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Validacija Yale-Brownove ljestvice opsesivno-kompulzivnih simptoma kod hrvatskih trudnica

/ Validation of the Yale-Brown Obsessive Compulsive Scale in a Sample of Croatian Pregnant Women

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Opsesivno-kompulzivni poremećaj (OKP) može se pojaviti tijekom peripartalnog razdoblja kada se opsesije uglavnom odnose na novorođenče. Yale-Brownova ljestvica opsesivno-kompulzivnih simptoma (Y-BOCS) smatra se "zlatnim standardom" za ispitivanje težine simptoma OKP-a. Prethodna istraživanja utvrdila su različite faktorske strukture Y-BOCS-a. Međutim validacija ove ljestvice nije provedena na hrvatskom uzorku ni tijekom trudnoće, što je cilj ovog transverzalnog istraživanja u kojem je sudjelovalo 569 trudnica koje su bile, u prosjeku, u 35,4. tjednu trudnoće. Osim Y-BOCS-a, kako bi se ispitala divergentna valjanost, sudionice su ispunile Edinburški upitnik poslijeporođajne depresivnosti (EPDS), Skalu depresije, anksioznosti i stresa – podljestvica anksioznosti (DASS) te Ljestvicu zabrinutosti u trudnoći (LJZT). U literaturi su utvrđeni jednofaktorski, dvofaktorski, trofaktorski modeli, modeli višeg reda i bifaktorski model upitnika zbog čega su navedeni modeli i provjereni konfirmatornom faktorskom analizom. Model faktora višeg reda s dva faktora drugog reda: opsesijama i kompulzijama, pokazao se kao najbolje rješenje na temelju empirijskih pokazatelja i teorijskih očekivanja. Pouzdanost je bila visoka. Divergentna valjanost, ispitana korelacijama sa simptomima depresije, općom anksioznošću i anksioznošću specifičnom za trudnoću, bila je dobra. Y-BOCS je pokazao dobra psihometrijska svojstva kod hrvatskih trudnica. Ukupna ljestvica i dvije podljestvice mogu se koristiti u peripartalnom razdoblju za probir simptoma OKP-a.

/ Obsessive-compulsive disorder (OCD) can occur during the peripartum period when obsessions are mainly focused on the baby. The Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) is considered the "golden standard" for the assessment of severity of OCD symptoms. Previous studies revealed different factor structures of the Y-BOCS. However, this scale has not been validated on a Croatian sample or during pregnancy, making it the aim of this cross-sectional study which involved 569 pregnant women who were, on average, 35.4 weeks pregnant. In order to examine the divergent validity, in addition to Y-BOCS, the participants filled out the Edinburgh Postnatal Depression Scale (EPDS), the Anxiety subscale of the Depression, Anxiety and Stress Scale (DASS), and the Pregnancy Concerns Scale (PCS). The 1-factor, 2-factor, 3-factor, higher order, and bifactor models of the questionnaire have been established in the literature, which is why we examined them using confirmatory factor analysis. The best fit to the data based on empirical indicators and theoretical expectations was obtained in the higher-order factor model with two second-order factors: obsessions and compulsions. Reliability was high. Divergent validity, examined by correlations with depressive symptoms, general anxiety, and pregnancy-specific anxiety, was acceptable. The Y-BOCS revealed good psychometric properties in the sample of Croatian pregnant women. The total scale and two subscales could be used in the peripartum period to screen for OCD symptoms.

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UVOD

Trudnoća je radosno, ali i stresno razdoblje u kojem se događaju mnoge promjene. Smatra se da je to razdoblje u kojem su žene osjetljive na različite probleme mentalnog zdravlja. Jedan od mogućih problema mentalnog zdravlja tijekom trudnoće, ali i tijekom cijelog peripartalnog razdoblja, je opsesivno-kompulzivni poremećaj (OKP) (1). To je poremećaj koji karakterizira prisutnost opsesija i/ili kompulzija. Dok su opsesije uporne i nametljive misli, porivi ili slike koje su neželjene, kompulzije se sastoje od ponavljajućih ponašanja ili mentalnih radnji za koje pojedinac osjeća da ih mora izvesti kao reakciju na opsesivnu misao ili na temelju pravila koja treba strogo slijediti (2).

Prevalencija simptoma OKP-a tijekom trudnoće je oko 4 % (3-5), dok se pokazalo da raste u razdoblju poslije porođaja na oko 7 % (3,4,6). U peripartalnom razdoblju mogući su različiti simptomi opsesivno-kompulzivnog poremećaja. Na primjer, uglavnom se pojavljuju opsesije i kompulzije vezane uz simetriju/točnost i čistoću. U razdoblju poslije porođaja česte su opsesivne misli usmjerene na dijete. Ove misli su uglavnom agresivnog sadržaja, a odnose se na majčin strah da će ozlijediti dijete. Nadalje, kompulzije provjeravanja i traženja potvrde

INTRODUCTION

Pregnancy is a joyful, but stressful time in which many changes take place. It is considered to be a period in which women are susceptible to various mental health issues. One of the possible mental health issues during pregnancy, but also through the entire peripartum period, is obsessive-compulsive disorder (OCD) (1). It is a disorder characterized by the presence of obsessions and/or compulsions. While obsessions represent persistent and intrusive thoughts, urges, or images that are unwanted, compulsions consist of repetitive behaviors or mental acts that a person feels driven to perform in response to an obsessive thought or based on rules that need to be rigidly followed (2).

The prevalence of OCD symptoms during pregnancy is around 4% (3–5), while it has been observed that it increases in the postpartum period to around 7% (3, 4, 6). In the peripartum period, various symptoms of the obsessive-compulsive disorder are possible. For example, obsessions and compulsions related to symmetry/accuracy and cleanliness mostly appear. In the postpartum period, obsessive thoughts focused on the child are common. These thoughts are mostly aggressive in content, and relate to the maternal fear of harming

također su uobičajeni simptomi tijekom tog razdoblja (1,7).

Iako postoje različite mjere simptoma OKP-a (8-13), Yale-Brownova ljestvica opsesivno-kompulzivnih simptoma (Y-BOCS) smatra se "zlatnim standardom" i utvrđeno je da je jedna od najčešće korištenih ljestvica za mjerenje učestalosti i težine simptoma OKP-a (14). Y-BOCS se često koristio na kliničkim uzorcima i za otkrivanje subkliničkih simptoma u nekliničkim uzorcima (15-17). Također, ta se ljestvica pokazala korisnom za mjerenje simptoma OKP-a tijekom trudnoće (5,18,19) i u razdoblju poslije porođaja (19-21). Osim Y-BOCS-a postoje još dvije verzije za odrasle: Yale-Brownova ljestvica opsesivno-kompulzivnih simptoma-drugo izdanje (Y-BOCS II) (22) i Dimenzionalna Yale-Brownova ljestvica opsesivno-kompulzivnih simptoma (DY-BOCS) (23) koja mjeri jačinu simptoma OKP-a unutar dimenzija koje kombiniraju slične opsesije i kompulzije. Kada je riječ o strukturi ljestvice Y-BOCS, izvorno je predložena dvofaktorska struktura s podljestvicama opsesivnih simptoma i kompulzivnih simptoma s mogućnošću izračuna ukupnog rezultata (14). Neka su istraživanja potvrdila takvu strukturu (npr. 24-26). Nadalje, neka istraživanja upućuju na moguću dvofaktorsku strukturu, ali s drugačijim faktorima, kao što su smetnje i težina simptoma (npr. 27,28) ili težina simptoma i otpor/kontrola (29). Trofaktorska struktura je također moguća i to sa sljedećim faktorima: jačina opsesija, jačina kompulzija i otpornost na simptome (25,30,31), dok je Fatori (32) dobio faktorsku strukturu višeg reda jačinom opsesija i jačinom kompulzija kao specifičnim faktorima. Dakle, konačnu faktorsku strukturu tek treba utvrditi. Sva gore navedena istraživanja koja su ispitivala faktorsku strukturu provedena su na kliničkim uzorcima. Istodobno, dvofaktorska struktura opsesija i kompulzija dobivena je i na nekliničkom uzorku studenata (16).

the baby. Furthermore, checking compulsions and seeking reassurance are also common symptoms during that period (1, 7).

Although various measures of OCD symptoms exist (8-13), the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) is considered the "golden standard" and has been determined as one of the most widely used scales for measuring the frequency and severity of OCD symptoms (14). Y-BOCS was widely used in clinical samples, as well as for detecting subclinical symptoms in non-clinical samples (15–17). Furthermore, the scale has proved useful for measuring OCD symptoms during pregnancy (5, 18, 19) and in the postpartum period (19–21). In addition to Y-BOCS, there are two more versions for adults: the Yale-Brown Obsessive-Compulsive Scale-Second Edition (Y-BOCS II) (22) and the Dimensional Yale-Brown Obsessive-Compulsive Scale (DY-BOCS) (23) which measures the severity of OCD symptoms within dimensions that combine similar obsessions and compulsions. Regarding the factor structure of the Y-BOCS, originally, a two-factor structure with subscales of obsessive symptoms and compulsive symptoms was proposed with the possibility of calculating a total score (14). Some studies confirmed such a structure (e.g., 24-26). Furthermore, some studies indicate a possible two-factor structure, but with different factors, such as disturbance and symptom severity (e.g., 27, 28) or symptom severity and resistance/control (29). A three-factor structure is also possible with the following factors: severity of obsessions, severity of compulsions, and resistance to symptoms (25, 30, 31), while Fatori (32) obtained a higher-order factor structure with severity of obsessions and severity of compulsions as specific factors. Therefore, the final factor structure still needs to be determined. All of the above-mentioned studies which examined the factor structure were conducted on clinical samples. At the same time, a two-factor structure of obsessions and compulsions was also obtained on a non-clinical sample of students (16).

CILJ ISTRAŽIVANJA

Y-BOCS dosad nije validiran u Hrvatskoj. Također, prema našim saznanjima, iako Y-BOCS nije validiran tijekom trudnoće, u razdoblju nakon porođaja pokazao je dobra psihometrijska svojstva (33). Stoga je cilj ovoga istraživanja bio validirati Y-BOCS kod trudnica u Hrvatskoj. Ispitana je faktorska struktura, pouzdanost i divergentna valjanost. Nažalost, konvergentnu valjanost nije bilo moguće provjeriti jer, prema našim saznanjima, do sada na hrvatskom jeziku nije validirana druga mjera simptoma OKP-a. Sukladno prethodnim istraživanjima faktorske strukture testirani su jednofaktorski, dvofaktorski, trofaktorski model, model višeg reda i bifaktorski model. Očekivali smo i zadovoljavajuću pouzdanost ljestvice na uzorku trudnica. Konačno, očekivali smo da će Y-BOCS biti nisko do umjereno povezan sa simptomima depresije i anksioznosti.

METODA

Sudionici

Sudjelovalo je 569 trudnica (tablica 1). U prosjeku su imale 31 godinu te bile trudne 35,4 tjedna. Polovici sudionica ovo je bila prva trudnoća. Gotovo sve sudionice bile su u braku ili izvanbračnoj zajednici (97,7 %). Najviše trudnica bilo je visoko obrazovano, odnosno završilo je fakultet (68,4 %). Većina sudionica svoje prihode smatra prosječnima ili iznadprosječnima (98,2 %). Uglavnom su živjele u urbanim sredinama, a većina nije imala pozitivan psihijatrijski hereditet (86,5 %).

Instrumenti

Yale-Brownova ljestvica opsesivno-kompulzivnih simptoma (engl. *Yale-Brown Opsessive Compulsive Scale - Y-BOCS*) (14) mjeri težinu simptoma OKP-a. Sastoji se od 10 čestica od kojih pet procjenjuju opsesije, dok ostalih pet procjenjuje

AIM

The Y-BOCS was not previously validated in Croatia. Moreover, to the best of our knowledge, although Y-BOCS was not validated during pregnancy, in the postpartum period it showed good psychometric properties (33). The aim of this study was, therefore, to validate the Y-BOCS on a sample of pregnant women in Croatia. Factor structure, reliability, and divergent validity were examined. Unfortunately, convergent validity could not be tested because, to the best of our knowledge, no other OCD symptoms scale has been validated in the Croatian language so far. In accordance with previous studies on factor structures, we tested the 1-factor, 2-factor, 3-factor, higher-order, and bifactor models. We also expected the reliability of the scale to be satisfactory on the sample of pregnant women. Finally, we anticipated that the Y-BOCS would have a low to moderate correlation with depression and anxiety symptoms.

METHOD

Participants

A total of 569 pregnant women participated in the study (Table 1). They were, on average, 31 years old and 35.4 weeks pregnant. For half of the participants, this was their first pregnancy. Almost all participants were married or cohabitating (97.7%). Most of the pregnant women had a higher education, i.e. a university or college degree (68.4%). Most of the participants perceived their income as average or above average (98.2%). They also mainly lived in urban areas, and the majority did not have positive psychiatric heredity (86.5%).

Instruments

The Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (14) measures the severity of OCD symptoms. It consists of 10 items, five of which

TABLICA 1. Sociodemografski podatci za uzorak trudnica (N = 569)
TABLE 1. Sociodemographic data for the sample of pregnant women (N = 569)

		M (SD)
Dob majke (godine) / Maternal age (years)		31,42 (5,01)
Tjedni trudnoće / Pregnancy weeks		35,43 (4,87)
		n (%)
Paritet[a] / Parity[a]	Prvorotkinja / Primipara	305 (54,1)
	Višerotkinja / Multipara	259 (45,9)
Bračni status / Marital status[a]	Udana / Married	429 (76,1)
	Izvanbračna zajednica / Cohabitating	122 (21,6)
	Drugo / Other	18 (2,3)
Obrazovanje[a] / Education[a]	Osnovna ili srednja škola / Elementary or secondary school	179 (31,6)
	Fakultet ili sveučilište / College or university	387 (68,4)
Socioekonomski status[a] / Socioeconomic status[a]	Ispod prosjeka / Below average	10 (1,8)
	Prosjek / Average	365 (64,7)
	Iznad prosjeka / Above average	189 (33,5)
Mjesto stanovanja[a] / Place of residence[a]	Grad (> 100,000 građana) / City (>100,000 citizens)	431 (76,1)
	Grad (< 100,000 građana) / City (<100,000 citizens)	77 (13,6)
	Ruralno područje / Rural area	58 (10,2)
Psihijatrijski hereditet / Psychiatric heredity[a]	Da / Yes	76 (13,5)
	Ne / No	489 (86,5)

Napomena: [a] – Neke sudionice nisu odgovorile na ovo pitanje.
/ *Note:* [a] – Some participants did not answer this question.

kompulzije. Odgovori na čestice bilježe se na ljestvici u rasponu od 0 do 4. Viši rezultat znači jače simptome OKP-a. Prethodna istraživanja pokazala su visoku pouzdanost cijele ljestvice (α između 0,80-0,90) (14).

Edinburški upitnik poslijeporođajne depresivnosti (engl. *Edinburgh Postnatal Depression Scale;* EPDS) (34) mjeri učestalost simptoma depresije u zadnjih sedam dana te je valjan za primjenu u trudnoći i nakon porođaja (35). Sastoji se od 10 čestica na koje se odgovara na ljestvici od 0 do 3. Viši rezultat znači jače simptome depresije. EPDS je prethodno preveden i validiran na hrvatski jezik (36). U ovom istraživanju dobivena je visoka pouzdanost izračunata McDonaldovom ω koja iznosi 0,84.

Ljestvica depresije, anksioznosti i stresa – podljestvica anksioznosti (engl. *Depression, Anxiety and Stress Scale - the anxiety subscale - DASS-21)*

assess obsession symptoms, while the other five assess compulsion symptoms. The responses to each item are marked on a scale ranging from 0 to 4. A higher score indicates stronger OCD symptoms. Previous studies have shown a high reliability of the total scale (α between 0.80-0.90) (14).

The *Edinburgh Postnatal Depression Scale* (EPDS) (34) measures the frequency of depressive symptoms in the past seven days and is valid for use during pregnancy and in the postpartum period (35). It consists of 10 items rated on a scale from 0 to 3. A higher score means stronger depressive symptoms. The EPDS was previously translated and validated in the Croatian language (36). This study showed high reliability, calculated with McDonald's ω which amounted to 0.84.

Depression, Anxiety and Stress Scale – the Anxiety subscale (DASS-21) (37) measures anxiety

(37) mjeri simptome opće anksioznosti tijekom prošlog tjedna. Sastoji se od sedam čestica, a odgovori se daju na ljestvici od 0 do 3. Ukupni rezultat se množi s 2 kako bi bio usporedan s duljom verzijom upitnika DASS-42. Ljestvica je prethodno predvedena na hrvatski jezik (38). U ovom istraživanju pouzdanost izmjerena McDonaldovom ω iznosila je 0,77 što znači da je prihvatljiva.

Ljestvica zabrinutosti tijekom trudnoće (LJZT) (39) mjeri specifične brige, strahove i brige tijekom trudnoće u zadnjem mjesecu. Sastoji se od 16 čestica. Odgovara se na ljestvici od 0 do 3. Viši rezultat ukazuje na veću specifičnu anksioznost. U izvornom istraživanju Cronbachov α je bio 0,80 (39) - isto kao i u našem istraživanju McDonald's ω = 0,80.

Postupak

Liječnik opstetričar je regrutirao trudnice da ispune upitnike metodom papir-olovka za vrijeme redovitih pregleda tijekom trudnoće. Sve su sudionice bile obaviještene o cilju istraživanja, dobrovoljnosti sudjelovanja i mogućem odustajanju u bilo kojem trenutku bez posljedica. Potpisale su informirani pristanak, a nakon popunjavanja upitnik su vratile opstetričaru u zatvorenoj omotnici. Sudionice nisu dobile nikakvu naknadu za svoje sudjelovanje. Ovo je bio dio većeg longitudinalnog istraživanja tijekom peripartalnog razdoblja. Istraživanje je dobilo odobrenje Etičkog odbora Hrvatskog katoličkog sveučilišta.

Statističke analize

S obzirom na cilj istraživanja izračunali smo veličinu uzorka od pet do deset sudionika po čestici (40), odnosno najmanje 100 sudionika, što je prilično premašeno. Prvo smo provjerili deskriptivne podatke (aritmetičke sredine i standardne devijacije) i normalnost distribucija (simetričnost, spljoštenost, Kolmogo-

symptoms over the past week. It consists of seven items, with responses on a scale from 0 to 3. The total score is multiplied by 2, in order to be comparable with the full DASS-42 version. The scale was previously translated into Croatian (38). In the current study, the reliability of McDonald's ω was 0.77, which means it was at an acceptable level.

Pregnancy Concerns Scale (PCS) (39) measures specific worries, fears and concerns during pregnancy in the last month. It consists of 16 items. Responses are rated on a scale ranging from 0 to 3. A higher score indicates higher specific anxiety. In the original study, Cronbach's α amounted to 0.80 (39) and in the current study, McDonald's ω was the same, amounting to 0.80.

Procedure

The obstetrician recruited pregnant women to fill in paper-and-pen questionnaires during their regular prenatal check-ups. All participants were informed about the study aim, voluntary participation, and possible withdrawal at any time without consequences. They signed the informed consent, and after completing the questionnaire, they sealed it in an envelope and returned it to the obstetrician. Participants did not receive any compensation for their participation. This was part of a larger longitudinal study covering the peripartum period. The study obtained ethical approval from the Ethics Committee of the Catholic University of Croatia.

Statistical analyses

Considering the aim of the study, we calculated the sample size as five to ten participants per item (40), i.e. at least 100 participants, which was fairly exceeded. We first checked the descriptive data (arithmetic means and standard deviations), and the normality of

rov-Smirnov test). Koristili smo Pearsonove korelacije za testiranje divergentne valjanosti, dok je pouzdanost ispitana kao unutarnja konzistentnost McDonaldovim ω koeficijentom. Sve navedene analize provedene su u programu *SPSS Statistics 29.0* za Windows. Univarijatni i multivarijatni *outlieri* su ispitani te ni jedan nije trebalo ukloniti. Univarijatna normalnost distribucije provjerena je izračunom *z* vrijednosti koje nisu bile veće od kritične vrijednosti 3,29 (41), dok se multivarijatno odstupanje od normalnosti distribucije ispitalo pomoću Mahalanobisove udaljenosti od grupnog centroida, faktorom inflacije varijance i izračunom multikolinearnosti (42). Konfirmatorna faktorska analiza korištena je za testiranje faktorske strukture u programu Mplus 8.10 (43). Kao metoda estimacije korišten je WLSMV s obzirom na to da su čestice na Y-BOCS bile ordinalne (44,45). Za procjenu pristajanja modela podatcima korišteni su sljedeći indikatori pristajanja: hi-kvadrat sa Satorra-Bentlerovom korekcijom, *Root Mean Square Error of Approximation* (RMSEA), *Standardized Root Mean Square Residual* (SRMR), *Comparative Fit Index* (CFI) i *Tucker-Lewis Index* (TLI). Pokazatelji dobrog pristajanja podataka bili su neznačajna vrijednost χ^2 (46), RMSEA ispod 0,06, uz *p* vrijednost pristajanja modela veću od 0,05, te CFI i TLI iznad 0,95 (47). RMSEA ispod 0,08 te CFI i TLI viši od 0,90 ukazuju na prihvatljivo pristajanje podatcima (47).

REZULTATI

Deskriptivna statistika

Deskriptivni podatci svih čestica ljestvice prikazani su u tablici 2. Četiri čestice nisu postigle puni teorijski raspon. Sudionice su u prosjeku označavale niže razine čestica, što znači da je ozbiljnost simptoma OKP-a bila relativno niska.

distributions (skewness, kurtosis, Kolmogorov-Smirnov test). We used Pearson's correlations to test divergent validity, while reliability was examined as internal consistency by McDonald's ω coefficient. All of the above-mentioned analyses were conducted using the SPSS Statistics 29.0 program for Windows. Univariate and multivariate outliers were examined, and there were no outliers that needed to be removed. Univariate normality of distribution was tested by calculating z-values, which did not exceed the critical value of 3.29 (41), while multivariate deviation from normality of distribution was examined using the Mahalanobis distance from the group centroid, the variance inflation factor, and the calculation of multicollinearity (42). Confirmatory factor analysis was used to test the factor structure in the Mplus 8.10 software (43). WLSMV was used as a method of estimation, given that items on Y-BOCS were ordinal (44, 45). The following model fit indices were used to assess the model's fit to the data: Chi-square with Satorra-Bentler correction, Root Mean Square Error of Approximation (RMSEA), Standardized Root Mean Square Residual (SRMR), Comparative Fit Index (CFI), and Tucker-Lewis Index (TLI). Indicators of good fit to the data were the nonsignificant χ^2 value (46), RMSEA below 0.06 with a model fit *p*-value greater than 0.05, and CFI and TLI above 0.95 (47). The RMSEA below 0.08 and CFI and TLI higher than 0.90 indicated an acceptable fit to the data (47).

RESULTS

Descriptive statistics

Descriptive data of all scale items are presented in Table 2. Four of the items did not obtain the full theoretical range. Participants, on average, reported lower levels of the items, meaning that the severity of each OCD symptom was relatively low.

TABLICA 2. Deskriptivni podatci za Yale-Brownovu ljestvicu opsesivno-kompulzivnih simptoma (N = 569)
TABLE 2. Descriptive data for the Yale-Brown Obsessive-Compulsive Scale (N = 569)

	M	SD	min	max	Asimetričnost / Skewness	Spljoštenost / Kurtosis	K-S
			Dobiveni raspon / Obtained range				
Y-BOCS 1	0,61	0,67	0	4	1,05	1,72	0,30**
Y-BOCS 2	0,26	0,51	0	4	2,27	7,17	0,47**
Y-BOCS 3	0,69	0,77	0	3	0,73	-0,48	0,30**
Y-BOCS 4	0,34	0,62	0	4	2,14	5,86	0,44**
Y-BOCS 5	0,61	0,69	0	4	1,20	2,48	0,30**
Y-BOCS 6	0,41	0,58	0	3	1,19	1,02	0,40**
Y-BOCS 7	0,16	0,40	0	2	2,31	4,66	0,51**
Y-BOCS 8	0,27	0,55	0	4	2,31	6,52	0,47**
Y-BOCS 9	0,33	0,70	0	4	2,51	6,75	0,46**
Y-BOCS 10	0,27	0,55	0	3	2,49	7,45	0,46**

Napomena: **p < .01; K-S = Kolmogorov-Smirnov test normalnosti distribucije.
/ *Note:* **p < .01; K-S = Kolmogorov-Smirnov test of normality of distribution.

