children and adolescents with attention deficit hyperactivity disorder: A meta-analytic review. Neuropsychology 2008;22(3):341-9.
48. Shaw P, Malek M, Watson B, Greenstein D, de Rossi P, Sharp W. Trajectories of Cerebral Cortical Development in Childhood and Adolescence and Adult Attention-Deficit/Hyperactivity Disorder. Biological Psychiatry 2013;74(8):599-606.

49. Hoogman M, Bralten J, Hibar DP, Mennes M, Zwiers MP, Schweren LSJ i sur. Subcortical brain volume differences in participants with attention deficit hyperactivity disorder in children and adults: a cross-sectional mega-analysis. Lancet Psychiatry 2017;4(4):310-9.
50. Hoogman M, Muetzel R, Guimaraes JP, Shumskaya E, Mennes M, Zwiers MP i sur. Brain Imaging of the Cortex in ADHD: A Coordinated Analysis of Large-Scale Clinical and Population-Based Samples. Am J Psychiatry 2019;176(7):531-42.
51. Cupertino RB, Soheili-Nezhad S, Grevet EH, Bandeira CE, Picon FA, Tavares ME de A i sur. Reduced fronto-striatal volume in attention-deficit/hyperactivity disorder in two cohorts across the lifespan. NeuroImage: Clinical 2020;28:102403.
52. Bernanke J, Luna A, Chang L, Bruno E, Dworkin J, Posner J. Structural brain measures among children with and without ADHD in the Adolescent Brain and Cognitive Development Study cohort: a cross-sectional US population-based study. Lancet Psychiatry 2022;9(3):222-31.
53. Albajara Sáenz A, Villemonteix T, Massat I. Structural and functional neuroimaging in attention-deficit/hyperactivity disorder. Developmental Medicine & Child Neurology 2018;61(4):399-405.
54. Sharma A, Couture J. A Review of the Pathophysiology, Etiology, and Treatment of Attention-Deficit Hyperactivity Disorder (ADHD). Ann Pharmacother 2013;48(2):209-25.
55. Arnsten AFT, Pliszka SR. Catecholamine influences on prefrontal cortical function: Relevance to treatment of attention deficit/hyperactivity disorder and related disorders. Pharmacology Biochemistry and Behavior 2011;99(2):211-6.
56. Parlatini V, Bellato A, Murphy D, Cortese S. From Neurons To Brain Networks, Pharmacodynamics Of Stimulant Medication For ADHD. Neurosci Biobehav Rev 2024;164:105841-1.
57. Aston-Jones G, Cohen JD. Adaptive gain and the role of the locus coeruleus-norepinephrine system in optimal performance. J Comparative Neurol 2005;493(1):99-110.
58. Beaulieu JM ., Gainetdinov RR. The Physiology, Signaling, and Pharmacology of Dopamine Receptors. Pharmacol Rev 2011;63(1):182-217.
59. Moore RY, Bloom FE. Central Catecholamine Neuron Systems: Anatomy and Physiology of the Dopamine Systems. Ann Rev Neuroscience. 1978;1(1):129-69.
60. del Campo N, Chamberlain SR, Sahakian BJ, Robbins TW. The Roles of Dopamine and Noradrenaline in the Pathophysiology and Treatment of Attention-Deficit/Hyperactivity Disorder. Biological Psychiatry [Internet]. 2011;69(12):145-57.
61. Mehta TR, Monegro A, Nene Y, Fayyaz M, Bollu PC. Neurobiology of ADHD: A Review. Current Developmental Disorders Reports [Internet]. 2019;6(4):235-40.
62. da Silva BS, Grevet EH, Silva LCF, Ramos JKN, Rovaris DL, Bau CHD. An overview on neurobiology and therapeutics of attention-deficit/hyperactivity disorder. Discover Mental Health [Internet]. 2023;3(1).