Faktorska struktura

U literaturi su utvrđena različita faktorska rješenja Y-BOCS-a. Fatori (32) je napravio sažetak svih faktorskih rješenja ispitanih na kliničkom uzorku pa smo stoga testirali jednofaktorski model, dva dvofaktorska modela (opsesije i kompulzije; smetnje i ozbiljnost simptoma), dva trofaktorska modela (s ozbiljnošću opsesija, ozbiljnošću kompulzija i otpornošću na simptome kao faktorima, ali s različitim pripadajućim česticama), model faktora višeg reda (ozbiljnost opsesija i ozbiljnost kompulzija, ali bez čestica 4 i 9). Provjerili smo i nova faktorska rješenja - hijerarhijski model s općim faktorom višeg reda te opsesijama i kompulzijama kao faktorima prvog reda, kao i bifaktorski model s općim faktorom, te kompulzijama i opsesijama kao specifičnim faktorima.

Kao što je prikazano u tablici 3, dvofaktorski model koji je uključivao smetnje i ozbiljnost simptoma, oba trofaktorska modela i model faktora višeg reda (s 8 čestica; ozbiljnost opsesija i ozbiljnost kompulzija) loše su pristajali podatcima. Bifaktorski model nije mogao konvergirati. Dvofaktorski model koji uključuje

Factor structure

Various factor solutions of the Y-BOCS were determined in the literature. Fatori (32) made a summary of all factor solutions tested in a clinical sample, therefore, we tested a 1-factor model, two 2-factor models (obsessions and compulsions; disturbance and symptom severity), two 3-factor models (with severity of obsessions, severity of compulsions and resistance to symptoms as factors, but with different composition of items), one higher-order factor model (severity of obsessions and severity of compulsions, but without items 4 and 9). We also tested new factor solutions - a hierarchical model with a general higher-order factor and obsessions and compulsions as first-order factors, as well as a bifactor model with a general factor, and compulsions and obsessions as specific factors.

As presented in Table 3, the 2-factor model which included disturbance and symptom severity, both 3-factor models, and the higher-order factor model (with 8 items; severity of obsessions, and severity of compulsions) had a bad fit to the data. The bifactor model could not converge. The 2-factor model which

TABLICA 3. Faktorski modeli i indeksi pristajanja modela (N = 569)
TABLE 3. Factor models and model fit indices *(*N = 569)

Modeli / Models	Faktori i čestice / Factors and Items	SBS-χ² (df)	RMSEA	SRMR	CFI	TLI
1-faktorski model[a] / 1-factor model[a]	Čestice 1-10 / Items 1-10	589,89 (35) *p* < 0,001	0,167 [0,155-0,179] *p* < 0,001	0,111	0,932	0,913
2-faktorski model[a] (22,26,28,54) / 2-factor model[a] (22,26,28,54)	Opsesije: 1-5 / Obsessions: 1-5 Kompulzije: 6-10 / Compulsions: 6-10	189,57 (34) *p* < 0,001	0,090 [0,077-0,102] *p* < 0,001	0,046	0,981	0,975
2-faktorski model[a]* (27,28) / 2-factor model[a]* (27,28)	Smetnje: 2,3,7,8 / Disturbance: 2,3,7,8 Jačina simptoma: 1,4,5,6,9,10 / Symptom severity: 1,4,5,6,9,10	586,51 (34) *p* < 0,001	0,169 [0,157-0,181] *p* < 0,001	0,111	0,932	0,911
3-faktorski model[a] (55) / 3-factor model[a] (55)	Jačina simptoma: 1,2,3 / Symptom severity: 1,2,3 Jačina kompulzija: 6,7,8 / Severity of compulsions: 6,7,8 Otpornost na simptome: 4,5,9,10 / Resistance to symptoms: 4,5,9,10	422,68 (32) *p* < 0,001	0,146 [0,134-0,159] *p* < 0,001	0,083	0,952	0,933
3-faktorski model[a] (30,31) / 3-factor model[a] (30,31)	Otpornost na simptome: 1,2,3,5 / Resistance to symptoms: 1,2,3,5 Jačina kompulzija: 6,7,8,10 / Severity of compulsions: 6,7,8,10 Otpornost na simptome: 4,9 / Resistance to symptoms: 4,9	340,81 (32) *p* < 0,001	0,130 [0,118-0,143] *p* < 0,001	0,070	0,962	0,947
Model višeg reda s opsesijama i kompulzijama kao prvim faktorima i bez simptoma tvrdokornosti [a] (32) / Higher order model with obsessions and compulsions as first factors and without resistance symptoms[a] (32)	Jačina opsesija: 1,2,3,5 / Severity of obsessions: 1,2,3,5 Jačina kompulzija: 6,7,8,10 / Severity of compulsions: 6,7,8,10 (Bez 4 & 9) / (Without 4 & 9)	428,63 (20) *p* < 0,001	0,189 [0,174-0,205] *p* < 0,001	0,114	0,937	0,911
Model višeg reda s opsesijama i kompulzijama kao prvim faktorima / Higher order model with obsessions and compulsions as first factors	Opsesije: 1-5 / Obsessions: 1-5 Kompulzije: 6-10 / Compulsions: 6-10	**189,57 (34)** ***p* < 0,001**	**0,090 [0,077-0,012]** ***p* < 0,001**	**0,046**	**0,981**	**0,975**
Bifaktorski model / Bifactor model	Opsesije: 1-5 / Obsessions: 1-5 Kompulzije: 6-10 / Compulsions: 6-10	Model nije mogao konvergirati. / Model could not converge.				

Napomena: Model koji dobro odgovara podatcima prikazan je podebljano. [a]Modeli, osim bifaktorskog modela, preuzeti su od Fatori i sur. (32). *Dva faktora su imala korelaciju veću od 1.
/ *Note:* Model with a good fit to the data was presented in bold. [a]Models, except for the hierarchical and bifactor models, were taken from Fatori et al. (32).
*Two factors had correlation higher than 1.

faktore opsesija i kompulzija te hijerarhijski model s generalnim faktorom višeg reda i dva faktora prvog reda (slika 1), jednako dobro su odgovarali podatcima, odnosno ekvivalentni su. Sve čestice u modelima su imale visoka faktorska zasićenja. S obzirom na to da je i u modelu s dva faktora dobivena visoka korelacija između opsesija i kompulzija (*r* = 0,68) smatramo da hijerarhijski model bolje opisuje postojeće podatke.

includes the factors of obsessions and compulsions, and the hierarchical model with a general higher-order factor and two first-order factors (Figure 1), both fit the data equally well, meaning they are equivalent. All items in the models had high factor loadings. Given that a high correlation was also found between obsessions and compulsions in the 2-factor model (*r* = 0.68), we believe that the hierarchical model better describes the existing data.

Pouzdanost

Pouzdanost smo testirali McDonaldovim koeficijentom ω za ukupnu ljestvicvu i podljestvice Opsesije i Kompulzije. Ukupna ljestvica (ω = 0,87), podljestvica Opsesija (ω = 0,86) te podljestvica Kompulzija (ω = 0,86) imale su visoku pouzdanost.

Reliability

We tested the reliability with McDonald's ω coefficient for the total scale, as well as for the Obsessions and Compulsions subscales. The total scale (ω = 0.87), Obsessions subscale (ω = 0.86), and Compulsions subscale (ω = 0.86) had high reliability.
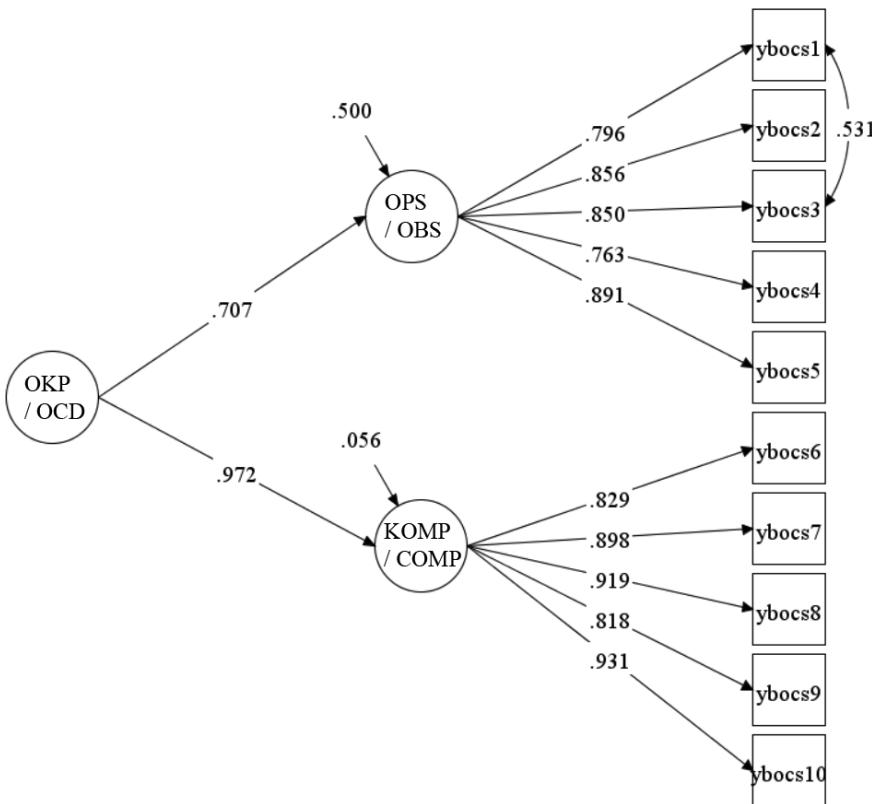
SLIKA 1. Hijerarhijski model s generalnim faktorom višeg reda i dva faktora prvog reda. *Napomena:* Sva faktorska zasićenja su značajna. Standardizirane vrijednosti su prikazane.

FIGURE 1. Hierarchical model with a general higher-order factor and two first-order factors. *Note:* All factor loadings are significant. Standardized values are presented.

Divergentna valjanost

Konvergentna valjanost nije se mogla ispitati, jer nijedna druga mjera simptoma OKP-a nije bila dostupna na hrvatskom jeziku. Međutim, ispitana je divergentna valjanost u odnosu na simptome depresije i anksioznosti (tablica 4). Očekivali smo niske do umjerene korelacije. Ukupni rezultat bio je pozitivno i visoko povezan sa simptomima depresije, umjereno povezan s općom anksioznosti te nisko povezan sa specifičnom anksioznosti tijekom trudnoće. Sličan obrazac korelacija primijećen je za podljestvicu Opsesija koja je pozitivno i visoko povezana sa simptomima depresije, umjereno s općom anksioznosti te nisko povezana sa specifičnom anksioznosti. Podljestvica Kompulzija bila je nisko pozitivno povezana sa simptomima depresije, općom anksioznosti i specifičnom anksioznosti.

Divergent validity

Convergent validity could not be examined because no other measure of OCD symptoms was available in the Croatian language. However, divergent validity was examined against depressive and anxiety symptoms (Table 4). We expected low to moderate correlations. The total score was positively and highly correlated with depressive symptoms, moderately correlated with general anxiety, and had a low correlation with pregnancy-specific anxiety. A similar pattern of correlations was observed for the Obsessions subscale which has positive and high correlations with depressive symptoms, moderate correlations with general anxiety, and low correlations with pregnancy-specific anxiety. The Compulsions subscale had low positive correlations with depressive symptoms, general anxiety, and pregnancy-specific anxiety.

TABLICA 4. Divergentna valjanost ukupne ljestvice i podljestvica
TABLE 4. Divergent validity of the total scale and its subscales

	Depresivni simptomi / Depressive symptoms	Opća anksioznost / General anxiety	Specifična anksioznost / Pregnancy-specific anxiety
Ukupna Y-BOCS / Total Y-BOCS	0,52**	0,45**	0,32**
Opsesije / Obsessions	0,53**	0,43**	0,34**
Kompulzije / Compulsions	0,37**	0,36**	0,22**

Napomena: **p < 0,01 / *Note*: **p < 0 .01

RASPRAVA

Hrvatska verzija Yale-Brownove ljestvice opsesivno-kompulzivnih simptoma primijenjena tijekom trudnoće imala je dobra psihometrijska svojstva što je u skladu s validacijama u drugim zemljama. Model faktora višeg reda s opsesijama i kompulzijama kao faktorima prvog reda dobro je odgovarao podatcima. Pri računanju rezultata mogu se koristiti ukupni rezultati i dvije podljestvice. Y-BOCS je imao visoku pouzdanost. Analizom povezanosti sa simptomima depresije, općom anksioznosti i specifičnom anksioznosti vezanom za trudnoću utvrdilo se da su ukupna ljestvica i podljestvica Opsesija imale umjerenu divergentnu valjanost, dok je podljestvica Kompulzija imala izvrsnu divergentnu valjanost.

Kao što je spomenuto, prethodna su istraživanja identificirala različite moguće faktorske strukture Y-BOCS-a. Međutim, treba uzeti u obzir da su ta istraživanja provedena na različitim uzorcima. Na primjer, na općem uzorku studenata dobivena je dvofaktorska struktura opsesija i kompulzija (16). Ista faktorska struktura dobivena je i u kliničkim uzorcima (14,25). Nadalje, na kliničkom uzorku pacijenata s OKP-om (32) dobiven je model višeg reda sa simptomima OKP-a kao čimbenicima višeg reda i simptomima Opsesija i Kompulzija kao čimbenikom prvog reda, ali bez čestica koje se odnose na tvrdokornost simptoma. U ovom smo istraživanju dobili faktorsku strukturu višeg reda s opsesijama i kompulzijama kao faktorima prvog reda, ali sa svih deset čestica. Dvofaktorsko rješenje koje uključuje simp-

DISCUSSION

The Croatian version of the Yale-Brown Obsessive Compulsive Scale administered during pregnancy had good psychometric properties consistent with validations in other countries. The higher-order factor model with Obsessions and Compulsions as first-order factors had a good fit to the data. When calculating the scores, both the total scores and the two subscales could be used. The Y-BOCS had high reliability. When compared against depressive symptoms, general anxiety and specific pregnancy-related anxiety, it was determined that the total scale and the Obsessions subscale had moderate divergent validity, while the Compulsions subscale had excellent divergent validity.

As mentioned above, previous studies identified various possible factor structures of the Y-BOCS. However, it should be considered that different samples were used in those studies. For example, in a general sample of students, a 2-factor structure of obsessions and compulsions was obtained (16). The same factor structure was obtained in the clinical samples (14, 25). Furthermore, in a clinical sample of patients with OCD (32), a higher-order model with OCD symptoms as the higher-order factors, and Obsessions and Compulsions symptoms as a first-order factor was established, but without items relating to symptoms resistance. In this study, we also obtained one higher-order factor structure with obsessions and compulsions as first-order factors, but with all ten items. The two-factor solution, which includes Obsession and Compulsion symptoms, fit the data equally well. We, therefore, believe that

tome Opsesija i Kompulzija jednako je dobro pristajalo podatcima. Stoga smatramo da se na uzorku trudnica iz Hrvatske mogu izračunati i ukupni rezultat i rezultati na podljestvicama Opsesija i Kompulzija.

S obzirom na to da je trudnoća specifično razdoblje života svaka trudnica ima mnogo briga, poput toga da mora biti oprezna jer bi na neki način mogla naštetiti rađanju zdravog djeteta (48). Tijekom tog vremena uglavnom se javljaju opsesije o čistoći, zagađenju i simetriji/točnosti, ali postoji mogućnost i za agresivne opsesije o djetetu (7,49). Fairbrother i Abramowitz (50) ističu studije slučaja koje pokazuju da su trudnice s OKP-om uglavnom imale opsesivne misli, koje nisu bile praćene kompulzijama već izbjegavajućim i zaštitničkim ponašanjem. Ovo može objasniti zašto je u našem uzorku trudnica faktor Kompulzija više pridonio faktoru višeg reda, koji se odnosi na simptome OKP-a, od faktora Opsesija. Moguće je da trudnice koje nemaju kliničke simptome imaju više briga i opsesivnih misli tijekom ovog osjetljivog razdoblja. Međutim, potrebna su daljnja istraživanja faktorske strukture ove ljestvice, posebice tijekom specifičnih razdoblja kao što su trudnoća i razdoblje poslije porođaja.

Utvrđena je visoka pouzdanost ukupne ljestvice, podljestvica Opsesija i Kompulzija. Ovi rezultati su u skladu s našim očekivanjima s obzirom na prethodna istraživanja u kojima je utvrđena zadovoljavajuća pouzdanost (14,25,32).

Kako bismo ispitali divergentnu valjanost, testirali smo povezanost između ukupnog rezultata, podljestvica Opsesija i Kompulzija sa simptomima depresije, općom anksioznosti i specifičnom anksioznosti u trudnoći. Ustanovili smo visoke korelacije između ukupne ljestvice i podljestvice Opsesija te simptoma depresije, umjerene korelacije s općom anksioznosti, te niske korelacije s specifičnom anksioznosti, pokazujući umjerenu divergentnu valjanost. Dodatno, podljestvica Kompulzija bila je nisko i pozitivno povezana sa simptomima

in the sample of pregnant women from Croatia, both the total score and the subscale scores for Obsessions and Compulsions can be calculated.

Given that pregnancy is a unique period of life, pregnant women have a lot of concerns, such as being careful because they could somehow harm the birth of a healthy child (48). During that time, obsessions about cleanliness, contamination and symmetry/accuracy mostly appear, but there is also a possibility that aggressive obsessions about the baby might appear (7, 49). Fairbrother and Abramowitz (50) highlight case studies showing that pregnant women with OCD mostly had obsessive thoughts which were not followed by compulsions, but rather by avoidant and protective behavior. This could explain why, in our sample of pregnant women, the Compulsions factor contributed more to the higher-order factor relating to OCD symptoms than the Obsessions factor. It could be that pregnant women without clinical symptoms tend to have more concerns and obsessive thoughts during this sensitive period. However, further research into the factor structure of this scale is necessary, especially during specific periods such as pregnancy and postpartum.

It was determined that the total scale, and the Obsessions and Compulsions subscales, had high reliability. Such findings are consistent with our expectations in view of previous studies in which satisfactory reliability had been determined (14, 25, 32).

In order to examine divergent validity, we tested associations of the total score and the Obsessions and Compulsions subscales with the depressive symptoms, general anxiety and pregnancy-specific anxiety. We determined high correlations between the total scale and Obsessions subscale, as well as depressive symptoms, moderate correlations with general anxiety, and low correlations with pregnancy-specific anxiety, demonstrating moderate divergent validity. Additionally, the Compulsions subscale had a low and positive correlation with depressive symptoms, general

depresije, općom anksioznosti i specifičnom anksioznosti pokazujući izvrsnu divergentnu valjanost. U ovom istraživanju korelacije su veće nego u prijašnjim studijama provedenim na trudnicama i majkama koje doje (51) te kod majki koje su nedavno rodile (52). Iako smo utvrdili dobru divergentnu valjanost, potrebna su dodatna istraživanja u peripartalnom razdoblju kako bi se potvrdili ovi rezultati te kako bi se interpretirala konvergentna valjanost Y-BOCS-a.

Ovo istraživanje ima i neka ograničenja. Istraživanje je bilo jednokratno korelacijsko tako da nismo mogli pratiti moguće razlike u faktorskoj strukturi u različitim vremenskim točkama tijekom trudnoće ili razdoblja poslije porođaja niti smo mogli ispitati test-retest pouzdanost. Budući da na hrvatskom jeziku nedostaju drugi instrumenti za simptome OKP-a, nismo uspjeli testirati konvergentnu valjanost Y-BOCS-a. Unatoč tome što je uzorak regrutiran u prenatalnoj klinici gradske bolnice, uzorak je bio donekle homogen, s većinom udanim i visokoobrazovanim sudionicama prosječnog socioekonomskog statusa. Neka su istraživanja pokazala više razine simptoma OKP-a kod sudionika s nižim obiteljskim prihodom (53) pa bi se moglo dogoditi da na reprezentativnijem uzorku budu više razine simptoma OKP-a. Treba naglasiti da je uzorak bio neklinički pa je moguće da bi se u kliničkom uzorku trudnica s OKP-om dobila nešto drugačija faktorska struktura. Stoga bi buduća istraživanja trebala istražiti faktorsku strukturu u kliničkim uzorcima tijekom peripartuma. Usporedba između kliničkih i nekliničkih uzoraka pomogla bi u određivanju osjetljivosti Y-BOCS ljestvice za njihovo razlikovanje.

ZAKLJUČAK

Yale-Brownova ljestvica opsesivno-kompulzivnih simptoma (Y-BOCS) valjana je i pouzdana mjera simptoma OKP-a u trudnoći. Ovo

anxiety and pregnancy-specific anxiety, demonstrating excellent divergent validity. In this study, correlations were higher than in previous studies on pregnant women and mothers who breastfeed (51), as well as in postpartum women (52). Although we found good divergent validity, further research is necessary in the peripartum period in order to confirm such findings, and also to interpret the convergent validity of the Y-BOCS.

There are some limitations to this study as well. This was a one-time correlational study, therefore we could not monitor for possible differences in the factor structure at different time points during pregnancy or in the postpartum period, nor could we examine test-retest reliability. As there is a lack of other instruments to measure OCD symptoms in the Croatian language, we were unable to test the convergent validity of the Y-BOCS. Despite the sample being recruited at a prenatal clinic of a city hospital, the sample was somewhat homogeneous, with the majority of participants being married, highly educated and of an average socioeconomic status. Some studies showed higher levels of OCD symptoms in participants with lower family income (53), therefore, it may be that higher levels of OCD symptoms would be obtained in a more representative sample. It should be noted that the sample was non-clinical, so it is possible that a somewhat different factor structure would be yielded in a clinical sample of pregnant women with OCD. Future studies should, therefore, examine the factor structure in clinical samples during the peripartum period. A comparison between clinical and non-clinical samples would help determine the sensitivity of the Y-BOCS in order to differentiate between them.

CONCLUSION

In conclusion, the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) is a valid and reliable measure of OCD symptoms during pregnancy. This is the first validation of this scale on a

je prva validacija ove ljestvice na hrvatskom uzorku i tijekom trudnoće. Na ovom je uzorku struktura ljestvice pokazala hijerarhijski model s generalnim faktorom višeg reda i dva faktora prvog reda - opsesijama i kompulzijama. S obzirom na to da je u drugim istraživanjima čak 4 % trudnica iskazalo povišene simptome OKP-a (4,5), stopu prevalencije OKP-a tek treba utvrditi u hrvatskom uzorku. Y-BOCS može biti koristan alat u probiru klinički relevantnih simptoma OKP-a tijekom peripartuma, a i drugih razdoblja s ciljem pravovremenog liječenja.

Croatian sample and during pregnancy. In this sample, the structure of the scale showed a hierarchical model with a general higher-order factor and two first-order factors - obsessions and compulsions. Given the substantial proportion of 4% of pregnant women reporting increased OCD symptoms in other studies (4, 5), the prevalence rate of OCD is still yet to be determined in a Croatian sample. The Y-BOCS can be a useful tool in screening for clinically relevant OCD symptoms both during the peripartum and in other periods, with the aim of providing timely treatment.

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Nove mogućnosti u liječenju terapijski rezistentne depresije

/ Novel Therapeutic Strategies for Treatment-Resistant Depression

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Terapijski rezistentna depresija (TRD) je nedostatak zadovoljavajućeg odgovora na standardnu antidepresivnu terapiju, izazov je za pacijente i kliničare, te postoji stalna potreba za novim terapijskim pristupima. Prikazujemo terapijske opcije za TRD fokusirajući se na personalizirani pristup liječenju. Opisujemo novu klasu antidepresiva, kao što su esketamin i kombinacija dekstrometorfan-bupropion, ističući njihovu učinkovitost u ciljanju glutamatnog sustava mozga. gepiron ER, ciljani lijek za serotonin 1A receptore, također obećavajući u tretmanu za pacijente s TRD-om. Uz farmakološke terapije, neuromodulacijske metode poput elektrokonvulzivne terapije (EKT), terapija svjetlom i transkranijske magnetske stimulacije (TMS), pokazale su pozitivne rezultate u tretiranju TRD-a. Nadalje, hormonska terapija, uključujući primjenu trijodtironina u kombinaciji s drugim lijekovima, te egzogeni oksitocin također mogu biti terapijske opcije. Pregledom dostupne literature vidljiva je potreba za daljnjim istraživanjima ovoga područja. Ovaj pregled donosi nova saznanja u području liječenja terapijski rezistentne depresije uključujući novu klasu lijekova, neuromodulacijske tehnike, hormonsku terapiju i druge tvari, kao obećavajuće strategije u borbi protiv TRD-a.