63. Alexander GE, DeLong MR, Strick PL. Parallel Organization of Functionally Segregated Circuits Linking Basal Ganglia and Cortex. Ann Rev Neuroscience 1986;9(1):357-81.
64. Gerfen CR, Clavier RM. Neural inputs to the prefrontal agranular insular cortex in the rat: Horseradish peroxidase study. Brain Res Bull 1979;4(3):347-53.
65. Zimmer L. Contribution of Clinical Neuroimaging to the Understanding of the Pharmacology of Methylphenidate. Trends in Pharmacological Sciences. 2017 [cited 2020 Jul 13];38(7):608-20.
66. Klein MO, Battagello DS, Cardoso AR, Hauser DN, Bittencourt JC, Correa RG. Dopamine: Functions, Signaling, and Association with Neurological Diseases. Cellular and Molecular Neurobiology. 2018;39(1):31-59.
67. Volkow ND, Wang G-J, Newcorn JH, Kollins SH, Wigal TL, Telang F i sur. Motivation deficit in ADHD is associated with dysfunction of the dopamine reward pathway. Molecular Psychiatry 2010;16(11):1147–54.
68. Staller JA, Faraone SV. Targeting the dopamine system in the treatment of attention-deficit/hyperactivity disorder. Exp Rev Neurother 2007;7(4):351–62.
69. Gizer IR, Ficks C, Waldman ID. Candidate gene studies of ADHD: a meta-analytic review. Human Genetics 2009;126(1):51–90.
70. Sharma A, Couture J. A Review of the Pathophysiology, Etiology, and Treatment of Attention-Deficit Hyperactivity Disorder (ADHD). Ann Pharmacother 2013;48(2):209-25.
71. del Campo N, Chamberlain SR, Sahakian BJ, Robbins TW. The Roles of Dopamine and Noradrenaline in the Pathophysiology and Treatment of Attention-Deficit/Hyperactivity Disorder. Biological Psychiatry 2011;69(12):145-57.
72. Dahl MJ, Mather M, Sander MC, Werkle-Bergner M. Noradrenergic Responsiveness Supports Selective Attention across the Adult Lifespan. J Neurosci 2020; 21;40(22):4372-90.
73. Kent L, Doerry U, Hardy E, Parmar R, Gingell K, Hawi Z i sur. Evidence that variation at the serotonin transporter gene influences susceptibility to attention deficit hyperactivity disorder (ADHD): analysis and pooled analysis. Molecular Psychiatry 2002;7(8):908-12.
74. Hawi Z, Dring M, Kirley A, Foley D, Kent L, Craddock N i sur. Serotonergic system and attention deficit hyperactivity disorder (ADHD): a potential susceptibility locus at the 5-HT1B receptor gene in 273 nuclear families from a multi-centre sample. Molecular Psychiatry 2002;7(7):718-25.
75. Wang CH, Liu C, Cong EZ, Xu GL, Ting-Ting Lv, Zhang YL i sur. Association of tryptophan hydroxylase-2 polymorphisms with oppositional defiant disorder in a Chinese Han population. Behav Brain Functions 2016;12(1)
76. Hu Y, Chen X, Gu H, Yang Y. Resting-State Glutamate and GABA Concentrations Predict Task-Induced Deactivation in the Default Mode Network. J Neuroscience. 2013;33(47):18566-73.
77. Coffin JM, Baroody S, Schneider K, O'Neill J. Impaired Cerebellar Learning in Children with Prenatal Alcohol Exposure: A Comparative Study of Eyeblink Conditioning in Children with ADHD and Dyslexia. Cortex 2005;41(3):389-98.

78. Milberger S, Biederman J, Faraone S, Chen L, Jones J. Is maternal smoking during pregnancy a risk factor for attention deficit hyperactivity disorder in children? Am J Psychiatry 1996;153(9):1138-42.
79. Ai Y, Zhao J, Shi J, Zhu TT. Antibiotic exposure and childhood attention-deficit/hyperactivity disorder: systematic review and meta-analysis. Psychopharmacology 2021;238(11):3055-62.