/ Treatment-resistant depression (TRD) is a lack of satisfactory response to standard antidepressant therapy, and poses a formidable challenge for both patients and clinicians, underscoring the constant need for innovative therapeutic strategies. This article delves into the therapeutic modalities for TRD, with a focal point on personalized treatment paradigms. We will describe a new cohort of antidepressants, such as esketamine and the dextromethorphan-bupropion combination, spotlighting their efficacy in targeting the cerebral glutamate system. Gepirone ER, a selective medication for serotonin 1A receptors, emerges as a promising therapeutic avenue for patients with TRD. In addition to pharmacological therapy, neuromodulation methodologies such as electroconvulsive therapy (ECT), light therapy and transcranial magnetic stimulation (TMS), have yielded promising results in the treatment of TRD. Furthermore, hormone therapy, including the utilization of triiodothyronine (T3) in tandem with other pharmacotherapies, alongside exogenous oxytocin, emerge as prospective therapeutic options. Upon reviewing the available literature, it is evident that continued research is required in this domain. This review underscores new insights into the treatment landscape of treatment-resistant depression, including a new class of medications, neuromodulation techniques, hormone therapy and other substances, as promising modalities in the battle against TRD.

UVOD

Terapijski rezistentna depresija (TRD) je složeno stanje u kliničkoj praksi i istraživanjima, karakterizirano nedostatkom zadovoljavajućeg odgovora na konvencionalne terapije za depresiju (1). Definiranje TRD-a je izazov zbog nedostatka striktnih kriterija za mjerenje klinički značajnih poboljšanja. Međunarodna klasifikacija bolesti, MKB-11, prepoznaje potrebu za jasnim razgraničenjem između TRD-a i depresije koja je podložna uspješnom liječenju (1,2).

U najnovijoj verziji MKB-11 depresivna epizoda se opisuje kao prisutnost najmanje pet od deset simptoma, koji se manifestiraju većinu vremena u danu, gotovo svaki dan tijekom najmanje dva tjedna. Minimalno jedan od tih simptoma mora biti depresivno raspoloženje ili značajan gubitak interesa i užitka u aktivnostima. Za postavljanje dijagnoze poremećaj raspoloženja mora značajno utjecati na oštećenje funkcioniranja, uz isključenje drugih mogućih uzroka bolesti. U ovoj najnovijoj verziji popis tih deset simptoma uključuje A- i B-simptome, te dodatno psihomotoričku usporenost ili nemir. Naveden je i simptom očaja (engl. *hopelessness*), koji se ne navodi u Dijagnostičkom i statističkom priručniku za mentalne poremećaje, DSM-5. U prethodnoj verziji, MKB-10 klasifikaciji, za dijagnozu je bilo potrebno minimalno četiri simptoma. Značajna razlika između klasifikacija MKB-11 i DSM-5 je u tumačenju žalovanja (3).

INTRODUCTION

Treatment-resistant depression (TRD) is a complex condition both in clinical practice and in research, characterized by a lack of satisfactory response to conventional depression therapies (1). Defining TRD poses a challenge due to the absence of strict criteria for measuring clinically significant improvements. The International Classification of Diseases, 11th Revision (ICD-11), acknowledges the need for a clear differentiation between TRD and depression amenable to successful treatment (1, 2).

In the latest version of ICD-11, a depressive episode is described as the presence of at least five out of a list of ten symptoms, which must occur most of the day, nearly every day, for at least two weeks. At least one of these symptoms must be either depressed mood or a markedly diminished interest and pleasure in activities. In order to set a diagnosis, the mood disorder must have a significant effect by impairing functioning, with the exclusion of other possible causes of disease. In this latest version, the list of the ten symptoms includes A- and B-symptoms, and additionally, psychomotor slowing or agitation. It also includes the symptom of hopelessness, which is not present in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5). In the previous version, ICD-10 classification required a minimum of four symptoms for diagnosis. A significant difference between ICD-11 and DSM-5 classifications lies in the interpretation of grief (3).

Prihvaćena definicija TRD-a obuhvaća situaciju u kojoj pacijent ne postiže zadovoljavajući odgovor nakon barem dvije uzastopne terapije različitim klasama antidepresiva u optimalnoj dozi i trajanju između 6 i 12 tjedana. Precizno definiranje kriterija i načina mjerenja terapijske rezistencije ključno je za dublje razumijevanje i efikasno upravljanje ovim specifičnim aspektom depresije (4).

Identificirano je pet modela stupnjevanja terapijske rezistencije, u kojem svaki model određuje minimalnu dozu i trajanje terapije, uz kompleksnije modalitete liječenja proporcionalno terapijskoj rezistenciji. Važno je napomenuti da se modeli stupnjevanja terapijske rezistencije razlikuju od tradicionalnog pristupa procjeni ozbiljnosti bolesti. U ovom kontekstu stupanj ne označava napredovanje bolesti od početnih simptoma do kroničnog stanja, već svaka razina označava korak u algoritmu liječenja depresije s povećanom stopom terapijske rezistencije (5).

U području liječenja depresije postoje različiti modeli koji stupnjuju terapijske strategije ovisno o težini i otpornosti depresije na uobičajene tretmane. Jedan od prvih takvih modela je *Thase i Rush Staging Model* (6). Ovaj model preporučuje početak terapije s antidepresivima prvog izbora, kao što su SIPPS (selektivni inhibitori ponovne pohrane serotonina) i/ili SNRI (inhibitori ponovne pohrane serotonina i noradrenalina). Ako ovi lijekovi nisu učinkoviti, sljedeći korak može biti uporaba starijih antidepresiva poput TCA (triciklički antidepresivi) ili MAOI (inhibitori monoaminooksidaze), uz optimizaciju doze ili dodatak drugih terapija. Tek kada se ove opcije iscrpe, razmatraju se neurostimulacijske strategije poput elektrokonvulzivne terapije (EKT) (1).

Kasnije razvijeni modeli, poput *Maudsley Staging Method* (MSM), dodatno pružaju strukturirani pristup (6,7). MSM koristi sustav bodovanja kako bi kvantificirao otpornost depresije na liječenje. Ovaj model analizira povijest liječenja uzimajući u obzir faktore poput broja

The accepted definition of TRD encompasses a situation where a patient does not achieve a satisfactory response after at least two consecutive treatments with different classes of antidepressants at optimal doses and in durations between 6 and 12 weeks. A precise definition of the criteria and the methods for measuring treatment resistance are crucial for a deeper understanding and effective management of this specific aspect of depression (4).

Five models of staging treatment resistance have been identified, with each model determining the minimum dose and duration of treatment, along with more complex treatment modalities proportional to the treatment resistance. It is important to note that the models of staging treatment resistance differ from the traditional approach to assessing disease severity. In this context, a stage does not denote disease progression from initial symptoms to a chronic state, but each level signifies a step in the algorithm of depression treatment with an increased rate of treatment resistance (5).

In the field of depression treatment, various models exist that stage treatment strategies depending on the severity and resistance of depression to common treatments. One of the first such models is the Thase and Rush Staging Model (6). This model recommends initiating therapy with first-line antidepressants, such as SSRIs (selective serotonin reuptake inhibitors) and/or SNRIs (serotonin-norepinephrine reuptake inhibitors). If these medications are not effective, the next step may involve the use of older antidepressants such as TCAs (tricyclic antidepressants) or MAO-Is (monoamino oxidase inhibitors), with dose optimization or addition of other treatments. Only when these options are exhausted are neurostimulation strategies like electroconvulsive therapy (ECT) considered (1).

Subsequently developed models, such as the Maudsley Staging Method (MSM), provide an additional structured approach (6, 7). The MSM utilizes a scoring system in order to quantify the resistance of depression to treatment. This model

neuspjelih tretmana, trajanje trenutne epizode depresije i težinu simptoma. Njegova uspješnost potvrđena je u predviđanju ishoda depresije koja je otporna na standardne terapije.

Sada, naziv novog modela je *Deconstructing Depression*, a nudi pristup posebno prilagođen pacijentima s perzistirajućim simptomima depresije, a koji nisu imali uspjeha s tradicionalnim antidepresivima te ispunjavaju kriterije za TRD (7). Ovaj model se temelji na personaliziranom biopsihosocijalnom pristupu liječenju. Ključna strategija ovog pristupa je istražiti trenutne okidače depresije kod pacijenta, identificirati čimbenike koji pridonose depresiji i onemogućuju postizanje remisije bolesti (1). Terapija se zatim prilagođava prema ovim specifičnim faktorima s posebnom pažnjom na svaki od njih, kako bi se povećala učinkovitost terapije. Ovaj holistički pristup naglašava važnost razumijevanja pacijentove jedinstvene situacije i potreba kako bi se pronašao najučinkovitiji put prema oporavku od depresije (4).

Postoje tri osnovne strategije koje se koriste u liječenju TRD-a (tablica 1). Studije su pokazale da se bolji postotak odgovora, čak do 70 %, može postići zamjenom antidepresiva i prelaskom na alternativnu klasu, kao što su antidepresivi druge generacije ili SIPPS/SNRI lijekovi koji djeluju drugačije. U konačnici, odabir strategije ovisi o individualnim karakteristikama pacijenta i njihovoj toleranciji na nuspojave. Nasuprot zamjeni antidepresiva, strategije augmentacije ili kombiniranja mogu biti učinkovitija i podnošljivija terapijska opcija u liječenju TRD-a (5-7).

Cilj ovog rada je prikazati nove terapijske strategije za liječenje terapijski rezistentne depresije. Ovaj rad je narativni pregledni rad, u kojem se je pregledavana literatura pomoću ključnih riječi kao što su "terapijski rezistentna depresija", "novi tretmani" i "strategije liječenja". Literatura je pregledavana u bazama podataka *PubMed, Cochrane Library* i *PsycINFO*. Uključni kriteriji za reference bile su studije objavljene u posljednjih deset godina koje su istraživale učinkovitost novih terapija za TRD, uz naglasak na kliničke pokuse i meta-analize.

analyzes treatment history, taking into account factors such as the number of failed treatments, duration of the current depressive episode, and severity of symptoms. Its success has been confirmed in predicting outcomes of depression resistant to standard treatments.

These days, the name of the new model is Deconstructing Depression, offering an approach specifically tailored to patients with persistent depressive symptoms who did not respond to traditional antidepressants and meet the TRD criteria (7). This model is based on a personalized biopsychosocial approach to treatment. The key strategy of this approach is to explore the current triggers of depression in the patient, and to identify the factors that contribute to depression and hinder remission (1). Treatment is then tailored according to these specific factors, paying particular attention to each of them to enhance treatment effectiveness. This holistic approach emphasizes the importance of understanding the patient's unique situation and needs in order to find the most effective path to recovery from depression (4).

Three main strategies are used in the treatment of TRD (Table 1). Studies have shown that a better response rate, up to 70%, can be achieved by switching antidepressants and transitioning to an alternative class, such as second-generation antidepressants or SSRI/SNRI medications with different mechanisms of action. Ultimately, the choice of strategy depends on the individual characteristics of the patient and their tolerance to side effects. In contrast to switching antidepressants, augmentation or combination strategies may be a more effective and better-tolerated therapeutic option in the treatment of TRD (5-7).

The aim of this paper is to present new therapeutic strategies for the treatment of treatment-resistant depression (TRD). This is a narrative review article, for which literature was examined using keywords such as "treatment-resistant depression", "new treatments" and "treatment strategies". The literature was searched in databases including PubMed, Cochrane Library and

TABLICA 1. Farmakološke strategije u liječenju terapijski rezistentne depresije
TABLE 1. Pharmacological strategies in the treatment of treatment-resistant depression

Augmentacija / Augmentation	Ova strategija uključuje primjenu dodatnog lijeka postojećem terapijskom režimu koji nije samostalno antidepresiv/ This strategy involves adding an additional medication to the existing therapeutic regimen that is not a standalone antidepressant.	Opcije za augmentaciju: Atipične antipsihotike: Poput aripiprazola, kvetiapina ili olanzapina. Dopaminergičke spojeve: Kao što je bupropion. Litij: Ima dokaze o učinkovitosti u TRD-u. Hormon štitnjače T3: Ponekad se koristi kao dodatak antidepresivima /Options for augmentation: Atypical Antipsychotics: Such as aripiprazole, quetiapine, or olanzapine. Dopaminergic Compounds: Such as bupropion. Lithium: Has evidence of efficacy in TRD. Thyroid Hormone T3: Sometimes used as an adjunct to antidepressants.
Kombiniranje antidepresiva / Combining Antidepressants	Ova strategija podrazumijeva dodavanje drugog lijeka uz već postojeći antidepresiv kako bi se pojačala njegova učinkovitost. / This strategy involves adding another medication to the existing antidepressant in order to enhance its effectiveness.	Različiti antidepresivi djeluju na različite mehanizme, pa kombinacija može biti korisna u postizanju boljeg terapijskog odgovora Primjer: 1. Početni režim: Pacijent uzima SIPPS (npr. fluoksetin) već neko vrijeme, ali simptomi depresije i dalje perzistiraju. 2. Kombiniranje: Liječnik odlučuje dodati drugi antidepresiv koji djeluje na drugačiji neurotransmiterski sustav. Na primjer: Bupropion: Bupropion je atipični antidepresiv koji djeluje na dopamin i noradrenalin. Dodavanje bupropiona uz fluoksetin može pojačati učinak i poboljšati simptome depresije. Venlafaksin: Venlafaksin je serotonin-noradrenalin reuptake inhibitor (SNRI) koji također može biti koristan u kombinaciji s SIPPS-om. 3.Praćenje: Pacijent se pažljivo prati kako bi se procijenio odgovor na kombiniranu terapiju. Ako dođe do poboljšanja simptoma, liječnik može prilagoditi doze ili trajanje terapije. / Various antidepressants act on different mechanisms, so combining them can be useful in achieving a better therapeutic response. Example: 1.Initial Regimen: The patient has been taking an SSRI (such as fluoxetine) for some time, but depressive symptoms persist. 2. Combining: The physician decides to add another antidepressant that acts on a different neurotransmitter system. For example: Bupropion: Bupropion is an atypical antidepressant that acts on dopamine and norepinephrine. Adding bupropion to fluoxetine can enhance its effects and improve depressive symptoms. Venlafaxine: Venlafaxine is a serotonin-norepinephrine reuptake inhibitor (SNRI) that can also be useful in combination with an SSRI. 3. Monitoring: The patient is closely monitored to assess the response to combination therapy. If there is an improvement in symptoms, the physician may adjust the doses or duration of the therapy.
Zamjena antidepresiva/Antidepressant switch	Ova strategija znači prestanak uzimanja neučinkovitog antidepresiva i prelazak na primjenu novog antidepresiva iz iste ili različite klase. / This strategy involves discontinuing an ineffective antidepressant and switching to a new antidepressant from the same or different class.	Zamjena antidepresiva i prelazak na alternativnu klasu, kao što su antidepresivi druge generacije ili SIPPS/SNRI lijekovi koji djeluju drugačije. Primjer: 1.Početni režim: Pacijent uzima fluoksetin (SIPPS) već nekoliko mjeseci, ali simptomi depresije i dalje perzistiraju. 2.Zamjena antidepresiva: Liječnik odlučuje prekinuti primjenu fluoksetina i započeti novi antidepresiv iz iste ili različite klase. Primjer zamjene: Fluoksetin → Sertralin: Sertralin je također SIPPS, ali može imati drugačiji profil djelovanja i bolji terapijski odgovor kod određenih pacijenata. Fluoksetin → Bupropion: Bupropion je atipični antidepresiv koji djeluje na dopamin i noradrenalin. Zamjena fluoksetina bupropionom može biti korisna ako pacijent ne reagira na SIPPS. Fluoksetin → Mirtazapin: Mirtazapin je tetraciklički antidepresiv s drugačijim mehanizmom djelovanja. Može se koristiti kao alternativa. 3.Praćenje: Pacijent se pažljivo prati nakon zamjene antidepresiva. Liječnik prilagođava doze i prati nuspojave te učinkovitost novog lijeka. / Switching antidepressants may involve transitioning to an alternative class, such as second-generation antidepressants or SSRI/SNRI medications that work differently. Example: 1. Initial Regimen: The patient has been taking fluoxetine (SSRI) for several months, but depressive symptoms persist. 2. Antidepressant Switch: The physician decides to discontinue fluoxetine and start a new antidepressant from the same or different class. Examples of switches: Fluoxetine → Sertraline: Sertraline is also an SSRI, but it may have a different action profile and better therapeutic response in certain patients. Fluoxetine → Bupropion: Bupropion is an atypical antidepressant that acts on dopamine and norepinephrine. Switching from fluoxetine to bupropion may be beneficial if the patient does not respond to an SSRI. Fluoxetine → Mirtazapine: Mirtazapine is a tetracyclic antidepressant with a different mechanism of action. It can be used as an alternative. 3. Monitoring: The patient is closely monitored after the antidepressant switch. The physician adjusts doses, monitors side effects, and evaluates the effectiveness of the new medication.

NOVI ANTIDEPRESIVI

Esketamin, S enantiomer ketamina, unazad dvije godine predstavlja jedan je od najrevolucionarnijih antidepresiva nudeći potpuno novi pristup u terapiji depresije (8). Ketamin, koji je inače anestetik, privukao je veliku pažnju zbog brzog ublažavanja simptoma depresije. Esketamin se primjenjuje intranazalno što je praktično u terapiji (9). Ovaj inovativni lijek djeluje na glutamatni sustav mozga, što je drugačije od uobičajenih antidepresiva koji djeluju na serotonin (10). Osim toga esketamin je kao i neki drugi antidepresivi pokazao sposobnost povećanja razine moždanog neurotrofnog čimbenika (engl. *Brain-Derived Neurotrophic Factor,* BDNF). BDNF je protein koji ima ključnu ulogu u rastu, preživljavanju i diferencijaciji neurona, te se smatra važnim za neuroplastičnost i oporavak mozga. Povećanje BDNF-a povezano je s poboljšanjem raspoloženja i smanjenjem simptoma depresije, što dodatno potvrđuje terapijski potencijal esketamina. Esketamin je odobren u Europi i Hrvatskoj za liječenje teške depresije koja nije odgovarala na prethodne terapije (11).

Dekstrometorfan-Bupropion je revolucionarni lijek za veliki depresivni poremećaj koji je kombinacija dekstrometorfana, antitusika, s bupropionom, antidepresivom. Dekstrometorfan modulira NMDA receptore povezane s depresijom, dok bupropion djeluje na noradrenalinske i dopaminske transportere (12). Ova dvostruka terapija cilja na više puteva depresije, što potencijalno povećava učinkovitost terapije i smanjuje nuspojave. Studije također pokazuju kako Dekstrometorfan-Bupropion može biti posebno učinkovit kod pacijenata s terapijski rezistentnom depresijom (13). Upravo ta multicentričnost djelovanja ovoga lijeka na različite receptore daje nove mogućnosti pacijentima s TRD-om koji nisu odgovorili na standardne antidepresive ili su imali ograničeno poboljšanje. Trenutno nije odobren u Hrvatskoj (14).

U listopadu 2023. FDA je odobrila Gepiron ER kao prvi izbor za liječenje velikog depresivnog

PsycINFO. The inclusion criteria for references were studies published in the last ten years that investigated the efficacy of new therapies for TRD, with an emphasis on clinical trials and meta-analyses.

NEW ANTIDEPRESSANTS

Over the past two years, esketamine, the S-enantiomer of ketamine, has emerged as one of the most revolutionary antidepressants, offering a completely new approach to depression treatment (8). Ketamine, originally an anesthetic, has garnered significant attention due to its rapid alleviation of depression symptoms. Esketamine is administered intranasally, which is convenient during treatment (9). This innovative medication affects the brain's glutamate system, which is different from conventional antidepressants that target serotonin (10). Additionally, just as some other antidepressants, esketamine has shown the ability to increase the levels of Brain-Derived Neurotrophic Factor (BDNF). BDNF is a protein that plays a crucial role in the growth, survival and differentiation of neurons, and is considered important for neuroplasticity and brain recovery. An increase in BDNF is associated with improved mood and reduced depression symptoms, further confirming esketamine's therapeutic potential. Esketamine has been approved in Europe and Croatia for the treatment of severe depression that has not responded to prior treatments (11).

Dextromethorphan-Bupropion is a revolutionary drug used for major depressive disorder that combines dextromethorphan, an antitussive, with bupropion, an antidepressant. Dextromethorphan modulates NMDA receptors associated with depression, while bupropion acts on norepinephrine and dopamine transporters (12). This dual therapy targets multiple pathways of depression, potentially enhancing treatment efficacy and reducing side effects. Studies also suggest that Dextromethorphan-Bupropion can be particularly effective in patients with treatment-resistant depression (TRD) (13). It is precisely this

poremećaja (15). Gepiron ER cilja serotonin 1A receptor u mozgu, što dovodi do regulacije serotonina i poticanja oslobađanja dopamina, ključne kemikalije za prijenos signala. Lijek se uzima jednom na dan, s kontroliranim otpuštanjem tijekom 24 sata, što omogućava bolju terapijsku suradnju s pacijentima. Njegov mehanizam djelovanja na multiple neurotransmiterske sustave i smanjeni potencijal za nuspojave poput seksualne disfunkcije i povećanja tjelesne težine čine ga privlačnom opcijom za pacijente s TRD-om. Međutim, potrebno je pratiti i lokalne regulative, budući da Gepiron ER još uvijek nije odobren u Hrvatskoj (16).

HORMONSKA NADOMJESNA TERAPIJA U SVRHU LIJEČENJA TRD-a

U skladu s recentnom literaturom su istraživanja Dwyera i suradnika u 2020. godini koji su ispitivali primjenu hormonske terapije u liječenju depresije, premda je evidentiran nedostatak uvjerljivih dokaza u tom području. U njihovom istraživanju istaknute su neke učinkovite terapijske strategije koje uključuju primjenu T3 (trijodtironina) u kombinaciji s TCA (triciklički antidepresivi) za ubrzanje i poboljšanje terapijskog učinka. Nadalje, pokazano je da primjena T3 u kombinaciji sa SIPPS-ima (selektivni inhibitori ponovne pohrane serotonina i noradrenalina) može biti korisna u terapiji rezistentne depresije uz uvjete da pacijent ima snižene razine tih hormona (17,18).

Dodavanje malih koncentracija levotiroksina u liječenju depresije može biti korisno u određenim slučajevima, posebno kod pacijenata s depresijom koji imaju subkliničku ili blagu hipotireozu. Levotiroksin je sintetički oblik tiroksina (T4), hormona štitnjače koji se koristi za nadomjesnu terapiju kod pacijenata s hipotireozom. Nepravilno doziranje može uzrokovati nuspojave poput psihomotornog nemira, anksioznosti, srčanih problema i poremećaja

multi-targeted action on various receptors that offers new possibilities for TRD patients who did not respond to standard antidepressants or who experienced limited improvement. It is currently not approved in Croatia (14).

In October 2023, the FDA approved Gepirone ER as first-line treatment for major depressive disorder (15). Gepirone ER targets the serotonin 1A receptor in the brain, leading to the regulation of serotonin and stimulation of dopamine release, a key signaling chemical. The medication is taken once a day, with controlled release over 24 hours, allowing for better therapeutic compliance with patients. Its mechanism of action on multiple neurotransmitter systems and reduced potential for side effects such as sexual dysfunction and weight gain make it an appealing option for patients with TRD. However, local regulations should be monitored, as Gepirone ER has not yet been approved in Croatia (16).

HORMONE REPLACEMENT THERAPY FOR THE TREATMENT OF TRD

The studies conducted in 2020 by Dwyer et al. are consistent with the recent literature, exploring the use of hormone therapy in the treatment of depression, although there is a noted lack of compelling evidence in this area. Their study highlighted some effective therapeutic strategies that include the use of T3 (triiodothyronine) in combination with TCAs (tricyclic antidepressants) to accelerate and improve treatment effects. Furthermore, it has been shown that the use of T3 in combination with SNRIs (serotonin-norepinephrine reuptake inhibitors) may be beneficial in the treatment of resistant depression, provided that the patient has reduced levels of these hormones (17, 18).

Adding small concentrations of levothyroxine in the treatment of depression may be beneficial in certain cases, particularly in patients with depression who have subclinical or mild hypothyroid-

spavanja (18). Levotiroksin može ulaziti u interakcije s drugim lijekovima, osobito ako pacijent uzima druge lijekove za depresiju. Ove interakcije mogu povećati rizik od nuspojava ili smanjiti učinkovitost jednog od lijekova zbog čega je u ovom tretmanu obvezna dobra suradnja i praćenje od endokrinologa (19).

Egzogeni oksitocin, peptidni hormon i neurotransmiter, pokazuje značajne potencijale u terapiji depresije zbog svojih neurobioloških i socioemocionalnih učinaka. Ova sintetička verzija oksitocina koristi se u terapijske svrhe kako bi se potaknuli određeni biološki učinci (20). U kontekstu farmakodinamike, egzogeni oksitocin može se primijeniti intranazalno, što omogućuje brzu apsorpciju u krvotok, gdje se zatim distribuira po tijelu. Kada egzogeni oksitocin dospije do svojih receptora u mozgu i drugim tkivima, aktivira biološke procese koji su povezani sa socijalnim povezivanjem, emocionalnom regulacijom i smanjenjem stresa. Oksitocinski receptori (OTR) su G-protein spregnuti receptori koji se nalaze u različitim tkivima, poput mozga, maternice i mliječnih žlijezda. Oksitocin se također brzo razgrađuje s pomoću enzima, što omogućuje njegovo učinkovito izlučivanje putem bubrega i jetre. Terapija oksitocinom može olakšati osjećaj izolacije i poboljšati emocionalnu bliskost s drugima, dok njegova sposobnost moduliranja emocionalnih odgovora može smanjiti stres i potaknuti osjećaj zadovoljstva, što je od iznimne važnosti u tretmanu depresije (21). Iako su istraživanja često fokusirana na razlike u primjeni oksitocina kod žena i muškaraca, važno je napomenuti da se oksitocin istražuje kao terapijski agens za depresiju kod oba spola.

Značajno je istraživanje mifepristona (antagonista glukokortikoidnog receptora) u terapiji depresivnog poremećaja s psihotičnim elementima. Kod postmenopauzalnih žena s depresivnim poremećajem estrogenska nadomjesna terapija ili kombinirana nadomjesna hormonska terapija pokazale su se manje djelotvornima kao samostalne terapije (17). Ipak, postoji

ism. Levothyroxine is a synthetic form of thyroxine (T4), a thyroid hormone used for replacement therapy in patients with hypothyroidism. Improper dosing can lead to side effects such as psychomotor agitation, anxiety, heart problems and sleep disturbances (18). Levothyroxine may interact with other medications, especially if the patient is taking other antidepressants. These interactions can increase the risk of side effects or reduce the effectiveness of one of the medications, emphasizing the need for good collaboration and monitoring by an endocrinologist during this treatment (19).

Exogenous oxytocin, a peptide hormone and neurotransmitter, shows significant potential in the treatment of depression due to its neurobiological and socioemotional effects. This synthetic version of oxytocin is used for therapeutic purposes in order to stimulate specific biological effects (20). In terms of pharmacodynamics, exogenous oxytocin can be administered intranasally, allowing for rapid absorption into the bloodstream, where it is then distributed throughout the body. When exogenous oxytocin reaches its receptors in the brain and other tissues, it activates biological processes associated with social bonding, emotional regulation, and stress reduction. Oxytocin receptors (OTR) are G-protein-coupled receptors found in various tissues, such as the brain, uterus, and mammary glands. Oxytocin also degrades rapidly with the help of enzymes, allowing for its efficient elimination through the kidneys and liver. Oxytocin therapy can ease the feeling of isolation and improve emotional closeness with others, while its ability to modulate emotional responses may reduce stress and promote a sense of pleasure, which is crucial in the treatment of depression (21). Although research often focuses on gender differences in oxytocin administration, it is important to note that oxytocin is being explored as a therapeutic agent for depression in both genders.

Significant research was conducted on mifepristone (a glucocorticoid receptor antagonist) in the treatment of depressive disorder with psychotic features. In the context of postmenopausal wom-

nekoliko studija koje upućuju na potencijalnu korist ovih terapija kao dodatne potpore uz primjenu SIPPS-a u terapiji depresije u gerijatrijskoj populaciji.

Kod muškaraca s depresijom uzrokovanom sekundarnim hipogonadizmom, istraživanja su ukazala na pozitivan utjecaj testosteronske nadomjesne terapije na raspoloženje i opću dobrobit (1,4,17). Napredak u razumijevanju uloge hormona u neurobiologiji depresije pruža temelj za razvoj novih terapijskih pristupa. Ovo uključuje istraživanje mogućnosti kombiniranja hormonske terapije s drugim psihoterapijskim pristupima ili novim farmakološkim agensima kako bi se poboljšale učinkovitost i tolerancija terapije.

OSTALI PSIHOTROPNI LIJEKOVI

U istraživanjima faza I-III farmakoloških pristupa za terapiju rezistentne depresije otkriveno je nekoliko obećavajućih terapijskih opcija. Među njima su selektivne metode koje su pokazale snažne dokaze u poboljšanju stanja TRD-a uključujući inhibiciju glutamatergične neurotransmisije putem antagonista NMDA i AMPA receptora te inhibiciju metabotropnog glutamatnog receptora 5 (mGlu5). Ovi pristupi ciljaju na ključne mehanizme povezane s patofiziologijom depresije (22).

Metabotropni glutamatni receptor 5 (mGlu5), koji je G-proteinom povezan receptor, ima ključnu ulogu u regulaciji glutamatne neurotransmisije (8). Basimglurant, selektivni negativni alosterni modulator mGlu5 receptora pokazao je obećavajuće rezultate u liječenju TRD-a. Iako točan mehanizam djelovanja ovih antagonista na mGlu5 receptore još nije potpuno razjašnjen, smatra se da moduliraju glutamatnu neurotransmisiju, što je ključno za razumijevanje depresije.

Druga potencijalno učinkovita terapijska opcija za TRD je modulacija opioidnog sustava putem antagonista κ receptora. Buprenorfin, opioidni

en with depressive disorder, estrogen replacement therapy or combined hormone replacement therapy have been less effective as standalone treatments (17). Nevertheless, there are several studies suggesting the potential benefit of these therapies as additional support along with the use of SSRIS in the treatment of depression in the geriatric population.

In the context of men with depression caused by secondary hypogonadism, studies have indicated a positive impact of testosterone replacement therapy on their mood and overall well-being (1, 4, 17). Furthermore, advancements in understanding the role of hormones in the neurobiology of depression provide a foundation for the development of new therapeutic approaches. This includes exploring the possibility of combining hormone therapy with other psychotherapeutic approaches or new pharmacological agents in order to improve the effectiveness and tolerance of therapy.

OTHER PSYCHOTROPIC DRUGS

In phase I-III studies of pharmacological approaches to treatment-resistant depression (TRD), several promising therapeutic options have been discovered. Among them are selective methods that have yielded strong evidence in improving TRD conditions, including the inhibition of glutamatergic neurotransmission through NMDA and AMPA receptor antagonists and the inhibition of metabotropic glutamate receptor 5 (mGlu5). These approaches target the key mechanisms associated with the pathophysiology of depression (22).

Metabotropic glutamate receptor 5 (mGlu5), a G-protein-coupled receptor, plays a crucial role in regulating glutamatergic neurotransmission (8). Basimglurant, a selective negative allosteric modulator of mGlu5 receptors, has yielded promising results in the treatment of TRD. Although the exact mechanism of action of these antagonists on mGlu5 receptors is not yet fully understood, it is believed they modulate glutamatergic neuro-

lijek koji je kombiniran s drugim spojevima za još jače djelovanje na μ i κ opioidne receptore, pokazuje umjereni antidepresivni učinak bez nuspojava povezanih s opijatima. Glavne mete djelovanja ovih spojeva su postsinaptički inhibicijski μ receptori i presinaptički κ receptori (22).

Mehanizam djelovanja psihodeličnih spojeva, poput psilocibina i ayahuasce, pretpostavlja se da je putem serotonergičkog/monoaminergičkog sustava. Psilocibin, prirodni spoj iz halucinogenih gljiva, metabolizira se u tijelu u psilocin, koji je djelomični agonist serotoninskih receptora 5-HT2 A, 5-HT2C, 5-HT1 A i 5-HT1B te inhibitor serotoninskih transportera. Tvar je bila relativno dobro podnošljiva, unatoč dobro poznatim nuspojavama koje ovise o dozi (senzorske iluzije, halucinacije, mučnina, povraćanje i glavobolja). Psilocibin je pokazao učinkovitost u liječenju poremećaja raspoloženja. U kombinaciji s precizno strukturiranom psihoterapijom, psilocibin se pokazao učinkovitim u tretiranju TRD-a (23).

Povećane razine C-reaktivnog proteina i citokina povezane su s TRD-om ukazujući na ulogu upale u ovom poremećaju. Inhibitori ciklooksigenaze-2 (COX-2) prvotno su istraživani kao potencijalni protuupalni tretmani za TRD. Ovi inhibitori djeluju blokirajući proizvodnju prostaglandina, molekula koje su povišene u krvi pacijenata s TRD-om pa njihova primjena može imati potencijalnu ulogu u liječenju TRD-a (1).

Trenutna istraživanja vezana uz primjenu rimfapicina (antibiotik iz skupine rifamicina) za terapiju rezistentne depresije su u ranim fazama. Doze rimfapicina za TRD se najčešće propisuju individualno, uzimajući u obzir pacijentove karakteristike, toleranciju lijeka i interakcije s drugim lijekovima. Istraživanja su pokazala da rimfapicin može imati pozitivan učinak na depresiju putem svoje sposobnosti da utječe na sustav CYP450 enzima. Iako je povećanje metabolizma antidepresiva obično povezano sa smanjenjem njihovih koncentracija i potencijalnim smanjenjem učinka u terapiji

transmission, which is crucial for understanding depression.

Another potentially effective therapeutic option for TRD is the modulation of the opioid system through κ receptor antagonists. Buprenorphine, an opioid drug combined with other compounds for more targeted action on μ and κ opioid receptors, shows moderate antidepressant effects without the side effects associated with opioids. The main targets of action of these compounds are postsynaptic inhibitory μ receptors and presynaptic κ receptors (22).

It is presumed that the mechanism of action of psychedelic compounds such as psilocybin and ayahuasca takes place through the serotonergic/monoaminergic system. Psilocybin, a natural compound from hallucinogenic mushrooms, metabolizes in the body into psilocin, which is a partial agonist of serotonin receptors 5-HT2 A, 5-HT2C, 5-HT1 A, and 5-HT1B and an inhibitor of serotonin transporters. Despite well-known dose-dependent side effects (sensory illusions, hallucinations, nausea, vomiting, and headaches), the substance has proved to be relatively well-tolerated. Psilocybin has shown efficacy in the treatment of mood disorders. In combination with precisely structured psychotherapy, psilocybin has been shown to be effective in treating TRD (23).

Elevated levels of C-reactive protein and cytokines are associated with TRD, suggesting an inflammatory role in this disorder. Cyclooxygenase-2 (COX-2) inhibitors were initially explored as potential anti-inflammatory treatments for TRD. These inhibitors act by blocking the production of prostaglandins, molecules that are elevated in the blood of patients with TRD, hence their use may have a potential role in the treatment of TRD (1).

Current research on the use of rifampicin (an antibiotic from the rifamycin group) for the treatment of treatment-resistant depression (TRD) is in its early stages. Rifampicin doses for TRD are usually prescribed individually, taking into account the patient's characteristics, drug tolerance, and interactions with other medications.

rezistentne depresije, ciljani mehanizam može imati korisne učinke. Ovaj sustav enzima sudjeluje u metabolizmu brojnih lijekova, uključujući antidepresive. Rimfapicin djeluje kao induktor CYP3A4 enzima, što može povećati metabolizam nekih antidepresiva poput sertralina, fluoksetina ili venlafaksina (24). Iako povećanje metabolizma može smanjiti koncentraciju tih lijekova, u nekim slučajevima može doći do optimizacije terapije poboljšanjem farmakokinetike i farmakodinamike lijekova, što može biti korisno kod pacijenata s TRD-om koji nisu odgovorili na standardne doze antidepresiva.

NEUROMODULACIJSKE METODE

Elektrokonvulzivna terapija (EKT) je vrhunski primjer napredne neurostimulativne terapije u psihijatriji, često primijenjene kao odgovor na neuspjehe farmakoloških metoda u liječenju depresije, posebno u teškim oblicima depresije kao što su unipolarni ili bipolarni poremećaji. Ova terapija se koristi u skladu sa smjernicama ne samo za liječenje depresije, već i za pet drugih značajnih psihičkih stanja, uključujući shizofreniju, bipolarni poremećaj, shizoafektivni poremećaj, shizofreniformni poremećaj i katatoniju.

Unatoč dokazanoj učinkovitosti mehanizam djelovanja EKT-a u liječenju terapijski rezistentne depresije ostaje izazov. Postoje četiri glavne teorije koje pokušavaju objasniti ovaj fenomen: klasična teorija monoaminskih neurotransmitera, neuroendokrina teorija, antikonvulzivna teorija i neurotropna teorija (25). Klasična teorija ukazuje da EKT ima povoljan učinak na dopaminski, serotoninski i adrenalinski sustav, što značajno poboljšava raspoloženje i ponašanje pacijenata. S druge strane, neuroendokrina teorija pretpostavlja da EKT potiče oslobađanje hormona iz hipotalamusa i hipofize, uključujući prolaktin i adrenokortikotropni hormon, što može imati dubok antidepresivni učinak. Antikonvulzivna teorija tvrdi da je učinkovitost EKT-a rezultat njegovog antikonvulzivnog

Studies have shown that rifampicin could have a positive effect on depression through its ability to affect the CYP450 enzyme system. Although increased metabolism of antidepressants is generally associated with their reduced concentrations and potential reduced efficacy in the context of TRD, the targeted mechanism may have beneficial effects. This enzyme system participates in the metabolism of numerous drugs, including antidepressants. Rifampicin acts as an inducer of the CYP3A4 enzyme, which can increase the metabolism of certain antidepressants such as sertraline, fluoxetine, or venlafaxine (24). Although increased metabolism may reduce the concentration of these drugs, in some cases, treatment optimization may occur through improved pharmacokinetics and pharmacodynamics of drugs, which can be beneficial for TRD patients who did not respond to standard antidepressant doses.

NEUROMODULATION METHODS

Electroconvulsive Therapy (ECT) represents a prime example of advanced neurostimulative therapy in psychiatry, often applied in response to failures of pharmacological methods in treating depression, especially in severe forms of depression such as unipolar or bipolar disorders. This therapy is employed according to guidelines not only for treating depression, but also for five other significant psychiatric conditions, including schizophrenia, bipolar disorder, schizoaffective disorder, schizophreniform disorder, and catatonia.

Despite its proven effectiveness, the mechanism of action of ECT in the treatment of treatment-resistant depression (TRD) remains a challenge. There are four main theories attempting to explain this phenomenon: the classical monoamine neurotransmitter theory, the neuroendocrine theory, the anticonvulsant theory, and the neurotrophic theory (25). The classical theory suggests that ECT (electroconvulsive therapy) has a beneficial effect on the dopaminergic, serotonergic and adrenergic systems, significantly improving

djelovanja, što se vidi u promjenama u pragu konvulzija tijekom terapije. Naposljetku, neurotropna teorija sugerira da EKT potiče neuroplastičnost i neurogenezu u mozgu, što dovodi do strukturnih promjena povezanih s poboljšanjem depresivnih simptoma (tablica 2). Sam postupak EKT-a uključuje seriju visokofrekventnih električnih impulsa, s elektrodama precizno postavljenim na određene dijelove mozga prema potrebama svakog pacijenta. Iako se EKT smatra iznimno učinkovitom terapijom za teške oblike TRD-a, važno je uzeti u obzir moguće rizike, uključujući potencijalne kognitivne nuspojave (1,4,22,25). Različite varijante EKT-a imaju svoje prednosti i ograničenja pa odluka o primjeni treba biti temeljena na pažljivoj procjeni koristi i rizika za svakog pacijenta.

Terapija svjetlom (fototerapija) u psihijatrijskom kontekstu primjenjuje se za terapiju

patients' mood and behavior. On the other hand, the neuroendocrine theory assumes that ECT stimulates the release of hormones from the hypothalamus and pituitary gland, including prolactin and adrenocorticotropic hormone, which can have a profound antidepressant effect. The anticonvulsant theory argues that the effectiveness of ECT results from its anticonvulsant action, as seen through changes in seizure thresholds during therapy. Finally, the neurotrophic theory suggests that ECT promotes neuroplasticity and neurogenesis in the brain, leading to structural changes associated with improvement in depressive symptoms (Table 2). The ECT procedure itself involves a series of high-frequency electrical impulses, with electrodes precisely placed on specific parts of the brain according to each patient's needs. Although ECT is considered an extremely effective therapy for severe forms of TRD, it is important to consider the possible risks, including

TABLICA 2.1. Pregled neuromodulacijske metode. Elektrokonvulzivna terapija i njezine karakteristike u liječenju terapijski rezistentne depresije.
TABLE 2.1. Overview of the Neuromodulation Method. Electroconvulsive Therapy and Its Characteristics in the Treatment of Treatment-Resistant Depression.

NEUROMODULACIJSKA METODA / NEUROMODULATORY METHOD	Elektrokonvulzivna terapija (EKT)/Electroconvulsive Therapy (ECT)
OPIS/ DESCRIPTION	Terapijski postupak koji uključuje primjenu kratkih električnih impulsa u mozak kako bi se izazvale kontrolirane epileptičke konvulzije. Ovaj postupak se primjenjuje u kontroliranim uvjetima pod anestezijom. /Therapeutic procedure involving the application of brief electrical pulses to the brain to induce controlled epileptic seizures. This procedure is administered under controlled conditions and anesthesia.
PRIMJENA / APPLICATION	Često se koristi kao odgovor na neuspjehe farmakoloških metoda u liječenju depresije, posebno u teškim oblicima depresije kao što su unipolarni ili bipolarni poremećaji. /Often used as a response to failures of pharmacological methods in treating depression, especially in severe forms such as unipolar or bipolar disorders.
MEHANIZMI DJELOVANJA /MECHANISMS OF ACTION	Klasična teorija monoaminskih neurotransmitera. Neuroendokrina teorija. Antikonvulzivna teorija. Neurotropna teorija. /Classical theory of monoaminergic neurotransmitters. Neuroendocrine theory. Anticonvulsant theory. Neurotrophic theory.
POSTUPAK / PROCEDURE	Serija visokofrekventnih električnih impulsa, s elektrodama precizno postavljenim na određene dijelove mozga. /Series of high-frequency electrical pulses with electrodes precisely placed on specific brain areas.
PREDNOSTI / ADVANTAGES	Izuzetna učinkovitost u teškim oblicima TRD-a. Širok spektar indikacija. /Exceptional efficacy in severe TRD cases. Wide range of indications.
NUSPOJAVE / SIDE EFFECTS	Glavobolja, mučnina, potencijalne kognitivne nuspojave, poremećaj spavanja, gubitak apetita, prolazne konfuzije ili dezorijentacije nakon terapije. /Headache, nausea, potential cognitive side effects, sleep disturbances, loss of appetite, transient confusion or disorientation post-therapy.

TABLICA 2.2. Pregled neuromodulacijske metode terapije svjetlom i njezine karakteristika u liječenju terapijski rezistentne depresije.
TABLE 2.2. Overview of the Neuromodulation Method Light Therapy and Its Characteristics in the Treatment of Treatment-Resistant Depression.

NEUROMODULACIJSKA METODA / NEUROMODULATORY METHOD	Terapija svjetlom (Fototerapija) / Light Therapy (Phototherapy)
OPIS / DESCRIPTION	Terapijski postupak koji uključuje izlaganje pacijenta umjetnom izvoru jakog svjetla vidljivog dijela spektra, bez UV zračenja / Therapeutic procedure involving exposure of the patient to an artificial source of bright light in the visible spectrum, without UV radiation.
PRIMJENA / APPLICATION	U tretmanu SAP-a, nesezonskog depresivnog poremećaja, kroničnih depresivnih stanja, te kao alternativni tretman za terapijski rezistentne depresivne bolesnike / Treatment for SAD, non-seasonal depressive disorder, chronic depressive conditions, and as an alternative treatment for treatment-resistant depressive patients.
MEHANIZMI DJELOVANJA / MECHANISMS OF ACTION	Regulacija cirkadijalnog ritma i biološkog sata Povećanje koncentracije serotonina u mozgu Aktivacija fotosenzitivnih ganglijskih stanica retine Povećanje koncentracije BDNF-a Modulacija oreksinergičkih, serotoninergičkih i dopaminergičkih neuronskih putova /Regulation of circadian rhythm and biological clock. Increase in serotonin concentration in the brain. Activation of photosensitive ganglion cells of the retina. Increase in BDNF concentration. Modulation of orexinergic, serotoninergic, and dopaminergic neuronal pathways.
POSTUPAK/PROCEDURE	Pacijent se izlaže svjetlu jakosti od 10000 lx, obično u jutarnjim satima, tijekom 2 do 5 tjedana. Doza se može postupno povećavati, a udaljenost od izvora svjetla je obično od 30 do 70 cm. / Patient is exposed to light intensity of 10,000 lux, usually in the morning, for 2 to 5 weeks. Dose may be gradually increased, and the distance from the light source is typically 30 to 70 cm.
PREDNOSTI / ADVANTAGES	Učinkovita u liječenju sezonskog i nesezonskog depresivnog poremećaja Manje nuspojava u usporedbi s drugim terapijama Brži učinak u kombinaciji s antidepresivima Poboljšanje raspoloženja i spavanja / Effective in treating SAD and non-seasonal depressive disorder. Fewer side effects compared to other therapies. Faster response when combined with antidepressants. Improvement in mood and sleep.
NUSPOJAVE / SIDE EFFECTS	Prolazne nuspojave poput glavobolje, osjećaja pijeska u očima i mučnine Rijetka ali potencijalno ozbiljna nuspojava je agitacija koja može voditi u maničnu epizodu ili suicidalno ponašanje / Transient side effects such as headache, feeling of sand in the eyes, and nausea. Rare but potentially serious side effect of agitation leading to manic episode or suicidal behavior.

Priredila Andrijana Šantić, dr. med. veljača, 2024. TRD – terapijski rezistentna depresija
/ Compiled by Andrijana Šantić, MD. February 2024. TRD - Treatment-Resistant Depression

depresivnih poremećaja, naročito sezonskog afektivnog poremećaja (SAP), putem izlaganja pacijenata određenim valnim duljinama i intenzitetima svjetla. Ovaj terapijski pristup aktivira fotosenzitivne ganglijske stanice retine (ipRGCs) putem svjetlosnih valova koji sadrže foto-pigment melanopsin osjetljiv na plavo svjetlo (480 nm). Ovo stimuliranje rezultira slanjem signala u suprahijazmatsku jezgru (SCN) mozga, ključnu za regulaciju cirkadijalnog ritma i proizvodnju melatonina, hormona odgovornog za regulaciju spavanja i raspoloženja (26). U terapiji rezistentnog depresivnog poremećaja fototerapija dodatno djeluje na regulaciju neurotransmiterskih sustava u mozgu, poput serotoninergičkog sustava. Istraživanje Kosanović Rajačić dalo je uvid u uspješnost fo-

the potential cognitive side effects (1, 4, 22, 25). Different variants of ECT have their advantages and limitations, therefore the decision to use it should be based on a careful assessment of benefits and risks for each patient.

Light Therapy (Phototherapy) in the psychiatric context is applied for the treatment of depressive disorders, especially seasonal affective disorder (SAD), through the exposure of patients to specific wavelengths and intensities of light. This therapeutic approach activates photosensitive ganglion cells of the retina (ipRGCs) via light waves, which contain the photo-pigment melanopsin sensitive to blue light (480 nm). This stimulation results in sending signals to the suprachiasmatic nucleus (SCN) of the brain, crucial for regulating the circadian rhythm and the production of melatonin,

TABLICA 2.3. Pregled neuromodulacijske metode. Transkranijska magnetska stimulacija i njezine karakteristika u liječenju terapijski rezistentne depresije.
TABLE 2.3. Overview of the Neuromodulation Method. Transcranial Magnetic Stimulation and Its Characteristics in the Treatment of Treatment-Resistant Depression.