80. Sanchez CE, Barry C, Sabhlok A, Russell K, Majors A, Kollins SH i sur. Maternal pre-pregnancy obesity and child neurodevelopmental outcomes: a meta-analysis. Obes Rev 2017;19(4):464-84.
81. Masarwa R, Platt RW, Filion KB. Acetaminophen use during pregnancy and the risk of attention deficit hyperactivity disorder: A causal association or bias? Paediatric and Perinatal Epidemiology 2020;34(3):309-17.
82. Leshem R, Bar-Oz B, Diav-Citrin O, Gbaly S, Soliman J, Renoux C i sur. Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) During Pregnancy and the Risk for Autism spectrum disorder (ASD) and Attention deficit hyperactivity disorder (ADHD) in the Offspring: a True Effect or a Bias? A Systematic Review & Meta-Analysis. Curr Neuropharmacol 2021;19(6).
83. Nilsen FM, Tulve NS. A systematic review and meta-analysis examining the interrelationships between chemical and non-chemical stressors and inherent characteristics in children with ADHD. Environ Res 2020;180:108884.
84. Gou X, Wang Y, Tang Y, Qu Y, Tang J, Shi J et al. Association of maternal prenatal acetaminophen use with the risk of attention deficit/hyperactivity disorder in offspring: A meta-analysis. Aust N Z J Psychiatry 2019;53(3):195-206.
85. Raz R, Gabis L. Essential fatty acids and attention-deficit-hyperactivity disorder: a systematic review. Developmental Medicine & Child Neurology. 2009;51(8):580-92.
86. Zeng Y, Tang Y, Yue Y, Li W, Qiu X, Hu P i sur. Cumulative evidence for association of parental diabetes mellitus and attention-deficit/hyperactivity disorder. Neuroscience & Biobehavioral Reviews 2019;117:129-39.
87. Brown N. Childhood trauma and ADHD: A complete overview & clinical guidance. ADDitude [Internet]. 2020 Nov 4; Available from: https://www.additudemag.com/adhd-and-trauma-overview-signs-symptoms/
88. Buitelaar JK. The role of the HPA-axis in understanding psychopathology: cause, consequence, mediator, or moderator? Eur Child & Adolescent Psychiatry 2013;22(7):387-9.
89. Liorens M, Barba M, Torralbas J, Nadal R, Armario A, Gagliano H i sur. Stress-related biomarkers and cognitive functioning in adolescents with ADHD: Effect of childhood maltreatment. J Psychiatr Res 2022;149:217-25.
90. Quaschner K, Theisen FM, Becker K. Hyperkinetische Störungen. U: Remschmidt H, Quaschner K, Theisen FM, ur. Kinder- und Jugendpsychiatrie. 6. izd. Stuttgart: Georg Thieme; 2011, 157-66.
91. Steinhausen HC. Psychische Störungen bei Kindern und Jugendlichen. 7. izd. München: Urban & Fischer; 2010.
92. Hopf H. Psychoanalyse von Aufmerksamkeits- und Hyperaktivitaetsstoerungen (ADHS). U: Hopf H, Windaus E (eds). Lehrbuch der Psychotherapie, 5: Analytische und tiefenpsychologisch fundierte Kinder- jugendlichenpsychotherapie. München: CIP Medien; 2009, 327-42.
93. Cerrillo-Urbina AJ, García-Hermoso A, Sánchez-López M, Pardo Guijarro MJ, Santos Gomez JL, Martinez Viscaino V. The effects of physical exercise in children with attention deficit hyperactivity disorder: a systematic review and meta-analysis of randomized control trials. Child Care Health Dev 2015;41(6):779-88.
94. Mattejat F, Schulte-Markwort M. Kinder- und Jugendpsychiatrie und -Psychotherapie. 5. izd. Bremen: UNI-MED, 2013.
95. Faraone SV. The pharmacology of amphetamine and methylphenidate: Relevance to the neurobiology of attention-deficit/hyperactivity disorder and other psychiatric comorbidities. Neurosci Biobehav Rev 2018;87:255-70.