NEUROMODULACIJSKA METODA / NEUROMODULATORY METHOD	Transkranijska magnetska stimulacija (TMS) / Transcranial Magnetic Stimulation (TMS)
OPIS/ DESCRIPTION	Neinvazivna metoda neuromodulacije koristeći elektromagnetizam u psihijatriji / Non-invasive neuromodulation method using electromagnetism in psychiatry.
PRIMJENA / APPLICATION	Dijagnostičke i terapijske svrhe, s naglaskom na depresiju. / Diagnostic and therapeutic purposes, with a focus on depression.
MEHANIZMI DJELOVANJA / MECHANISMS OF ACTION	Poticanje aktivnosti mozga. Povećanje biološke dostupnosti antidepresiva. Poticanje oslobađanja neurotransmitera Neuroplastične promjene / Stimulation of brain activity. Increase in biological availability of antidepressants. Stimulation of neurotransmitter release. Neuroplastic changes.
POSTUPAK / PROCEDURE	Magnetski stimulansi induciraju električne struje u mozgu kroz vlasište, modulirajući aktivnost korteksa. Modaliteti: Visokofrekventna (≥1 Hz) i niskofrekventna (≤1 Hz). / Magnetic stimulators induce electrical currents in the brain through the scalp, modulating cortical activity. Modalities: High-frequency (≥1 Hz) and low-frequency (≤1 Hz).
PREDNOSTI / ADVANTAGES	Neinvazivna Učinkovita kao dodatak farmakoterapiji / Non-invasive. Effective as an adjunct to pharmacotherapy.
NUSPOJAVE / SIDE EFFECTS	Manje nuspojave u usporedbi s EKT-om / Fewer side effects compared to ECT.

Priredila Andrijana Šantić, dr. med. veljača, 2024. SAP- sezonski afektivni poremećaj, BDNF-moždani neurotrofni čimbenik / Compiled by Andrijana Šantić, MD. February 2024. SAD - Seasonal Affective Disorder, BDNF - Brain-Derived Neurotrophic Factor

TABLICA 2.4. Pregled neuromodulacijske metode. Intermitentna stimulacija teta valova (iTBS) i njezine karakteristika u liječenju terapijski rezistentne depresije
TABLE 2.4. Overview of the Neuromodulation Method. Intermittent Theta Burst Stimulation (iTBS) and Its Characteristics in the Treatment of Treatment-Resistant Depression.

NEUROMODULACIJSKA METODA / NEUROMODULATORY METHOD	Intermitentna stimulacija teta valova (iTBS) / Intermittent Theta Burst Stimulation (iTBS)
OPIS / DESCRIPTION	Nova tehnika TMS-a s većim količinama stimulacije u kraćem vremenu. Jedan od modaliteta rTMS-a /New TMS technique with higher amounts of stimulation in a shorter time. One of the rTMS modalities.
PRIMJENA / APPLICATION	Brzo smanjenje simptoma depresije koja ne reagira na standardne terapije. /Rapid reduction of depression symptoms not responsive to standard therapies.
MEHANIZMI DJELOVANJA / MECHANISMS OF ACTION	Ciljanje i poticanje kortikalne plastičnosti./ Targeting and promoting cortical plasticity.
POSTUPAK / PROCEDURE	Kao i TMS samo što postupak uključuje aplikaciju kratkih, visoko-intenzivnih teta valova na specifične dijelove mozga, obično kroz repetitivne sesije tijekom nekoliko tjedana. / Similar to TMS but involves the application of brief, high-intensity theta bursts to specific brain areas, usually through repetitive sessions over several weeks.
PREDNOSTI / ADVANTAGES	Brzo smanjenje simptoma, jednako učinkovita kao visokofrekventni rTMS, bolja tolerancija, kraće trajanje tretmana, potencijal za dugoročne efekte, sigurnost. /Rapid reduction of symptoms, Equally effective as high-frequency rTMS, Better tolerance, Shorter treatment duration, Potential for long-term effects, Safety.
NUSPOJAVE / SIDE EFFECTS	Glavobolja, umor, mučnina / Headache, fatigue, nausea.

Priredila Andrijana Šantić, dr. med. veljača, 2024. EKT- Elektrokonvulzivna terapija / Compiled by Andrijana Šantić, MD. February 2024. ECT - Electroconvulsive Therapy

toterapije u ublažavanju depresivnih simptoma kod pacijentica s terapijski rezistentnim depresivnim poremećajem. Nalazi studije pokazali su kako su pacijentice koje su dobro odgovorile na a hormone responsible for regulating sleep and mood (26). In the context of treatment-resistant depressive disorder, phototherapy further affects the regulation of neurotransmitter systems in the

TABLICA 2.5. Pregled neuromodulacijske metode. Duboka stimulacija mozga (DBS) i njezine karakteristika u liječenju terapijski rezistentne depresije.
TABLE 2.5. Overview of the Neuromodulation Method. Deep Brain Stimulation (DBS) and Its Characteristics in the Treatment of Treatment-Resistant Depression.

NEUROMODULACIJSKA METODA / NEUROMODULATORY METHOD	Duboka stimulacija mozga /Deep Brain Stimulation (DBS)
OPIS / DESCRIPTION	Složeni kirurški post upak za ozbiljne oblike depresije. / Complex surgical procedure for severe forms of depression.
PRIMJENA / nAPPLICATION	Kada standardne terapije nisu uspjele. / When standard therapies have failed.
MEHANIZMI DJELOVANJA / MECHANISMS OF ACTION	Utječe na aktivnost specifičnih dijelova mozga, potičući oslobađanje neurotransmitera. / Affects the activity of specific brain areas, stimulating neurotransmitter release.
POSTUPAK / PROCEDURE	Kirurški postupak za implantaciju elektroda u mozak. Moguće mete:Subkalozalni cingularni girus, medijalni snop prednjeg mozga, nukleus accumbens, itd. / Surgical procedure for implanting electrodes into the brain. Possible targets: Subcallosal cingulate gyrus, medial forebrain bundle, nucleus accumbens, etc.
PREDNOSTI / ADVANTAGES	Značajno poboljšanje simptoma kod teške depresije./ Shown significant symptom improvement in severe depression cases.
NUSPOJAVE/ SIDE EFFECTS	Hipomanija, privremeno pogoršanje depresije. / Hypomania, temporary worsening of depression.

Priredila Andrijana Šantić, dr. med. veljača, 2024. TMS - Transkranijska magnetska stimulacija, rTMS – repetitivna transkranijska magnetska stimulacija / Compiled by Andrijana Šantić, MD. February 2024. TMS - Transcranial Magnetic Stimulation; rTMS - Repetitive Transcranial Magnetic Stimulation

TABLICA 2.6. Pregled neuromodulacijske metode. Neuromodulacija zatvorene petlje (CLS)i njezine karakteristika u liječenju terapijski rezistentne depresije.
TABLE 2.6. Overview of the Closed-Loop. Neuromodulation (CLS) Method and Its Characteristics in the Treatment of Treatment-Resistant Depression.

NEUROMODULACIJSKA METODA / NEUROMODULATORY METHOD	Neuromodulacija zatvorene petlje /Closed-Loop Neuromodulation (CLS)
OPIS / DESCRIPTION	Personalizirani pristup putem automatskog prilagođavanja stimulacije prema aktivnosti mozga pacijenta. / Personalized approach using automatic adjustment of stimulation according to the patient's brain activity.
PRIMJENA / APPLICATION	TRD , dugotrajna depresija, visoki rizik od samoubojstva. /Treatment-resistant depression, chronic depression, high suicide risk.
MEHANIZMI DJELOVANJA / MECHANISMS OF ACTION	Poticanje neuroplastičnosti i neurogeneze u mozgu. / Promotes neuroplasticity and neurogenesis in the brain.
POSTUPAK / PROCEDURE	Postavljanje elektroda na skalp pacijenta, praćenje moždane aktivnosti putem EEG-a, ciljano stimuliranje specifičnih područja mozga. / Placement of electrodes on the patient's scalp, monitoring brain activity through electroencephalography (EEG), targeted stimulation of specific brain regions.
PREDNOSTI / ADVANTAGES	Poboljšanje simptoma depresije. Povećanje raspoloženja i kvalitete života. /Improvement in depression symptoms. Increased mood and quality of life.
NUSPOJAVE/ SIDE EFFECTS	Obično blage i prolazne. / Typically mild and transient.

Priredila Andrijana Šantić, dr. med. veljača, 2024. / Compiled by Andrijana Šantić, MD. February 2024.

fototerapiju imale značajan porast koncentracije moždanog neurotrofnog čimbenika i interleukina-6 (IL-6) u plazmi. Ovi rezultati pokazuju korisnost ove terapijske opcije potencijalno utječući na regulaciju neurotrofnih čimbenika i upalnih procesa uz naglasak na važnost indi-

brain, such as the serotonergic system. A study conducted by Kosanović Rajačić provided insight into the effectiveness of phototherapy in alleviating depressive symptoms in patients with treatment-resistant depressive disorder. The study's findings showed that patients who responded

TABLICA 2.7. Pregled neuromodulacijske metode. Transkranijska stimulacija istosmjernom strujom (tDCS) i njezine karakteristika u liječenju terapijski rezistentne depresije.
TABLE 2.7. Overview of the Transcranial Direct Current Stimulation (tDCS) Method and Its Characteristics in the Treatment of Treatment-Resistant Depression.

NEUROMODULACIJSKA METODA / NEUROMODULATORY METHOD	Transkranijska stimulacija istosmjernom strujom / Transcranial Direct Current Stimulation (tDCS)
OPIS / DESCRIPTION	Neuromodulacijska terapijska tehnika koja koristi blage električne struje kako bi utjecala na aktivnost mozga. / Neuromodulation therapy technique using mild electrical currents to impact brain activity.
PRIMJENA / APPLICATION	TRD, Kronična bol, Fibromialgija, PTSP. / TRD, chronic pain, fibromyalgia, PTSD.
MEHANIZMI DJELOVANJA / MECHANISMS OF ACTION	Ciljano moduliranje aktivnosti mozga; utječe na aktivnost lijevog dorzolateralnog prefrontalnog korteksa. /Targeted modulation of brain activity; affects left dorsolateral prefrontal cortex activity.
POSTUPAK / PROCEDURE	Blage električne struje kroz vlasište. /Mild electrical currents applied through the scalp.
PREDNOSTI / ADVANTAGES	Smanjenje simptoma depresije s malo nuspojava. Relativno jednostavna i sigurna metoda. /Reduction in depression symptoms with minimal side effects. Relatively simple and safe method.
NUSPOJAVE / SIDE EFFECTS	Blaga nelagoda ili peckanje ispod elektroda, glavobolju, mučninu, umor, prolazno pogoršanje simptoma te moguće promjene u raspoloženju /Mild discomfort or tingling under electrodes, headache, nausea, fatigue, transient worsening of symptoms, and possible mood changes.

Priredila Andrijana Šantić, dr. med. veljača, 2024. TRD- terapijski rezistentna depresija, EEG – Elektroencefalogram

TABLICA 2.8. Pregled neuromodulacijskih metoda. Stimulacija vagusnog živca (VNS) i transkutana stimulacija vagusnog živca (tVNS)i njezinih karakteristika u liječenju terapijski rezistentne depresije.
TABLE 2.8. Overview of the Neuromodulation Methods. Vagus Nerve Stimulation (VNS) and Transcutaneous Vagus Nerve Stimulation (tVNS) and Their Characteristics in the Treatment of Treatment-Resistant Depression.

NEUROMODULACIJSKA METODA / NEUROMODULATORY METHOD	Stimulacija vagusnog živca (VNS) i transkutana stimulacija vagusnog živca (tVNS). / Vagus Nerve Stimulation (VNS) and Transcutaneous Vagus Nerve Stimulation (tVNS)
OPIS / DESCRIPTION	Terapijska metoda koja uključuje stimulaciju vagusnog živca električnim impulsima kako bi se postigao terapijski učinak. /Therapeutic method involving stimulation of the vagus nerve with electrical impulses to achieve a therapeutic effect
PRIMJENA / APPLICATION	TRD, Pacijenti s visokim rizikom od samoubojstva. / TRD, Patients at high risk of suicide.
MEHANIZMI DJELOVANJA / MECHANISMS OF ACTION	Stimulacija vagusnog živca, promjene u neurotransmiterskoj aktivnosti mozga. /Vagus nerve stimulation, changes in brain neurotransmitter activity.
POSTUPAK / PROCEDURE	VNS podrazumijeva implantaciju malog uređaja, sličnog pejsmejkeru, na vagusni živac u vratu, koji zatim šalje električne impulse u mozak tVNS uključuje postavljanje elektroda na kožu vrata, koje zatim šalju blagu električnu stimulaciju vagusnom živcu radi modulacije aktivnosti mozga. / VNS involves the implantation of a small device, similar to a pacemaker, on the vagus nerve in the neck, which then sends electrical impulses to the brain. tVNS involves placing electrodes on the skin of the neck, which then send mild electrical stimulation to the vagus nerve to modulate brain activity.
PREDNOSTI / ADVANTAGES	Učinkovitost u smanjenju simptoma depresije. /Effectiveness in reducing depression symptoms.
NUSPOJAVE / SIDE EFFECTS	Minimalne nuspojave, kao što su prolazna glavobolja ili umor. / Minimal side effects, such as transient headache or fatigue.

Priredila Andrijana Šantić, dr. med. veljača, 2024. TRD- terapijski rezistentna depresija, PTSP- Posttraumatski stresni poremećaj./ Compiled by Andrijana Šantić, MD. February 2024. TRD - Treatment-Resistant Depression

vidualnih čimbenika poput pušenja i anamneze o suicidu, u predikciji odgovora pacijentica na fototerapiju (27).

well to phototherapy had a significant increase in the concentration of brain-derived neurotrophic factor (BDNF) and interleukin-6 (IL-6) in plas-

Transkranijska magnetska stimulacija (engl. *Transcranial magnetic stimulation,* TMS) je neinvazivna metoda neuromodulacije koja koristi elektromagnetizam u psihijatriji za dijagnostičke i terapijske svrhe (tablica 2). TMS koristi magnetske stimulanse kako bi inducirao električne struje u mozgu putem vlasišta, što dovodi do modulacije kortikalne pobudljivosti i aktivnosti u specifičnim područjima mozga, posebno frontalnog režnja (28). U kliničkoj praksi repetitivna TMS (rTMS) se primjenjuje kao pet tjednih sesija tijekom tri do šest tjedana, ukupno 20 do 30 sesija. Postoje dvije glavne modalnosti rTMS-a: visokofrekventna (≥1 Hz), koja potiče aktivnost mozga i niskofrekventna (≤1 Hz), s inhibicijskim učinkom. Osim toga, postoji teorija koja sugerira da rTMS može pojačati djelovanje antidepresivnih lijekova povećanjem njihove biološke dostupnosti ili ubrzavanjem početka djelovanja. Učinkovitost rTMS-a potvrđena je brojnim studijama sa stopama odgovora od 50 do 55 % i stopama remisije od 30 do 35 % kod teške depresije. Često se koristi kao dodatak farmakoterapiji za depresiju, s većom učinkovitošću u usporedbi s placebo tretmanima. Osim toga, rTMS može poticati oslobađanje neurotransmitera poput serotonina, dopamina i noradrenalina, ključnih za regulaciju raspoloženja, te izazvati neuroplastične promjene u mozgu, što dovodi do dugotrajnih poboljšanja u raspoloženju i kognitivnoj funkciji.

Uvođenje nove tehnike, intermitentne stimulacije teta valova (iTBS), pruža veće količine stimulacije mozga u kraćem vremenskom razdoblju. iTBS cilja i potiče kortikalnu plastičnost na način koji je bliži prirodnom funkcioniranju mozga nego konvencionalni TMS (28). Istraživanja su pokazala da je iTBS jednako učinkovit kao i visokofrekventni rTMS u liječenju pacijenata s TRD-om. Brzi protokoli iTBS-a i visokofrekventnog rTMS-a su također pokazali obećavajuće rezultate u brzom smanjenju simptoma kod depresije koja ne reagira na standardne terapije (29). Ova nova tehnika otvara vrata za napredak u neuromodulacijskom liječenju

ma. These results suggest the usefulness of this therapeutic option, potentially affecting the regulation of neurotrophic factors and inflammatory processes, with an emphasis on the importance of individual factors such as smoking and suicide history, in predicting the response of patients to phototherapy (27).

Transcranial Magnetic Stimulation (TMS) is a non-invasive neuromodulation method that uses electromagnetism in psychiatry for diagnostic and therapeutic purposes (Table 2). TMS utilizes magnetic stimulators to induce electrical currents in the brain through the scalp, leading to a modulation of cortical excitability and activity in specific brain areas, especially the frontal cortex (28). In clinical practice, repetitive TMS (rTMS) is applied in the form of five daily sessions over the course of three to six weeks, totaling in 20 to 30 sessions. There are two main modalities of rTMS: high-frequency (≥1 Hz), which enhances brain activity, and low-frequency (≤1 Hz), with an inhibitory effect. Additionally, there is a theory suggesting that rTMS may enhance the action of antidepressant medications by increasing their bioavailability or by speeding up their onset of action. The effectiveness of rTMS has been confirmed by numerous studies, with response rates of 50 to 55% and remission rates of 30 to 35% in cases of severe depression. It is often used as an adjunct to pharmacotherapy for the treatment of depression, with greater efficacy compared to placebo treatments. Moreover, rTMS can stimulate the release of neurotransmitters such as serotonin, dopamine and norepinephrine, which are crucial for mood regulation, and can induce neuroplastic changes in the brain, leading to long-lasting improvements in mood and cognitive function.

The introduction of a new technique, intermittent Theta Burst Stimulation (iTBS), provides higher amounts of brain stimulation in a shorter period. iTBS targets and promotes cortical plasticity in a way that is closer to natural brain functioning than conventional TMS (28). Research has shown that iTBS is equally effective as high-frequency rTMS in treating patients with TRD. Rapid iTBS

TRD-a omogućujući precizniju i djelotvorniju terapiju.

Duboka stimulacija mozga (engl. *Deep brain stimulation,* DBS) je složeni kirurški postupak koji se istražuje kao terapija za teške oblike depresije koji ne reagiraju na standardne terapije. DBS cilja precizne dijelove mozga kako bi se regulirala aktivnost koja je ključna za psihičko zdravlje. Mehanizam djelovanja DBS-a u liječenju teške depresije još nije u potpunosti razjašnjen, ali se smatra da utječe na aktivnost specifičnih dijelova mozga, potičući oslobađanje neurotransmitera poput dopamina i serotonina. Odabir ciljanih područja mozga za DBS temelji se na modelima koji identificiraju strukture mozga povezane s različitim aspektima depresivnih simptoma. Moždane strukture koje su mete DBS-a, osim subkalozalnog cingularnog girusa, uključuju medijalni snop prednjeg mozga, nukleus akumbens, ventralni strijatum, striju terminalis, pedunkulus talami inferior, te habenulu lateralis (29). Iako je kirurški zahvat invazivan, DBS je pokazao značajno poboljšanje simptoma kod teške depresije. Važno je napomenuti moguće nuspojave, poput hipomanije ili privremenog pogoršanja depresije, no većina se može kontrolirati prilagodbom stimulacijskih parametara (30).

Neuromodulacija zatvorene petlje (engl. *Closed-loop stimulation,* CLS) je inovativna terapijska metoda koj se koristi u liječenju terapijski rezistentne depresije. Ova terapija automatski prilagođava stimulaciju prema aktivnosti mozga pacijenta, omogućavajući preciznu i individualiziranu terapiju. Cilja specifična područja mozga povezana s depresijom, potičući neuroplastičnost i neurogenezu, što dovodi do strukturnih promjena u mozgu povezanih s poboljšanjem depresivnih simptoma (31). Indikacije za CLS terapiju uključuju terapijski rezistentnu depresiju koja nije reagirala na tradicionalne terapije, pacijente s dugotrajnom depresijom koja značajno utječe na kvalitetu života te one s visokim rizikom od samoubojstva ili teškim simptomima depresije. Uz pozitivne terapijske

and high-frequency rTMS protocols have also shown promising results in rapidly reducing symptoms of depression that does not respond to standard therapies (29). This new technique opens doors for advancements in neuromodulation treatment of TRD, allowing for more precise and effective therapy.

Deep Brain Stimulation (DBS) is a complex surgical procedure which is being explored as a treatment for severe forms of depression that do not respond to standard treatments. DBS targets specific parts of the brain in order to regulate activity that is crucial for mental health. The mechanism of action of DBS in treating severe depression is not yet fully understood, but it is believed that it affects the activity of specific brain areas, promoting the release of neurotransmitters such as dopamine and serotonin. The selection of target brain areas for DBS is based on models that identify brain structures associated with different aspects of depressive symptoms. Brain structures targeted by DBS, besides the subcallosal cingulate gyrus, include the medial forebrain bundle, nucleus accumbens, ventral striatum, stria terminalis, inferior thalamic peduncle, and the lateral habenula (29). Although the surgical procedure is invasive, DBS has yielded significant improvement in symptoms of severe depression. It is important to note the possible side effects, such as hypomania or temporary worsening of depression, but most can be managed by adjusting the stimulation parameters (30).

Closed-Loop Neuromodulation (CLN) is an innovative therapeutic method used in the treatment of treatment-resistant depression. This therapy automatically adjusts stimulation based on the brain activity of the patient, allowing for precise and individualized therapy. It targets specific areas of the brain associated with depression, promoting neuroplasticity and neurogenesis, which leads to structural changes in the brain associated with improvement in depressive symptoms (31). Indications for CLN therapy include treatment-resistant depression that has not responded to traditional therapies, patients

rezultate koji uključuju poboljšanje simptoma depresije, povećanje raspoloženja i kvalitete života te smanjenje rizika od recidiva depresije, CLS terapija pruža nadu pacijentima s TRD-om kod kojih nije bilo uspjeha s dosadašnjom psihofarmakoterapijom. Nuspojave CLS terapije su obično blage i prolazne, poput prolazne glavobolje, blage mučnine ili umora tijekom početnih faza terapije (29,31).

Transkranijska stimulacija istosmjernom strujom (engl. *Transcranial direct current stimulation,* tDCS) je eksperimentalna terapijska metoda koja ima za cilj direktno utjecati na aktivnost lijevog dorzolateralnog prefrontalnog korteksa (dlPFC), područja mozga ključnog za regulaciju raspoloženja. Ova tehnika koristi blage električne struje koje se primjenjuju na skalp pacijenta kako bi se modulirala aktivnost mozga. Tim malim električnim stimulacijama tDCS ima potencijal smanjiti simptome depresije s relativno malo nuspojava, što je čini atraktivnom opcijom za liječenje terapijski rezistentne depresije (4,29).

Stimulacija vagusnog živca (engl. *Vagus nerve stimulation,* VNS) je tradicionalna terapijska metoda koja se koristi za TRD. Ova terapija uključuje implantiranje malog uređaja, sličnog pejsmejkeru, koji se postavlja na vagusni živac u vratu. VNS terapija koristi električne impulse za stimulaciju vagusnog živca, što rezultira promjenama u neurotransmiterskoj aktivnosti mozga. Novija verzija ove terapije je transkutana stimulacija vagusnog živca (tVNS) koja se također pokazala sigurnom i učinkovitom u liječenju TRD-a (32).

tVNS je neinvazivna terapija koja koristi blagu električnu stimulaciju putem elektroda koje se postavljaju na kožu vrata. Ova terapija pokazuje slične učinke kao i VNS, pružajući stimulaciju vagusnog živca, ali bez potrebe za kirurškim zahvatom. tVNS se smatra sigurnom i obećavajućom opcijom za pacijente s TRD-om, s potencijalom za smanjenje simptoma depresije i poboljšanje kvalitete života, uz minimalne nuspojave (29,32).

with prolonged depression significantly affecting their quality of life, and those at high risk of suicide or with severe depression symptoms. Along with positive therapeutic results which include improvement in depressive symptoms, increased mood and quality of life, and reduced risk of depression relapse, CLN therapy provides hope for patients with TRD who have not had success with previous psychopharmacotherapy. The side effects of CLN therapy are usually mild and transient, such as transient headaches, mild nausea or fatigue during the initial phases of therapy (29, 31).