96. Cortese S, Adamo N, Del Giovane C, Mohr-Jensen C, Hayes AJ, Carucci S i sur. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. Lancet Psychiatry 2018;5(9):727-38.
97. Coghill D, Banaschewski T, Cortese S, Asherson P, Brandeis D, Buitelaar J et al. The Management of ADHD in Children and Adolescents: Bringing Evidence to the clinic: Perspective from the European ADHD Guidelines Group (EAGG). Eur Child & Adolescent Psychiatry. 2021;32(8).
98. Pliszka S. Practice Parameter for the Assessment and Treatment of Children and Adolescents With Attention-Deficit/Hyperactivity Disorder. J of American Academy of Child & Adolescent Psychiatry 2017;46(7):894-921.
99. Bolea-Alamañac B, Nutt DJ, Adamou M, Asherson P, Bazire S, Coghill D i sur. Evidence-based guidelines for the pharmacological management of attention deficit hyperactivity disorder: Update on recommendations from the British Association for Psychopharmacology. J Psychopharmacol 2014;28(3):179-203.
100. National Institute for Health and Care Excellence. Attention Deficit Hyperactivity disorder: Diagnosis and Management | Guidance | NICE [Internet]. Nice.org.uk. NICE; 2018. Available from: https://www.nice.org.uk/guidance/ng87
101. Cortese S. Pharmacologic Treatment of Attention Deficit–Hyperactivity Disorder. Ropper AH, editor. N Engl J Med 2020;383(11):1050-6.
102. Fawns T. Attention Deficit and Hyperactivity Disorder. Primary Care: Clinics in Office Practice 2021;48(3):475-91.
103. De Deyn PP, Buitelaar J. Risperidone in the management of agitation and aggression associated with psychiatric disorders. Eur Psychiatry [Internet]. 2006;21(1):21-8.
104. Aman MG, Binder C, Turgay A. Risperidone Effects in the Presence/Absence of Psychostimulant Medicine in Children with ADHD, Other Disruptive Behavior Disorders, and Subaverage IQ. J Child and Adolescent Psychopharmacol 2004;14(2):243-54.
105. Dehkordi A, Safavi P, Ghasemi N. Comparison of the effects of methylphenidate and the combination of methylphenidate and risperidone in preschool children with attention-deficit hyperactivity disorder. J Advanced Pharmaceutical Technology & Research 2016;7(4):144.

106. Correia Filho AG, Bodanese R, Silva TL, Alvares JP, Aman M, Rohde LA. Comparison of Risperidone and Methylphenidate for Reducing ADHD Symptoms in Children and Adolescents With Moderate Mental Retardation. J Am Acad Child Adolescent Psychiatry 2005;44(8):748-55.
107. Devlin AM, Panagiotopoulos C. Metabolic side effects and pharmacogenetics of second-generation antipsychotics in children. Pharmacogenomics 2015;16(9):981-96.
108. Rosenbloom AL. Hyperprolactinemia with Antipsychotic Drugs in Children and Adolescents. Int J Pediatr Endocrinol 2010;2010:1-6.
109. Zimmer L. Contribution of Clinical Neuroimaging to the Understanding of the Pharmacology of Methylphenidate. Trends in Pharmacological Sciences. 2017;38(7):608-20.
110. Wilens TE. Effects of Methylphenidate on the Catecholaminergic System in Attention-Deficit/Hyperactivity Disorder. J Clin Psychopharmacol 2008;28(Suppl. 2):S46-53.
111. Swanson CJ, Perry KW, Koch-Krueger S, Katner J, Svensson KA, Bymaster FP. Effect of the attention deficit/hyperactivity disorder drug atomoxetine on extracellular concentrations of norepinephrine and dopamine in several brain regions of the rat. Neuropharmacology 2006;50(6):755-60.