Transcranial Direct Current Stimulation (tDCS) is an experimental therapeutic method aimed at directly affecting the activity of the left dorsolateral prefrontal cortex (dlPFC), a brain area crucial for mood regulation. This technique uses mild electrical currents applied to the patient's scalp in order to modulate brain activity. Through these small electrical stimulations, tDCS has the potential to reduce symptoms of depression with relatively few side effects, making it an attractive option for treating treatment-resistant depression (4, 29)

Vagus Nerve Stimulation (VNS) is a traditional therapeutic method used for TRD. This therapy involves implanting a small device, similar to a pacemaker, which is placed on the vagus nerve in the neck. VNS therapy uses electrical impulses to stimulate the vagus nerve, resulting in changes in the neurotransmitter activity of the brain. A newer version of this therapy is transcutaneous Vagus Nerve Stimulation (tVNS), which has also proved to be safe and effective in treating TRD (32).

tVNS is a non-invasive therapy that uses mild electrical stimulation through electrodes placed on the skin of the neck. This therapy has similar effects to VNS, providing vagus nerve stimulation, but without the need for surgery. tVNS is considered a safe and promising option for patients with TRD, with the potential to reduce depressive symptoms and improve the quality of life, with minimal side effects (29, 32).

ZAKLJUČAK

Terapijski rezistentna depresija (TRD) je složeno i izazovno stanje u kliničkoj praksi koje zahtijeva personalizirani i multidisciplinarni pristup. Definiranje TRD-a je ključno kako bi se omogućilo pravilno razumijevanje i učinkovito liječenje pacijenata koji ne reagiraju na standardne terapije. Klasične farmakološke strategije, poput antidepresiva prvog i drugog izbora, i dalje su temelj liječenja, ali pojava novih terapijskih opcija otvara vrata inovativnim pristupima.

S napretkom u razumijevanju neurobiologije depresije razvijeni su novi antidepresivi poput Esketamina, Dekstrometorfana-Bupropiona i Gepirona ER. Istražuje se i hormonska nadomjesna terapija, posebno primjena T3 i levotiroksina, dok egzogeni oksitocin pokazuje značajne potencijale u terapiji depresije. Kao moguća terapijska opcija istražuje se i rimfapicin.

Osim novih farmakoloških agensa, nadu za pacijente s TRD-om daju neuromodulacijske metode poput elektrokonvulzivne terapije (EKT), terapije svjetlom, transkranijske magnetske stimulacije (TMS) i duboke stimulacije mozga (DBS). Iako je EKT kontroverzna, pokazala je iznimnu učinkovitost u teškim oblicima TRD-a. TMS i iTBS su neinvazivne metode neuromodulacije s obećavajućim rezultatima, dok se DBS istražuje kao terapija za teške oblike depresije koji ne reagiraju na standardne terapije.

Kombinacija farmakoloških i neuromodulacijskih pristupa, uz personaliziranu terapiju koja uzima u obzir individualne karakteristike pacijenata, je najbolji put prema efikasnom upravljanju i liječenju terapijski rezistentne depresije. Ovi novi terapijski pristupi otvaraju vrata nadolazećim istraživanjima i razvoju još boljih terapijskih strategija za sveobuhvatnu brigu o pacijentima s TRD-om.

CONCLUSION

Treatment-resistant depression (TRD) represents a complex and challenging condition in clinical practice which requires a personalized and multidisciplinary approach. Defining TRD is crucial in order to enable a proper understanding and effective treatment for patients who do not respond to standard therapies. Classical pharmacological strategies, such as first and second-line antidepressants, still form the basis of treatment, but the emergence of new therapeutic options opens the door to innovative approaches.

With advances in understanding the neurobiology of depression, new antidepressants such as Esketamine, Dextromethorphan-Bupropion and Gepirone ER have been developed. Hormone replacement therapy, especially the use of T3 and levothyroxine, is also being explored, while exogenous oxytocin shows significant potential in the treatment of depression. Additionally, rifampicin is being explored as a possible therapeutic option.

In addition to new pharmacological agents, neuromodulation methods such as electroconvulsive therapy (ECT), light therapy, transcranial magnetic stimulation (TMS), and deep brain stimulation (DBS) offer hope for patients with TRD. Although ECT is controversial, it has shown exceptional efficacy in severe forms of TRD. TMS and iTBS are non-invasive neuromodulation methods with promising results, while DBS is being explored for the treatment of severe forms of depression that do not respond to standard therapies.

The combination of pharmacological and neuromodulation approaches, along with personalized therapy that takes into account individual patient characteristics, represents the best path towards effectively managing and treating treatment-resistant depression. These new therapeutic approaches pave the way for future research and the development of even better therapeutic strategies for a comprehensive care of patients with TRD.

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Poremećaj ovisnosti o psihoaktivnim tvarima u osoba s poremećajem pažnje/hiperaktivnosti

/ Substance Use Disorder in Individuals with Attention Deficit Hyperactivity Disorder

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Poremećaj pažnje/ hiperaktivnosti (engl. *attention deficit hiperactivity disorder*, ADHD) jedan je od najčešćih neurorazvojnih poremećaja. Riječ je o trajnom i kompleksnom stanju koje se reflektira u svim životnim područjima. Kod osoba s ADHD-om prisutni su česti komorbidni poremećaji uključujući poremećaj ovisnosti o psihoaktivnim tvarima. Cilj ovog narativnog pregleda je ukazati na problem ovisnosti o psihoaktivnim tvarima kod pacijenata s ADHD-om te sumirati dosadašnje rezultate istraživanja koji ukazuju na važnost prepoznavanja ADHD-a kod pacijenata s poremećajem ovisnosti o psihoaktivnim tvarima. Istraživanja ukazuju kako rano prepoznavanje ADHD-a i tretman mogu kod nekih osoba prevenirati, tj. smanjiti rizik za poremećaj ovisnosti o psihoaktivnim tvarima. Preklapanje u simptomima ADHD-a i ovisnosti o psihoaktivnim tvarima otežava postavljanje dijagnoze ADHD-a. Pacijenti s ADHD-om imaju raniji početak ovisnosti, kod njih je više recidiva i problemi su kompleksniji što zahtijeva drugačiji tretman i pristup u odnosu na pacijente s poremećajem ovisnosti koji nemaju ADHD.

/ Attention deficit hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorder. It is a persistent and complex condition that affects all areas of life. Patients with ADHD often have comorbid disorders, including substance use disorder (SUD). The aim of this narrative review is to highlight the problem of substance use disorder in patients with ADHD and to summarize the studies conducted so far which indicate the importance of recognizing ADHD in patients with SUD. Research suggests that early recognition of ADHD and its treatment can prevent, i.e. reduce the risk of substance use disorder in some individuals. The overlap between the symptoms of ADHD and SUD makes ADHD difficult to diagnose. In patients with ADHD, addiction sets in earlier, there are more relapses and the problems are more complex, requiring a different treatment and approach compared to patients with SUD who do not have ADHD.

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Tretman ovisnika / *Treatment of Addicts*

UVOD

Poremećaj pažnje/hiperaktivnosti (engl. *attention deficit hyperactivity disorder*, ADHD) jedan je od najčešćih neurorazvojnih poremećaja koji karakteriziraju simptomi poremećaja pažnje i/ili hiperaktivnosti i impulzivnosti (1). Prema svjetskim podatcima prevalencija ADHD-a kod djece je između 2,6 i 4,5 %, (2) dok je kod odraslih oko 2, 9 % (3).

Istraživanja pokazuju da kod osoba s ADHD-om postoji značajan deficit izvršnih funkcija, primarno inhibicije, radnog pamćenja i planiranja (4). U usporedbi s općom populacijom imaju više poteškoća u odnosima, rizik za uključivanjem u delinkventna ponašanja je veći (5), uspjeh u školi je često niži (6), a odrasli se suočavaju s poteškoćama u radnom okruženju i svakodnevnim obavezama (7). ADHD je trajno, kompleksno stanje koje rezultira trajnim, dugoročnim posljedicama u svim aspektima života (8).

ADHD dolazi često u komorbiditetu s raznim drugim poremećajima uključujući poremećaj ovisnosti o psihoaktivnim tvarima.

Cilj ovog narativnog preglednog rada je da prikazom istraživanja o poremećaju ovisnosti o psihoaktivnim tvarima kod osoba s ADHD-om odgovori na pitanje zašto je važno posebno obratiti pažnju na ovu skupinu pacijenata. Konkretnije, ovim radom sažeto će se prikazati teorije i nalazi istraživanja o mehanizmima u podlozi povezanosti ADHD-a i poremećaja ovisnosti o psihoaktivnim tvarima. Obrazložit će se kompleksnost problema kod osoba s ADHD-om i komorbidnim poremećajem ovisnosti o psihoaktivnim tvarima. Prikazat će se sažeto dosadašnje spoznaje o spolnim razlikama u ovisnosti o psihoaktivnim tvarima kod osoba s ADHD-om. Obrazložit će se i važnost dijagnosticiranja ADHD-a kod pacijenata s poremećajem ovisnosti o psihoaktivnim tvarima te općenito važnost ranog postavljanja dijagnoze ADHD-a.

Kako bi se odgovorilo na postavljene ciljeve pretražene su u razdoblju od 10. 10. do 18. 11. 2023.

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders characterized by symptoms of attention and/or hyperactivity and impulsivity disorders (1). According to the worldwide data, the prevalence of ADHD in children is between 2.6 and 4.5 % (2), while in adults it is around 2.9 % (3).

Studies show that there is a significant deficit in executive functions in ADHD patients, primarily relating to inhibition, working memory and planning (4). Compared to the general population, they experience more difficulties in relationships, have a higher risk of engaging in delinquent behavior (5), their academic success is often lower (6), and adults face difficulties in the work environment and in their daily responsibilities (7). ADHD is a persistent, complex condition that leads to lasting, long-term consequences for all aspects of life (8).

ADHD often occurs in comorbidity with various other disorders, including substance use disorder (SUD).

The aim of this narrative review is to answer the question of why it is important to pay particular attention to this patient group by presenting research on SUD in individuals with ADHD. Specifically, this paper briefly presents the theories and study findings relating to the underlying mechanisms of the connection between ADHD and SUD. The complexity of the problem in individuals with ADHD and comorbid SUD will be explained. We will present a summary of the current findings regarding the gender differences in terms of SUD in individuals with ADHD. The importance of diagnosing ADHD in patients with SUD and the importance of early diagnosis of ADHD in general will be explained.

In order to achieve the set objectives, the databases Google Scholar and *Scopus* were searched in the period from October 10 to November 18,

baze podataka *Google Scholar* i koristeći pristup koji je postavljen široko i koristi kombinacije ključnih riječi ADHD ili *attention deficit hyperactivity disorder* sa SUD ili *substance use disorder* ili *drug dependence* ili *alcohol disorder/dependence*; ili *nicotine dependence*. Kriterij odabira bili su cjeloviti znanstveni radovi na engleskom ili hrvatskom jeziku u području poremećaja ovisnosti o psihoaktivnim tvarima kod osoba s ADHD-om.

2023 using a broad approach which searched for combinations of the keywords ADHD or *attention deficit hyperactivity disorder* with SUD or *substance use disorder* or *drug dependen*ce or *alcohol disorder/dependence*; or *nicotine dependence*. The selection criteria included complete scientific papers written in English or Croatian in the field of SUD in individuals with ADHD.

MEHANIZMI U PODLOZI POVEZANOSTI ADHD-a I OVISNOSTI O PSIHOAKTIVNIM TVARIMA

Postoje dokazi za neurobiološka preklapanja ADHD-a i poremećaja ovisnosti o psihoaktivnim tvarima. U PET i fMRI studijama pronađene su sličnosti između pacijenata s ADHD-om i onih sa poremećajem ovisnosti o psihoaktivnim tvarima (9). Studije na blizancima i cjelogenomske studije pridruživanja upućuju također na zajedničku nasljednu podlogu kod ADHD-a i poremećaju ovisnosti o psihoaktivnim tvarima (10,11).

Young i Sedgwick (12) u recentnom radu navode kako je vjerojatno da složeno međudjelovanje nekoliko medijacijskih čimbenika ima ulogu u konzumiranju psihoaktivnih tvari kod osoba s ADHD-om te navode o postojanju dokaza za više teorijskih modela poput teorije deficita / disfunkcije dopamina, teorije samoliječenja, teorije bihevioralne dezinhibicije, teorije komorbiditeta. Isto tako istraživanja ukazuju na okolinske rizike za razvoj ovisnosti o psihoaktivnim tvarima, a koji su prisutniji u populaciji osoba s ADHD-m (13,14).

Teorije deficita /disfunkcije dopamina i bihevioralne dezinhibicije

Prema teoriji deficita/disfunkcije dopamina simptomi ADHD-a mogu se dijelom objasniti izmijenjenom regulacijom dopamina, posebice

MECHANISMS UNDERLYING THE ASSOCIATION BETWEEN ADHD AND SUBSTANCE USE DISORDER

There is evidence of neurobiological overlap between ADHD and substance use disorder. Similarities were observed between ADHD patients and SUD patients in PET and fMRI studies (9). Studies conducted on twins and genome-wide association studies also point to a common hereditary basis for ADHD and substance use disorder (10, 11).

In a recent paper, Young and Sedgwick (12) observed that the complex interaction of multiple mediating factors likely plays a role in psychoactive substance use in individuals with ADHD, and postulated that there is evidence to support several theoretical models such as dopamine deficiency/dysfunction theory, self-medication theory, behavioral disinhibition theory and comorbidity theory. Studies also point to environmental risks for the development of psychoactive substance use, which are more prevalent in the population of people with ADHD (13, 14).

Dopamine deficiency/dysfunction and behavioral disinhibition theories

According to the dopamine deficiency/dysfunction theory, ADHD symptoms can be partly explained by altered dopamine regulation, particularly relating to dopamine transport-

prijenosnika dopamina (15). Dopamin ima važnu ulogu u kontroli pokreta, kognitivnim funkcijama, emocijama, motivaciji i mehanizmu nagrađivanja. Teorija deficita transfera dopamina predlaže da se neki od simptoma ADHD-a mogu objasniti time što dopaminergičke stanice, koje kod neurotipičnih osoba predviđaju nagradu prije nego što se ona pojavi, kod osoba s ADHD-om to ne uspijevaju (16).

Slično je sa poremećajem ovisnosti o psihoaktivnim tvarima. Tako je primjerice dostupnost dopaminskih receptora smanjena kod osoba s poremećajem ovisnosti o alkoholu, smanjeno je i otpuštanje dopamina u limbičkim područjima mozga, što ukazuje na smanjenu osjetljivost na nagradu kod osoba s poremećajem ovisnosti o alkoholu (17). Ova teorija djelomično može objasniti simptome poput hiperaktivnosti i impulzivnosti te ju možemo povezati s teorijom bihevioralne dezinhibicije prema kojoj su zbog slabe samokontrole i impulzivnosti osobe s ADHD-om sklonije isprobavati nove stvari i tražiti uzbuđenja (12). Dva moždana puta koji imaju ključnu ulogu u procesiranju nagrade su mezolimbički i mezokortikalni moždani putevi te se oni povezuju i s ovisnošću i s ADHD-om (18). Mezolimbički put je povezan s impulzivnošću i motivacijom, dok je mezokortikalni put povezan s prepoznavanjem pogrešaka, izvršnim funkcijama i održavanjem cilju usmjerenih ponašanja (18). Kod mnogih osoba početno konzumiranje droga povezano je s impulzivnošću i traženjem uzbuđenja (18), a impulzivnost odnosno poteškoća samoregulacije jedan je od glavnih simptoma ADHD-a (19). Impulzivnost je također povezana s povećanom konzumacijom alkohola i povećanim rizikom za razvoj ovisnosti o alkoholu i drogama (20,21).

Moglo bi se reći da ADHD karakterizira abnormalna senzitivnost na odgađanje nagrade, jer njihove dopaminergičke stanice ne predviđaju pojačanje, odnosno nagradu na adekvatan način (16). Smanjena osjetljivost na nagradu, kao posljedica smanjene razine dopamina kod oso-

ers (15). Dopamine plays an important role in movement control, cognitive functions, emotions, motivation, and reward mechanisms. The theory of dopamine transfer deficiency suggests that some of the symptoms of ADHD can be explained by the fact that dopaminergic cells, which in neurotypical individuals predict a reward before it appears, are not successful in individuals with ADHD (16).

A similar situation is with the substance use disorder. For example, the availability of dopamine receptors is reduced in individuals with alcohol use disorder, and the release of dopamine in the limbic regions of the brain is also reduced, indicating a reduced receptivity to reward in individuals with alcohol use disorder (17). This theory can partially explain symptoms such as hyperactivity and impulsivity, and we can link it with the theory of behavioral disinhibition according to which ADHD patients tend to try new things and seek excitement due to a lack of self-control and pronounced impulsivity (12). The two brain pathways that play a key role in reward processing are the mesolimbic and mesocortical brain pathways, which have been linked both to addiction and ADHD (18). The mesolimbic pathway is associated with impulsivity and motivation, while the mesocortical pathway is associated with error detection, executive functions and maintaining goal-directed behavior (18). In many people, initial substance use is connected with impulsivity and sensation-seeking (18), and impulsivity i.e. difficulty with self-regulation is one of the main symptoms of ADHD (19). Impulsivity is also associated with increased alcohol consumption and an increased risk of alcohol and drug dependence (20, 21).

It could be said that ADHD is characterized by abnormal sensitivity to reward delays, because their dopaminergic cells do not adequately predict reinforcement or reward (16). Reduced susceptibility to rewards due to lower dopamine levels stimulates behaviors related to im-

ba s ADHD-om potiče ponašanja koja uključuju impulzivno traženje nagrade i traženje novosti (18).

Teorija samoliječenja

Prema teoriji samoliječenja osobe s ADHD-om sklonije su zloporabi psihoaktivnih tvari zbog potrebe za smanjenjem simptoma deficita pažnje, impulzivnosti i hiperaktivnosti.

U više studija utvrđeno je kako se kod osoba s ADHD-om koji su uzimali nikotin preko flastera poboljšala pažnja (22-24). Isto tako pacijenti koji su uzimali flastere nikotina izvijestili su o poboljšanju pažnje i općenito poboljšanju svog stanja za razliku od kontrolne grupe koja je dobivala placebo (25). U jednom je istraživanju nikotin poboljšao bihevioralnu kontrolu kod visoko impulzivnih osoba (26). Slično je utvrđeno s konzumacijom kokaina. Osobe s ADHD-om i poremećajem ovisnosti o psihoaktivnim tvarima mogu doživjeti kratkoročne prednosti uzimanja kokaina kompenzirajući dopaminergički nedostatak (27). Druge supstancije kao što su kanabis i alkohol same po sebi ne smanjuju simptome ADHD-a, ali neki pojedinci smatraju kako im pomažu da se osjećaju smirenije i lakše se nose sa stresom (28).

Teorije komorbiditeta

ADHD je često u komorbiditetu s drugim poremećajima poput poremećaja u ponašanju, opozicijsko protestnog poremećaja, anksioznosti i depresivnog poremećaja, a koji se povezuju s poremećajem ovisnosti o psihoaktivnim tvarima. Mnogi s poremećajima ovisnosti o psihoaktivnim tvarima imaju također poremećaj raspoloženja ili anksiozni poremećaj; prema jednoj studiji čak 63,2 % (29). Van Emmerik-van Oortmerssen *et al.* (30) su utvrdili u međunarodnoj studiji na velikom uzorku ispitanika kako je prevalencija antisocijalnog poremećaja, graničnog poremećaja ličnosti i poremećaja raspo-

pulsive reward seeking and novelty seeking in individuals with ADHD (18).

Self-medication theory

According to the self-medication theory, individuals with ADHD tend to abuse psychoactive substances in order to reduce the symptoms of attention deficit, impulsivity and hyperactivity.

Multiple studies have found that individuals with ADHD who used nicotine patches improved their attention (22-24). Likewise, patients taking nicotine patches also reported improvements in attention and an overall improvement in their condition as opposed to the placebo control group (25). In one study, nicotine improved behavioral control in highly impulsive individuals (26). Similar results were obtained with regard to cocaine use. Individuals with ADHD and substance use disorder may experience short-term benefits from cocaine use thus compensating for the dopaminergic deficiency (27).

Other substances such as cannabis and alcohol do not reduce ADHD symptoms in their own right, but some individuals believe that they help them feel calmer and cope better with stress (28).

Comorbidity theories

ADHD is often in comorbidity with other disorders such as behavioral disorders, oppositional defiant disorder, anxiety and depressive disorders, which are all associated with substance use disorder. Many individuals with substance use disorder also suffer from a mood or anxiety disorder, and according to one study their prevalence is as much as 63.2 % (29). In an international study conducted on a large sample of respondents, Van Emmerik-van Oortmerssen et al. (30) found that the prevalence of antisocial disorder, borderline personality disorder and mood disorder is higher in addicts who also have ADHD, compared to addicts without ADHD.

loženja veća kod ovisnika koji imaju i ADHD u odnosu na ovisnike bez ADHD-a.

Iako postoje studije u kojima se pokazalo da je ADHD prediktor ovisnosti o psihoaktivnim tvarima neovisno o poremećaju u ponašanju (31-34), u više longitudinalnih i transverzalnih studija utvrđeno je kako se osobe s dijagnozom ADHD-a koje nisu imali komorbidni poremećaj u ponašanju ili opozicijsko protestni poremećaj nisu razlikovale u zloporabi droga u odnosu na kontrolnu grupu (35-37).

Okolinski čimbenici rizika za ovisnost o psihoaktivnim tvarima

Okolinski čimbenici poput nepovoljnih životnih iskustava, vršnjačkog pritiska i dostupnost psihoaktivnih supstancija mogu pridonijeti razvoju ovisnosti o psihoaktivnim tvarima.

Budući da su djeca s ADHD-om izloženija nepovoljnim životnim iskustvima u odnosu na djecu bez ADHD-a (38,39) za pretpostaviti je da je poveznica između nepovoljnih okolinskih prilika kod djece i mladih s ADHD-om i poremećaja ovisnosti o psihoaktivnim tvarima još snažnija, što je potvrđeno u nekim istraživanjima koja slijede.

Obiteljske prilike utječu na razvoj ovisnosti o psihoaktivnim tvarima; negativne interakcije roditelj-dijete, visoke razine negativnog utjecaja i emocionalni stres povećavaju rizik od poremećaja ovisnosti o drogama kod adolescenata (40). Roditelji djece s ADHD-om češće imaju lošiju komunikaciju sa svojom djecom i pružaju manje podrške, što može utjecati na početak konzumacije nikotina (41). Utvrđeno je također kako adolescenti s ADHD-om češće imaju roditelje pušače (42). S druge strane, pozitivni aspekti roditeljstva poput znanja o tome što dijete radi, s kim se druži, u koje je aktivnosti uključen i sl. smanjuju rizik za ovisnost o drogama i ta veza je još jača u obiteljima djece s ADHD-om, nego kod tipičnih obitelji (41).

Although the results of some studies have shown that ADHD is a predictor of substance use disorder independent of a behavioral disorder (31-34), it was observed in several longitudinal and cross-sectional studies that there was no difference between individuals diagnosed with ADHD who did not have a comorbid behavioral disorder or oppositional defiant disorder and the control group when it came to substance abuse (35-37).

Environmental risk factors for psychoactive substance use

Environmental factors such as unfavorable life experiences, peer pressure and availability of psychoactive substances can contribute to the development of psychoactive substance use.

Since children with ADHD are more exposed to adverse life experiences when compared to children without ADHD (38, 39), it is to be assumed that the link between adverse environmental conditions of children and young people with ADHD and substance use disorder is even stronger, as confirmed in some of the following studies.

Family circumstances affect the development of psychoactive substance use; negative parent-child interactions, high levels of negative influence and emotional stress increase the risk of drug addiction disorder in adolescents (40). Parents of children with ADHD are more likely to have poor communication with their children and to provide less support, which may affect the start of nicotine consumption (41). It was also observed that adolescents with ADHD more frequently have parents who smoke (42). On the other hand, the positive aspects of parenting, such as knowing what the child is doing, who they associate with, what activities they are involved in etc., reduce the risk of drug addiction and this relationship is even stronger in families of children with ADHD than in typical ones (41).

Zlostavljanje je rizični faktor za zloporabu opojnih sredstava te jedno istraživanje pokazuje kako je još veći rizični faktor kod osoba s ADHD-om (13). Temeljem podataka velike studije koja uključuje internacionalni uzorak više europskih zemalja utvrđeno je kako je veća stopa ADHD-a kod pacijenata s poremećajem ovisnosti o psihoaktivnim tvarima koja su bila izložena traumama u djetinjstvu (verbalno, fizičko, seksualno i emocionalno zlostavljanje ili zanemarivanje te obiteljsko nasilje) u usporedbi s onima bez traume (43). Za razliku od tog istraživanja Garcia *et al.* nisu potvrdili medijacijski utjecaj ADHD-a između zlostavljanja i ovisnosti o psihoaktivnim tvarima. U jednom se istraživanju neuspjeh u školi pokazao kao medijator veze između ADHD-a i pušenja cigareta kod adolescenata (45).