112. Adler LA, Dirks B, Deas PF, Raychaudhuri A, Dauphin MR, Lasser RA i sur. Lisdexamfetamine Dimesylate in Adults With Attention-Deficit/ Hyperactivity Disorder Who Report Clinically Significant Impairment in Executive Function. J Clin Psychiatry 2013;74(07):694-702.
113. Brown TE, Chen J, Robertson B. Relationships Between Executive Function Improvement and ADHD Symptom Improvement With Lisdexamfetamine Dimesylate in Adults With ADHD and Executive Function Deficits. Prim Care Companion CNS Disord 2020 28;22(3).
114. Tamminga HGH, Reneman L, Huizenga HM, Geurts HM. Effects of methylphenidate on executive functioning in attention-deficit/hyperactivity disorder across the lifespan: a meta-regression analysis. Psychol Med 2016;46(9):1791-807.
115. Volkow ND, Wang GJ, Newcorn J, Telang F, Solanto MV, Fowler JS i sur. Depressed Dopamine Activity in Caudate and Preliminary Evidence of Limbic Involvement in Adults With Attention-Deficit/Hyperactivity Disorder. Arch Gen Psychiatry 2007;64(8):932.
116. Posner J, Polanczyk GV, Sonuga-Barke E. Attention-deficit Hyperactivity Disorder. Lancet 2020;395(10222):450-62.
117. Castells X, Ramos-Quiroga JA, Rigau D, Bosch R, Nogueira M, Vidal X i sur. Efficacy of Methylphenidate for Adults with Attention-Deficit Hyperactivity Disorder. CNS Drugs 2011;25(2):157-69.
118. Upadhyaya HP, Desaiah D, Schuh KJ, Bymaster FP, Kallman MJ, Clarke DO i sur. A review of the abuse potential assessment of atomoxetine: a nonstimulant medication for attention-deficit/hyperactivity disorder. Psychopharmacology 2013;226(2):189-200.
119. Clemow DB, Bushe CJ. Atomoxetine in patients with ADHD: A clinical and pharmacological review of the onset, trajectory, duration of response and implications for patients. J Psychopharmacol 2015;29(12):1221-30.
120. Strattera® (atomoxetine capsules) [strattera prescribing information] Indianapolis, IN: Eli Lilly and Company; 2009.
121. Strattera® (atomoxetine capsules) [strattera summary of product characteristics] Hampshire: Eli Lilly and Company Ltd; 2015.
122. Wang M, Ramos BP, Paspalas CD, Shu Y, Simen A, Duque A i sur. Alpha2A-adrenoceptors strengthen working memory networks by inhibiting cAMP-HCN channel signaling in prefrontal cortex. Cell 2007;129(2):397-410.
123. Sallee FR, Lyne A, Wigal T, McGough JJ. Long-Term Safety and Efficacy of Guanfacine Extended Release in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder. J Child Adolescent Psychopharmacol 2009;19(3):215-26.
124. Schwartz S, Correll CU. Efficacy and Safety of Atomoxetine in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder: Results From a Comprehensive Meta-Analysis and Metaregression. J Am Acad Child Adolescent Psychiatry. 2014;53(2):174-87.
125. Konrad K, Neufang S, Fink GR, Herpertz-Dahlmann B. Long-Term Effects of Methylphenidate on Neural Networks Associated With Executive Attention in Children With ADHD: Results From a Longitudinal Functional MRI Study. J Am Acad Child Adolescent Psychiatry 2007;46(12):1633-41.
126. Man KKC, Häge A, Banaschewski T, Inglis SK, Buitelaar J, Carucci S i sur. Long-term safety of methylphenidate in children and adolescents with ADHD: 2-year outcomes of the Attention Deficit Hyperactivity Disorder Drugs Use Chronic Effects (ADDUCE) study. Lancet Psychiatry [Internet]. 2023 May 1;10(5):323–33.