Postoje istraživanja koja povezuju stigmatizaciju koju doživljavaju osobe s ADHD-om s posezanjem za psihoaktivnim tvarima. Stigmatizacija okoline kod osoba s ADHD-om može naime dovesti do smanjenog samopoštovanja i lošije prilagodbe, što u konačnici može dovesti do problema u ponašanju i problema mentalnog zdravlja, između ostalog i do zloporabe opojnih sredstava (46).

Osobe s ADHD zbog teškoća koja proizlaze iz tog poremećaja imaju manje pozitivnih interakcija s vršnjacima i veća je vjerojatnost za udruživanjem s devijantnim vršnjačkim grupama (14). Pripadnost devijantnim vršnjačkim grupama ima medijacijski učinak između ADHD-a i uporabe psihoaktivnih supstanci (14) što znači kako je vjerojatnije da će se djeca s ADHD-om nego djeca bez ADHD-a družiti s devijantnim vršnjacima i, kao rezultat toga, vjerojatnije će koristiti psihoaktivne tvari. Štoviše, odnos između devijantne pripadnosti vršnjacima i upotrebe supstanci bio je snažniji za adolescente s ADHD-om, što ukazuje da jednom kada su uronjeni u devijantnu grupu vršnjaka, adolescenti s ADHD-om su ranjiviji na negativne društvene utjecaje te skupine. Slične rezultate

Abuse is a risk factor for substance abuse and one study shows that it is an even higher risk factor in individuals with ADHD (13). Based on data from a large study involving an international sample from several European countries, it was determined that ADHD rates were higher in patients with substance use disorder who had been exposed to trauma (verbal, physical, sexual and emotional abuse or neglect, and family violence) in childhood, when compared to patients without trauma (43). In contrast to this study, Garcia et al. were unable to confirm the mediating influence of ADHD between abuse and psychoactive substance use. One study determined that poor school performance mediates the relationship between ADHD and cigarette smoking in adolescents (45).

In some studies, a link was found between the stigmatization experienced by individuals with ADHD and the use of psychoactive substances. In individuals with ADHD, stigmatization from the environment can lead to reduced self-esteem and poorer adjustment, which can ultimately lead to behavioral and mental health problems, including, among other things, substance abuse (46).

Due to issues arising from the disorder, individuals with ADHD have fewer positive interactions with peers and are more likely to associate with deviant peer groups (14). Associating with deviant peer groups has a mediating effect between ADHD and the use of psychoactive substances (14), which means that children with ADHD are more likely to associate with deviant peers than children without ADHD and, as a result, are more likely to use psychoactive substances. Moreover, the connection between deviant peer groups and substance use was stronger in adolescents with ADHD, suggesting that once immersed in a deviant peer group, adolescents with ADHD are more vulnerable to the negative social impacts of that group. Similar results were obtained by Garcia et al. while studying the connection between deviant peer groups and marijuana consumption (44).

dobili su Garcia *et al.* proučavajući vezu između devijantne vršnjačke grupe i konzumiranja marihuane (44).

VEĆI RIZIK ZA OVISNOST O PSIHOAKTIVNIM TVARIMA OSOBA S ADHD-om

Eme (18) navodi kako, sudeći po prevalenciji adolescenata i mladih s ADHD-om koji su u tretmanima za ovisnost u odnosu na opću populaciju te longitudinalnim praćenjima osoba s ADHD-om, možemo zaključiti o većem riziku za ovisnost o psihoaktivnim tvarima kod osoba s ADHD-om. Istraživanja pokazuju da je među onima koji su u tretmanu za ovisnost o drogama veliki postotak osoba s ADHD-om i kreće se između 20 % za mlade i oko 30 % za odrasle s ADHD-om (47,48); slično je i za ovisnost o alkoholu i nikotinu (49,50). Između 17 % i 45 % odraslih osoba s ADHD-om ima povijest ovisnosti o alkoholu ili zloporabe alkohola te između 9 % i 30 % ima povijest ovisnosti ili zloporabe droga (51). Osobe s ADHD-om češće su ovisnici o nikotinu neovisno o tome imaju li konduktivni poremećaj (52). Biederman i sur. proveli su istraživanje u kojem su ispitivali konzumaciju alkohola kod osoba kojima je kao djeci postavljena dijagnoza ADHD-a u usporedbi s kontrolnom skupinom (32). Pokazalo se da ispitanici s ADHD-om imaju jednaku šansu razvoja ovisnosti o alkoholu kao i neurotipični ispitanici, no postojala je statistički veća šansa da ispitanici s ADHD-om razviju ovisnost o alkoholu u kombinaciji s ovisnošću o drogama.

Longitudinalnim praćenjem pokazalo se kako je ADHD rizični čimbenik za poremećaj ovisnosti o psihoaktivnim tvarima (53-55). Osobe s ADHD-om imaju dva do tri puta veći izgled za razvoj poremećaja zloporabe psihoaktivnih supstancija (4,56). Tako je, primjerice u jednoj studiji, ovisnost o kokainu kod odraslih s ADHD-om iznosila 21 %, a kod osoba bez ADHD-a 10 % (57). Djeca kojima je dija-

HIGHER RISK OF PSYCHOACTIVE SUBSTANCE USE IN INDIVIDUALS WITH ADHD

Eme (18) states that, based on the prevalence of adolescents and young population with ADHD undergoing addiction treatment as compared to the general population, and the longitudinal observation of ADHD patients, we can conclude that there is a higher risk of psychoactive substance use in ADHD patients. Studies show that there is a high percentage of individuals with ADHD among those being treated for drug addiction, ranging from 20% in adolescents to around 30% for adults with ADHD (47, 48). Similar results were obtained for alcohol and nicotine dependence as well (49, 50). Between 17% and 45% of adults with ADHD have a history of alcohol dependence or abuse, and between 9% and 30% have a history of drug dependence or abuse (51). Individuals with ADHD are more likely to develop nicotine dependence, regardless of whether they have a conductive disorder (52). Biederman et al. (32) conducted a study in which they analyzed alcohol consumption in individuals diagnosed with ADHD in childhood, compared to a control group. It was found that respondents with ADHD had the same odds of developing alcohol dependence as the neurotypical respondents, but there was a statistically higher chance that respondents with ADHD would develop alcohol dependence in combination with drug dependence.

The results of longitudinal monitoring showed that ADHD is a risk factor for substance use disorder (53-55). Individuals with ADHD are two to three times more likely to develop substance use disorder (4, 56). In one study, for example, the prevalence of cocaine addiction in adults with ADHD amounted to 21 %, while it was 10 % in individuals without ADHD (57). Children diagnosed with ADHD are almost three times more likely to try marijuana (56). Biederman et al. (32) found that adults with ADHD are twice as likely to develop drug ad-

gnosticiran ADHD imaju gotovo tri puta veću vjerojatnost da će probati marihuanu (56). Biederman *et al.* su utvrdili da odrasli s ADHD-om imaju dvostruko veće izglede za razvoj ovisnosti o drogama u usporedbi s općom populacijom, čak i kada su povezani psihijatrijski poremećaji kontrolirani (32). Isto tako, u studijama u kojima je kontroliran utjecaj drugih komorbidnih poremećaja poput anksioznosti, depresivnosti nađena je izravna veza ADHD-a i ovisnosti o psihoaktivnim tvarima (53,55).

Naročito su simptomi nepažnje povezani s ovisnostima o nikotinu (33,58), alkoholu i drogama (33).

U Hrvatskoj nedostaje istraživanja o konzumiranju psihoaktivnih tvari kod osoba s ADHD-om. U nedavnom istraživanju provedenom za potrebe diplomskog rada utvrđeno je na prigodnom uzorku kako ne postoji razlika u konzumaciji nikotina i alkohola između odraslih osoba s ADHD-om i onih bez ADHD-a, no osobe s ADHD-om u značajno većoj mjeri konzumiraju ilegalne droge (59). S obzirom na veći udio ispitanika ženskog spola ove rezultate možemo smatrati preliminarnima i uzeti ih s oprezom.

SPOLNE RAZLIKE U OVISNOSTI O PSIHOAKTIVNIM TVARIMA KOD OSOBA S ADHD-om

Dosadašnja istraživanja o eventualnim spolnim razlikama s obzirom na vjerojatnost za razvoj ovisnosti o psihoaktivnim tvarima i težinu poremećaja kod osoba s ADHD-om daju oprečne rezultate.

U nešto ranijim istraživanjima nisu utvrđene spolne razlike u kroničnom uzimanju droga (60) ili je stopa ADHD-a bila veća kod muških adolescenata, ovisnika od drogama (61).

Prema novijim istraživanjima djevojke i odrasle žene s ADHD-om u većem su riziku za

diction when compared to the general population, even when the associated psychiatric disorders are controlled (32). Moreover, studies in which the influence of other comorbid disorders such as anxiety and depression was controlled, found a direct link between ADHD and substance use disorder (53, 55).

Attention deficit symptoms are particularly associated with dependence on nicotine (33, 58), alcohol and drugs (33).

There are no studies in Croatia on the use of psychoactive substances among individuals with ADHD. A recent study conducted on a convenience sample as part of a diploma thesis, found that there is no difference in nicotine and alcohol consumption between adults with ADHD and those without ADHD, however, those with ADHD consume illegal substances to a significantly higher extent (59). Given the higher proportion of female respondents, these results should be regarded as preliminary and treated with caution.

GENDER-SPECIFIC DIFFERENCES IN PSYCHOACTIVE SUBSTANCE USE IN INDIVIDUALS WITH ADHD

Previous studies on possible gender differences when it came to the likelihood of developing substance use disorder and the severity of the disorder in individuals with ADHD have yielded contradictory results.

Some earlier studies found no gender differences in chronic drug abuse (60), or the ADHD rates were higher in male adolescents, drug addicts (61).

According to recent studies, girls and adult women with ADHD are at a higher risk of developing drug, or alcohol (64), dependence disorder compared to male individuals with ADHD (62-64). The results of a recent study also show that impulsivity and hyperactivity have greater

razvoj poremećaja ovisnosti o drogama u odnosu muške osobe s ADHD-om (62-64) te o alkoholu (64). Rezultati jedne studije ukazuju kako impulzivnost i hiperaktivnost imaju veću prediktivnu snagu za poremećaj ovisnosti o alkoholu i drogama i zloporabu alkohola i droga kod djevojaka (65). Isto tako žene s ADHD-om koje puše duhan imaju veće simptome kod odvikavanja za vrijeme rane apstinencijske faze (66).

KOMPLEKSNOST PROBLEMA KOD OSOBA S KOMORBIDNIM ADHD-om I POREMEĆAJEM OVISNOSTI O PSIHOAKTIVNIM TVARIMA

Dosadašnja istraživanja ukazuju na kompleksnije teškoće kod ovisnika s ADHD-om u odnosu na ovisnike bez komorbidnog ADHD-a. Tako je nepovoljan utjecaj droga, alkohola na kognitivne funkcije potvrđen u više istraživanja. Konzumacija alkohola kod adolescenata smanjuje volumen sive tvari i razvoj bijele tvari (67), povećava deficit pažnje (68) i dovodi do poteškoća u verbalnom pamćenju, vizuospacijalnim funkcijama, brzini procesuiranja informacija i kognitivne kontrole (69). Budući da su ove kognitivne funkcije kod osoba s ADHD-om već oštećene (70), učestala konzumacija alkohola još nepovoljnije djeluje na razvoj adolescenata koji imaju ADHD (71). Konzumacija alkohola također povećava impulzivnost, a osobe s ADHD-om osjetljivije su na akutni dezinhibirajući učinak alkohola (72). Slično je s kokainom pa su utvrđena veća oštećenja kognitivnih funkcija u skupini ovisnika o kokainu koji imaju ADHD u odnosu na skupinu ovisnika koji nemaju ADHD (73). U usporedbi s osobama bez ADHD-a, oni s ADHD-om ranije počinju konzumirati kokain te ga konzumiraju češće i više (74). Isto tako, osobe s ADHD-om imaju veća oštećenja povezana s konzumacijom marihuane i drugih zabranjenih droga, neovisno o

predictive power for alcohol and drug dependence disorders, and alcohol and drug abuse in girls (65). In addition, women with ADHD who smoke tobacco have more severe cessation symptoms in the early withdrawal phase (66).

COMPLEXITY OF THE ISSUE IN INDIVIDUALS WITH COMORBID ADHD AND SUBSTANCE USE DISORDER

Previous studies have shown that addicts with ADHD experience more complex difficulties compared to addicts without comorbid ADHD. The adverse effect of drugs and alcohol on cognitive function have been confirmed in a number of studies. Alcohol consumption in adolescents reduces grey matter volume and white matter development (67), increases attention deficit (68) and leads to problems with verbal memory, visuospatial functions, speed of information processing and cognitive control (69). As these cognitive functions are already impaired in individuals with ADHD (70), frequent alcohol consumption has an even more unfavorable effect on the development of adolescents with ADHD (71). Alcohol consumption also increases impulsivity, and individuals with ADHD are more sensitive to the acute disinhibitory effects of alcohol (72). It is similar with cocaine, as cocaine addicts with ADHD have been found to have higher cognitive impairment than non-ADHD addicts (73). Compared to individuals without ADHD, those with ADHD start using cocaine earlier, and use it more frequently and in larger amounts (74). Similarly, individuals with ADHD have greater impairments associated with the consumption of marijuana and other illicit drugs, regardless of whether they have a comorbid behavior disorder (52).

In addition to the more adverse effect on cognitive functions in addicts with ADHD, studies

tome imaju li komorbidni poremećaj ponašanja (52).

Osim nepovoljnijeg učinka na kognitivne funkcije kod ovisnika s ADHD-om istraživanja ukazuju na veću izraženost drugih problema poput ranijeg početka, više recidiva, većih teškoća pri odvikavanju, kompleksnijeg tijeka poremećaja.

Veći broj istraživanja jasno pokazuje kako adolescenti s komorbidnim poremećajem ovisnosti o drogama/alkoholu i ADHD-om imaju raniji početak i teži tijek poremećaja ovisnosti o drogama te je u njih više recidiva (57,74-79).

Slično je s konzumacijom duhana. Veća je vjerojatnost da će osobe s ADHD-om početi pušiti duhan u ranoj dobi i da će brže doći do faze redovne konzumacije duhana u odnosu na tipičnu populaciju (80). Odrasli pušači s ADHD-om imaju veću ovisnost o nikotinu (80). Podatci o broju konzumiranih cigareta/dan u odnosu na opću populaciju su neujednačeni. Prema rezultatima istraživanja Sanchez Garcia i suradnika osobe s ADHD-om puše više cigareta/dan (81), dok prema rezultatima Rhodes i suradnika nema razlike u broju cigareta/dan (80). Intenzivniji su simptomi odvikavanja od pušenja (49, 82) te osobe s ADHD-om mogu imati više poteškoća s prestankom pušenja u usporedbi s onima bez tog poremećaja (83,84).

also suggest a greater severity of other problems, such as earlier onset, more relapses, greater difficulty in withdrawal, and a more complex course of the disorder.

The results of numerous studies clearly show that adolescents with comorbid drug/alcohol use disorder and ADHD have an earlier onset and a more severe course of addiction, and tend to relapse more frequently (57, 74-79).

The situation is similar with tobacco consumption. Individuals with ADHD are more likely to start smoking tobacco at a young age, and reach the regular tobacco use stage sooner than the typical population (80). Adult smokers with ADHD are more addicted to nicotine (80). Data on the number of cigarettes consumed per day compared to the general population is inconsistent. According to a study conducted by Sanchez Garcia et al., individuals with ADHD smoke more cigarettes per day (81), while according to Rhodes et al., there is no difference in the number of cigarettes per day (80). Symptoms of smoking cessation (49, 82) are more intense and individuals with ADHD may have more difficulty quitting smoking than those without the disorder (83, 84).

VAŽNOST DIJAGNOSTICIRANJA ADHD-a U OSOBA S POREMEĆAJEM OVISNOSTI O PSIHOAKTIVNIM TVARIMA S OBZIROM NA SPECIFIČNOSTI TRETMANA

ADHD je važno prepoznati i dijagnosticirati kod ovisnika o psihoaktivnim tvarima, jer je tim osobama s komorbidnom dijagnozom ADHD-a potreban drugačiji pristup i tretman. Schellekens *et al.* (85) temeljem rezultata istraživanja predlažu da bi probir za ADHD trebao biti standardna procedura u liječenju osoba s

IMPORTANCE OF DIAGNOSING ADHD IN INDIVIDUALS WITH SUBSTANCE USE DISORDER WITH REGARD TO THE TREATMENT SPECIFICITIES

It is important to recognize and diagnose ADHD in those addicted to psychoactive substances, as these individuals with a comorbid diagnosis of ADHD require a different approach and treatment. Based on their study results, Schellekens et al. (85) suggest that screening for ADHD should be a standard procedure in the treatment of individuals with addiction, i.e. substance use disorder.

ovisnošću, odnosno poremećajem zloporabe supstancija.

Zbog sličnosti u simptomima, ADHD se, ako nije dijagnosticiran u djetinjstvu, često previdi u ovisnika (86), budući da dugotrajna zloporaba psihoaktivnih tvari poput marihuane, kokaina, metamfetamina, alkohola i sl. dovodi do oštećenja kognitivnih funkcija, pažnje, pamćenja, izvršnih funkcija (87). Unatoč navedenim sličnostima u simptomima istraživanja pokazuju kako je moguće pouzdano dijagnosticirati ADHD čak i kod onih koji nisu u potpunosti apstinenti (47), a Van de Glind *et al.* (54) su uspjeli dokazati na međunarodnom uzorku kako je upitnik za samoprocjenu simptoma ADHD-a kod odraslih *The Adult ADHD Self-Report Scale* (ASRS) dovoljno dobra mjera za probir ADHD-a u populaciji pacijenata s ovisnosti o psihoaktivnim tvarima. Procjena ADHD-a uključuje kompletnu anamnezu uključujući razvojnu povijest bolesti, kao i mentalno stanje pojedinca te funkcioniranje u svim situacijama; podatke koji se prikupljaju od pacijenta ali i od bliskih srodnika (54). Osobito je važno prikupiti podatke o simptomima koji su bili prisutni prije poremećaja ovisnosti o psihoaktivnim tvarima i koji su prisutni u razdoblju apstinencije kako bi se utvrdilo radi li se o primarnim simptomima ili su potaknuti konzumacijom psihoaktivnih tvari (88).

Dijagnozu ADHD-a važno je postaviti što ranije u dječjoj dobi, budući da liječenje stimulansima tijekom djetinjstva može smanjiti rizik od razvoja poremećaja ovisnosti o psihoaktivnim tvarima, osobito ako se s terapijom započne rano (53,58,90). Isto tako psihosocijalne intervencije usmjerene na djecu s ADHD-om, ali i na roditelje, učitelje i vršnjake mogu prevenirati razvoj poremećaja ovisnosti o psihoaktivnim tvarima (81,91).

Osim toga, važno je što ranije dijagnosticirati ADHD kod pacijenata s poremećajem ovisnosti o psihoaktivnim tvarima jer, kao što dosadašnja istraživanja pokazuju, tretman ovi-

Due to the similarity of symptoms, ADHD in addicts is often overlooked if it had not been diagnosed in childhood (86), since long-term abuse of psychoactive substances such as marijuana, cocaine, methamphetamine, alcohol etc. leads to impaired cognitive, as well as attention, memory and executive functioning (87). Despite these similarities in symptoms, studies have shown that ADHD can also be reliably diagnosed even in individuals who are not completely abstinent (47), and the authors Van de Glind et al. (54) were able to demonstrate on an international sample that the Adult ADHD Self–Report Scale (ASRS), a self-assessment questionnaire of ADHD symptoms in adults, is a sufficient measure for ADHD screening in the population of patients with psychoactive substance use. The assessment of ADHD involves a complete medical history, including developmental and medical history, as well as the individual's mental state and functioning in all situations; and the data collected from the patients, but also from their close relatives (54). It is particularly important to collect data on the symptoms that were present before the substance use disorder and those that are present during the period of abstinence, in order to determine whether they are primary symptoms or whether they were triggered by the use of psychoactive substances (88).

It is important to diagnose ADHD as early as possible in childhood, since stimulant therapy in childhood can reduce the risk of developing substance use disorder, especially if therapy is started early (53, 58, 90). Similarly, psychosocial interventions aimed at children with ADHD, but also at parents, teachers and peers, can prevent the development of substance use disorder (81, 91).

In addition, it is important to diagnose ADHD as early as possible in patients with substance use disorder because, as previous research suggests, the treatment of addiction should probably be different for people with a diagnosis of

snosti kod osoba s komorbidnom dijagnozom ADHD-a vjerojatno treba biti drugačiji. U preglednom radu Zaso *et al.* (92) zaključuju kako je znanje o liječenju komorbidnog ADHD-a i ovisnosti o psihoaktivnim tvarima u adolescenciji ograničeno. Čini se da tretman koji bi uključivao medikamentnu terapiju nije naročito učinkovit u liječenju poremećaja ovisnosti o psihoaktivnim tvarima u osoba s ADHD-om. Istraživanja pokazuju da osobe koje imaju izraženije simptome ADHD-a i koje su u tretmanu zbog poremećaja zloporabe tvari imaju manju dobit od terapije (60) te postoji manja vjerojatnost da će napredovati tijekom terapije i ostati u terapiji (86). Buduća bi se istraživanja trebala usmjeriti na donošenje odgovora o najboljoj medikamentnoj terapiji za osobe s ADHD-om koje imaju komorbidni poremećaj zloporabe tvari (85).

Zulauf i sur. (18) zaključuju kako je u tretman adolescenata i mladih odraslih osoba s ADHD-om i poremećajem ovisnosti o psihoaktivnim tvarima potrebno uključiti obitelj. Nakon što je uzimanje psihoaktivnih tvari pod kontrolom, u liječenju mogu biti učinkovite strukturirane psihoterapije poput kognitivno bihevioralnog tretmana (18). No, potrebna su buduća placebom kontrolirana klinička ispitivanja na velikim uzorcima kako bi se ispitala učinkovitost psihoterapijskih intervencija, budući da u dosadašnjim istraživanjima ne možemo isključiti alternativna objašnjenja poput utjecaja placeba ili tzv. efekta Hawthorne (92).

RASPRAVA

Dosadašnja istraživanja jasno su utvrdila vezu između ADHD-a i ovisnosti o psihoaktivnim tvarima, što ukazuje na potrebu probira na ADHD kod ovisnika o psihoaktivnim tvarima. Temeljem pregleda istraživanja o mehanizmima povezanosti ADHD-a i poremećaja ovisnosti možemo zaključiti kako nema jednoznačnog odgovora o razlozima povezanosti te je vjero-

comorbid ADHD. In their review article, Zaso et al. (92) concluded that knowledge about the treatment of comorbid ADHD and adolescent psychoactive substance use is limited. Medication-only treatment does not appear to be particularly effective in the treatment of substance use disorder in individuals with ADHD. Studies show that people with more severe ADHD symptoms who are being treated for substance use disorder are less likely to benefit from therapy (60), and they are less likely to make progress during therapy and remain in therapy (86). Future studies should focus on finding the best medication therapy for ADHD patients with comorbid substance use disorder (85).

Zulauf et al. (18) observed that family involvement is necessary in the treatment of adolescents and young adults with ADHD and substance use disorder. Once psychoactive substance use is under control, structured psychotherapies such as cognitive behavioral therapy can be effective in treatment (18). However, future placebo-controlled clinical trials on large samples are necessary in order to investigate the effectiveness of psychotherapeutic interventions, because studies conducted so far could not rule out alternative explanations such as the placebo effect or the so-called Hawthorne effect (92).

DISCUSSION

Previous studies have clearly established an association between ADHD and substance use disorder, indicating the need for screening for ADHD in individuals using psychoactive substances. Based on a review of studies addressing the mechanisms of association between ADHD and substance use disorder, we can conclude that there is no clear answer as to the reasons for the association, and that a combination of neurobiological and environmental factors is likely to be the cause. There

jatno odgovorna kombinacija neurobioloških i okolinskih čimbenika. Postoje dokazi o zajedničkoj genetskoj podlozi, o neurobiološkim preklapanjima. Isto tako postoje istraživanja koja upućuju na okolinske čimbenike povezanosti. Važno je nastaviti ispitivanje rizičnih i protektivnih čimbenika okoline kako bismo unaprijedili prevenciju razvoja ovisnosti o psihoaktivnim tvarima kod osoba s ADHD-om.

Neka istraživanja idu u prilog teoriji komorbiditeta, no s druge strane rezultati drugih istraživanja opovrgavaju ovu teoriju. Preporučuje se nastaviti s kontroliranim longitudinalnim studijama s međunarodnim uzorcima kako bi se donijeli jasniji zaključci.

S obzirom na oprečne rezultate potrebno je daljnje istraživanje spolnih razlika kod osoba s komorbidnim ADHD-om i poremećajem ovisnosti o psihoaktivnim tvarima. Moguće je da se s godinama stopa zloporabe psihoaktivnih tvari u žena s ADHD-om povećala. ADHD u žena se sve više otkriva, za razliku od prije kada je smatran većinom muškim poremećajem, što je također moglo utjecati na razlike između ranijih i recentnijih istraživanja. Ono što posebno nedostaje u dosadašnjim istraživanjima jest usmjeravanje na moguće različite tretmane i metode prevencije s obzirom na različitosti u razvoju i funkcioniranju muškaraca i žena. Moguće je da su različiti rizični, ali i protektivni faktori važni za razvoj poremećaja ovisnosti kod žena s ADHD-om u odnosu na muškarce s ADHD-om.

Za sada nema definitivnog odgovora na pitanje o najboljem tretmanu za pacijente s poremećajem ovisnosti s komorbidnim ADHD-om jer ima malo istraživanja na ovom području. Ono što se do sada zna jest da klasičan tretman za poremećaj ovisnosti nije dovoljan, kao ni medikamentna terapija namijenjena ADHD-u. Istraživanja podržavaju multimodalni tretman koji bi uključivao adekvatan odabir medikamenata zajedno s odgovarajućom psihosocijalnom intervencijom.

is evidence of a common genetic background, neurobiological overlaps. There are also studies that point to environmental factors in terms of association. It is important to further investigate the environmental risk and protective factors in order to improve the prevention of psychoactive substance use development in individuals with ADHD.

Some studies support the theory of comorbidity, but on the other hand, the results of other studies refute this theory. It is recommended to continue with controlled longitudinal studies on international samples, in order to draw clearer conclusions.

Given the conflicting results, further research on the gender differences in individuals with comorbid ADHD and substance use disorder is necessary. It is possible that the rate of psychoactive substance abuse in women with ADHD has increased over the years. ADHD in women is being identified more frequently, unlike in the past when it was considered primarily a male disorder, which may also have influenced the differences between the earlier and more recent studies. What is particularly lacking in previous studies is a focus on possible different treatments and prevention methods, considering the differences in development and functioning between males and females. It is possible that different risk and protective factors are important for the development of addictive disorders in women with ADHD compared to men with ADHD.

There is so far no definitive answer to the question of the best treatment for patients with substance use disorder and comorbid ADHD, because there are few studies in this area. What is known so far is that traditional treatment for substance use disorder is not sufficient, nor is the medication treatment intended for ADHD. Studies support a multimodal treatment that would include an adequate selection of medications along with an appropriate psychosocial intervention.

ZAKLJUČAK

Ovim narativnim pregledom nastojalo se u prikazu istraživanja odgovoriti na pitanje zašto je važno posebno obratiti pažnju na skupinu pacijenata s poremećajem ovisnosti o psihoaktivnim tvarima s komorbidnim ADHD-om. Istraživanja jasno pokazuju povezanost između tih dvaju poremećaja. Iako uzroci čestog komorbiditeta nisu do kraja razjašnjeni, rezultati istraživanja idu u prilog zaključku kako je riječ o kombinaciji neurobioloških čimbenika i čimbenika okoline. Kod ove skupine pacijenata lošije su prognoze s obzirom na poremećaj ovisnosti zbog čestih recidiva i izraženijih simptoma poremećaja, a rano prepoznavanje ADHD-a i terapija stimulansima mogu smanjiti rizik za poremećaj ovisnosti o psihoaktivnim tvarima. Rezultati istraživanja ukazuju na potrebu za drugačijim tretmanom ovisnika s komorbidnim ADHD-om koji bi osim medikamentne terapije uključivao i druge pristupe. Iduća istraživanja trebala bi se usmjeriti na dobivanje odgovora na pitanje o najboljem tretmanu za poremećaj ovisnosti o psihoaktivnim tvarima u pacijenata s ADHD-om te se dodatno usmjeriti na spolne razlike s obzirom na spefičnosti procjene i tretmana.

CONCLUSION

This aim of this narrative review was to answer the question of why it is important to pay particular attention to the group of patients with substance use disorder and comorbid ADHD. Studies clearly show an association between these two disorders. Although the causes of frequent comorbidity are not yet fully understood, research results suggest that it is a combination of neurobiological and environmental factors. The prognosis for this patient group is poorer in terms of substance use disorder, due to frequent relapses and more pronounced symptoms of the disorder. Early recognition of ADHD and stimulant therapy can reduce the risk of substance use disorder. Study findings point to the need for a different treatment of addicts with comorbid ADHD, which includes other approaches in addition to medication. Future studies should focus on obtaining an answer to the question of the best treatment for substance use disorder in patients with ADHD, and should additionally focus on gender differences, taking into account the specificity of assessment and treatment.

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Forenzička obilježja počinitelja ubojstva intimne partnerice

/ Forensic Traits of Intimate Partner Femicide Perpetrators

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Prevencija partnerskog nasilja kao i počinjenja kaznenih djela ubojstva prema intimnoj partnerici stalni su izazov u otkrivanju rizičnih faktora i prepoznavanja vjerojatnosti da se dogode uz pružanje što ranijih intervencija kako bi se spriječili. Cilj rada je dati pregled dosadašnjih istraživanja koja se odnose na počinitelje ubojstava intimnih partnerica, kako od tipologije počinitelja, ranijeg nasilnog ponašanja, postojanja psihičkih poremećaja, utjecaja alkohola i droga, tako do utjecaja depresije i suicidalnih ideja na počinjenje ubojstva ili ubojstva-samoubojstva. Zaključno se ističe važnost prepoznavanja mogućih počinitelja od stručnjaka s kojima počinitelji potencijalno dolaze u susret, iz područja zdravstva, policije, socijalne skrbi, pravosudnog sustava, kao i važnost edukacije javnosti o potencijalnoj opasnosti i mogućim fatalnim posljedicama najtežih kaznenih djela kako bi se pružile što ranije zaštitne i terapijske intervencije žrtvama partnerskog nasilja.

/ Prevention of intimate partner violence and the criminal offense of intimate partner femicide represent a constant challenge for identifying the risk factors and recognizing the likelihood of their occurrence, while providing the earliest possible interventions in order to prevent them. The aim of this paper is to present an overview of the previous studies addressing the topic of intimate partner femicide perpetrators, both in terms of the typology of perpetrators, their previous violent behavior, existence of mental disorders, the influence of alcohol and drug abuse, as well as the influence of depression and suicidal ideations on the perpetration of homicide or homicide-suicide. In conclusion, the importance of professionals recognizing the possible perpetrators among those they potentially encounter is emphasized, whether from the areas of health, police, social welfare or the judicial system, along with the importance of educating the public about the potential danger and the possible fatal consequences of the most serious criminal offenses, in order to provide protective and therapeutic interventions to the victims of intimate partner violence as soon as possible.

ADRESA ZA DOPISIVANJE /
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UVOD

Obiteljsko nasilje i borba protiv nasilja stalno je u fokusu zakonskih i drugih intervencija društva, kako bi se pružila zašita žrtvama i preveniralo nasilje. – Prema Savezu za prevenciju nasilja (*Violence Prevention Alliance*, VPA) Svjetske zdravstvene organizacije, a definirano u Svjetskom izvješću o nasilju i zdravlju (*World Report on Violence and Health*, WRVH), nasilje je „namjerna uporaba fizičke sile ili moći, prijetnje ili stvarne, protiv sebe, druge osobe ili protiv skupine ili zajednice, što rezultira ili postoji velika vjerojatnost da će rezultirati ozljedama, smrću, psihičkim ozljedama, lošim razvojem ili uskraćenošću" (1). Kod žrtava partnerskog nasilja, naročito kod kontinuiranog zlostavljanja može doći do brojnih posljedica na mentalno zdravlje žrtve kao što su razvoj depresije, suicidalnosti i posttraumatskog stresnog poremećaja (2). Počinjenje kaznenih djela prema intimnoj partnerici izazov je za prevenciju i identifikaciju faktora rizika te prepoznavanja opasnosti da se dogode, kao i pružanja što ranijih intervencija kako bi se spriječila. Najteža kaznena djela počinjenja pokušaja ubojstva ili ubojstva, kao i ubojstva-samoubojstva u obitelji, predstavljaju posebno tragične događaje nakon kojih se postavljaju pitanja da li je počinitelj imao neki od psihičkih poremećaja (3), da li je od ranije bilo postojanja nasilja i određenih specifičnosti kod počinitelja koji su mogli pomoći prepoznavanju i sprječavanju mogućeg zločina. S jedne strane, moguće je da se nasilje odvija prema ponavljajućem obrascu agresivnosti i može, ali i ne mora, završiti ubojstvom, dok je s druge strane moguće da se ubojstvo dogodi bez prethodnih epizoda nasilja (4). Obiteljska ubojstva su fatalan oblik obiteljskog nasilja i tragičan događaj (5). Ubojstva se često događaju nakon intenzivne interakcije žrtve i počinitelja, što daje mogućnost prepoznavanja određenih pokazatelja koji mogu dovesti do ubojstva, kao što su dinamika odnosa sa žrtvom, prethodna povijest nasilja, ovisnost o alkoholu i drugi čimbenici (6), a kumulacijom

INTRODUCTION

Domestic violence and fight against violence are constantly the focus of legal and other interventions in the society, all with the aim of providing protection for the victims and to prevent violence. According to the WHO Violence Prevention Alliance (VPA), and as defined in the World report on violence and health (WRVH), violence is "the intentional use of physical force or power, threatened or actual, against oneself, another person, or against a group or community, that either results in or has a high likelihood of resulting in injury, death, psychological harm, maldevelopment or deprivation" (1). Experiencing intimate partner violence, particularly on a continuous basis, can lead to numerous consequences for the mental health of the victims, such as depression, suicidality and post-traumatic stress disorder (2). The commission of criminal offenses against one's intimate partner is a challenge for the prevention and identification of risk factors, and for recognizing the danger of their occurrence, as well as the provision of the earliest possible interventions in order to prevent them. The most serious criminal offenses of attempted homicide or homicide, as well as family homicide-suicide, are especially tragic events after which questions arise as to whether the perpetrator suffered from a mental disorder (3), whether there were earlier occurrences of violence and certain specificities as regards the perpetrator which could have helped recognize and prevent the possible crime. On the one hand, it is possible for violence to occur according to a repeating pattern of aggression, and it can, but does not have to, end in homicide, while on the other hand, it is possible for homicide to occur without previous episodes of violence (4). Family homicides are a fatal form of domestic violence and a tragic event (5). Homicides are often the result of an intense interaction between the victim and the perpetrator, which enables us to identify certain indicators that may lead to their occurrence, such as the dynamics of the relationship with the victim, previous history of violence, alcohol addiction and other factors (6), while a cumulation of various previous forms

prethodnih različitih oblika zlostavljanja postoji rizik za počinjenje ubojstva bliske osobe (7).

Počinjenje ubojstva intimnog partnera je namjerno ubojstvo sadašnjeg ili bivšeg intimnog partnera (8). Teški oblici nasilja, kao i počinjenja pokušaja ili izvršena ubojstva intimne partnerice tragični su događaji. Dok se desetljećima primjećuju trendovi pada stopa ubojstava, stope ubojstva intimne partnerice ostale su stabilne (3), a istraživanja iz europskih zemalja o stopama i karakteristikama relativno su rijetka. Ubojstvo intimne partnerice i ubojstvo-samoubojstvo predstavlja ozbiljan društveni, kaznenopravni i javnozdravstveni problem (9).

U svrhu ovog narativnog preglednog rada proučena su istraživanja o počiniteljima ubojstava i ubojstava-samoubojstava intimnih partnerica koristeći se bazama PubMed, SCOPUS i Google Scholar za literaturu objavljenu od 2000. do danas. Ključne riječi bile su „homicid", „homicid-suicide", „intimate partner", „femicid", „mental health", „domestic violence", „forensic", „psychiatric", „perpetrators", „depression". Izdvojena su relevantna istraživanja važna za razumijevanje forenzičkih karakteristika počinitelja u svrhu boljeg razumijevanja rizičnih faktora te dobivanje uvida u neke od trenutnih spoznaja u navedenom području, što bi moglo pomoći u svakodnevnom stručnom interdisciplinarnom radu u prevenciji najtežih kaznenih djela prema intimnim partnericama.

SOCIODEMOGRAFSKE KARAKTERISTIKE POČINITELJA I SITUACIJSKI RIZIČNI FAKTORI

Istraživanje Cechova-Vayleux i sur. (10) pokazalo je da je prosječna dob 32 počinitelja ubojstava intimne partnerice bila 37,8 godina, uglavnom su bili fizički radnici. U 69 % ispitanika bilo je evidentirano ranije psihijatrijsko liječenje i ranije kažnjavanje (31 %), a depresija i suicidalne ideje bile su češće nego kod poči-

of violence represents a risk for the occurrence of family homicide. (7).

Intimate partner homicide is the intentional killing of one's current or former intimate partner (8). Serious forms of violence, as well as attempted or committed intimate partner femicide, are tragic events, however, while downward trends in homicide rates have been observed for decades, intimate partner femicide rates have remained stable (3) and studies addressing their rates and characteristics in European countries are relatively rare. Intimate partner femicide and homicide-suicide represent a serious social, criminal justice and public health issue (9).

For the purpose of this narrative review, studies on the perpetrators of intimate partner femicide and homicide-suicide were analyzed using the databases PubMed, SCOPUS and Google Scholar for the literature published since 2000. The key words used were *"homicide", "homicide-suicide", "intimate partner", "femicide", "mental health", "domestic violence", "forensic", "psychiatric", "perpetrators", "depression"*. Relevant studies important for the understanding of the forensic traits of perpetrators were singled out for the purpose of providing a better understanding of the risk factors, as well as to gain insight into some of the current findings in this area, which might help in the daily professional interdisciplinary work in terms of preventing the most serious criminal offenses against female intimate partners.

SOCIODEMOGRAPHIC TRAITS OF PERPETRATORS AND SITUATIONAL RISK FACTORS

A study conducted by Cechova-Vayleux et al. (10) revealed that the average age of the 32 monitored intimate partner femicide perpetrators was 37.8 years, and they were mainly manual workers. A total of 69% of respondents had undergone previous psychiatric treatment and had previous convictions (31%), while depression and suicidal ideations were more common than in non-do-

nitelja ubojstva izvan obitelji. Kod polovine počinitelja postojao je traumatični događaj prije osamnaeste godine. U odnosu na počinitelje ubojstava izvan obitelji rjeđe su imali raniju kažnjavanost. U najvećem broju slučajeva ubojstvo se dogodilo u večernjim satima, u kući žrtve, dok je počinitelj bio u alkoholiziranom stanju, uz ostajanje na mjestu zločina. Pavliček i sur. (6) također navode da su u preko 90 % slučajeva počinitelji odmah poznati i u pravilu zatečeni na mjestu događaja, priznaju počinjenje kaznenog djela. Ubojstva u obitelji u pravilu se čine situacijski, u manjem broju slučajeva je postojala namjera za počinjenje ubojstva tijekom duljeg razdoblja uz pripremne radnje. Dostupnost vatrenog oružja i odvajanje od žrtve faktori su rizika za počinjenje ubojstva intimne partnerice (11,12), što je u pojedinim profesijama i dostupnije, a vatreno oružje povećava rizik i za počinjenje samoubojstva nakon ubojstva. Ljubomora, svađe i sukobi te nesposobnost prihvaćanja prekida veze mogu biti čimbenici odnosno motivi počinjenja ubojstva intimne partnerice (9,12).

Znatan udio počinitelja evidentiran je zbog ranijeg nasilja prema žrtvi, koje je bilo u domeni prekršajne odgovornosti, ali i kaznenih djela (6). Vezano za karakteristike počinitelja ubojstva Soria i sur. (4) navode njihovu potrebu za prikazivanjem društvene slike „dobre obitelji" te su imali jače nezadovoljstvo neostvarenim idealom žene, koristili manje verbalnih prijetnji tijekom napada te nisu skloni objašnjavati unutarnje sukobe para i obitelji široj obitelji i drugima.

U odnosu na muškarce počinitelje ubojstva kod kojih je jedan od najčešćih motiva prijetnja prekida veze, žene najčešće ubijaju svog intimnog partnera nakon dugotrajnog zlostavljanja, a ubojstvo je reakcija na nasilje (13,14). Istraživanje u Švedskoj objavljeno 2024. godine (15), koje je provedeno od 2000. do 2016. g. o počiniteljima ubojstva intimnog partnera pokazuje da su muški počinitelji imali značajno

mestic homicide perpetrators. Half of the respondents had experienced a traumatic event before the age of 18. Compared to non-domestic homicide perpetrators, previous convictions were less common. In the majority of the cases, the homicide occurred in the evening, in the victim's home, while the perpetrator was intoxicated and remained at the crime scene. Pavliček et al. (6) also state that the perpetrators are immediately known in 90% of the cases and are generally found at the crime scene, admitting to having committed the criminal offense. Family homicides are typically situational, while a smaller number of cases involved intent to commit homicide over a longer period of time and included preparatory actions. The availability of firearms and separation from the victim are risk factors for the commission of intimate partner femicide (11, 12), and they are more accessible in some professions, while the possession of firearms also increases the risk of suicide after committing homicide. Jealousy, arguments and conflicts, as well as inability to accept the termination of a relationship, can be factors i.e. motives for intimate partner femicide (9, 12).

A significant share of perpetrators already had criminal records due to previous acts of violence against the victim which fell under the category of misdemeanor, but also criminal offenses (6). In relation to the traits of homicide perpetrators, Soria et al. (4) point to their need for presenting a social image of a "good family" and stronger dissatisfaction with an unfulfilled female ideal, use of verbal threats during attacks and refusal to explain the internal conflicts of the couple and family to the extended family and others.

As opposed to male perpetrators, for whom the main motive is usually the threat of ending the relationship, women most often kill their intimate partners after being subjected to violence for long periods of time, and homicide is a reaction to the violence suffered (13, 14). A study addressing the perpetrators of intimate partner homicide which was conducted in Sweden in the period between 2000 and 2016 and was published in 2024 (15), indicates that male perpetrators had significantly

više registriranih zdravstvenih kontakata i psi-
hičkih poremećaja ili poremećaja ponašanja u
mjesecu i godini prije ubojstva uključujući i dan
ubojstva te da su osim kontakta s primarnom i
specijaliziranom ambulantom bili nezaposleni
i primali socijalnu pomoć.

TIPOLOGIJA POČINITELJA

U literaturi postoje različite podjele na tipolo-
gije počinitelja ubojstava u obitelji. Tako npr.
Holtzworth-Munroe (16) navodi podjelu poči-
nitelja na one bez jasne psihopatologije i pore-
mećaja ličnosti kod kojih je moguća niska do
umjerena razina depresije i zloporaba psiho-
aktivnih tvari te umjerena razina ljutnje (17).
Kod disforično/graničnog tipa uočava se često
granična ili shizoidna ličnost uz veće razine
ljutnje i visoku vjerojatnost dijagnoze depre-
sije, a kod antisocijalnih počinitelja sa sklono-
šću konzumaciji psihoaktivnih tvari rijetka je
depresija, a stupanj ljutnje je srednjeg intenzi-
teta. Kivisto (8) muške počinitelje partnerskog
ubojstva dijeli na osobe sa psihičkim smetnja-
ma, nedovoljno kontrolirane/disregulirane,
kronične zlostavljače i pretjerano kontrolira-
ne/katatimične. Osobe sa psihičkim smetnja-
ma često u vrijeme počinjenja djela iskazuju
simptome bolesti, a od ranije pokazuju rijetko
nasilno ponašanje ili zloporabu sredstava ovi-
snosti. Kod nedovoljno kontroliranog/disregu-
liranog podtipa može biti prisutna dijagnoza
poremećaja raspoloženja ili anksioznosti, no
s manje akutne psihopatologije. Kod takvih
osoba postoje i znakovi graničnog poremećaja
ličnosti sa značajnom disregulacijom raspo-
loženja, uz afektivno uzrokovano nasilje sa
strahovima od napuštanja i osjećajima ljubo-
more. Kod njih je vjerojatnija ranija zloporaba
sredstava ovisnosti te je moguć umjereni rizik
od pokušaja samoubojstva nakon ubojstva.
Podtip kroničnog zlostavljača pokazuje manje
afektivne disregulacije te su to često osobe s
dijagnozom disocijalnog ili narcističkog po-

more registered medical contacts and mental dis-
orders or behavioral disorders in the month and
year prior to the homicide, including the day it
was committed, and in addition to contacts with
primary and specialized health clinics, they were
unemployed and received social welfare assis-
tance.

THE TYPOLOGY OF PERPETRATORS

There are different classifications in the literature
as regards the typology of domestic homicide per-
petrators. Thus, for example, Holtzworth-Munroe
(16) classifies perpetrators to those without clear
psychopathology and personality disorders, for
which there is a possibility of low to moderate
level of depression and psychoactive substance
abuse, and a moderate level of anger (17). In
the dysphoric/borderline type, a borderline or
schizoid personality often occurs, with a higher
degree of anger and high likelihood of being di-
agnosed with depression, while depression is rare
in antisocial perpetrators with a tendency to use
psychoactive substances and their degree of an-
ger is of medium intensity. Kivisto (8) classifies
male perpetrators of intimate partner homicide
into the mentally ill, the undercontrolled/dys-
regulated, chronic batterer, and overcontrolled/
catathymic subtypes. Individuals who are men-
tally ill often present symptoms of illness while
committing the crime, and have on rare occasions
presented with violent behavior or addictive sub-
stance abuse before. In the undercontrolled/
dysregulated subtype, they could be diagnosed
with mood or anxiety disorder, however, with
less acute psychopathology. In such individuals,
there are also signs of borderline personality dis-
order with significant emotional dysregulation,
in addition to affective violence accompanied by
the fear of abandonment and feelings of jealou-
sy. They are more likely to have had a history of
addictive substance abuse and there is a mod-
erate risk of a suicide attempt after committing
homicide. The chronic batterer subtype shows

remećaja ličnosti. Napuštanje je čest uzrok ubojstva, a moguć je i rizik od samoubojstva. Pretjerano kontrolirani muški počinitelji imaju bolju razinu funkcioniranja, minimalnu psihopatologiju te dijagnozu ovisnog ili shizoidnog poremećaja osobnosti. Ranije nasilje postoji u malom broju slučajeva, a neočekivani eksplozivni ispad impulzivnog, često destruktivnog ponašanja razumljiv je u smislu nesvjesne motivacije (8). Vignola-Lévesque (18) navodi podjelu na napuštenog partnera, općenito ljutitog/agresivnog, kontrolirajućeg nasilnog partnera te nestabilno ovisnog partnera. Također ističe doprinos postojanja aleksitimije kod počinitelja.

PSIHIČKI POREMEĆAJI KOD POČINITELJA UBOJSTVA INTIMNE PARTNERICE

Kada se govori o psihološko-psihijatrijskom aspektu nasilja, podrazumijeva se nasilje osoba sa psihičkim poremećajima, no osobe sa shizofrenijom i sličnim poremećajima najčešće nisu nasilnici, nego su to osobe iz skupine sa psihičkim poremećajima u dijagnostičkoj kategoriji poremećaja ličnosti kao što su npr. disocijalni, granični i paranoidni (19).

Počinitelji ubojstva intimne partnerice obično su manje emocionalno stabilni, odnosno imaju visoki neuroticizam kao i nisku ekstraverziju, pokazuju sklonost bizarnosti, agresivniji su ili manje empatični odnosno imaju visoki psihoticizam (20). Istraživanje Caman i sur. (3) provedeno u Švedskoj na 179 ubojstava od 2007. do 2009. godine počinjenih od muškaraca od kojih su 26 % bila ubojstva partnerica pokazala je da je jedna trećina počinitelja, bez obzira na vrstu ubojstva, imala od ranije dijagnosticiran psihički poremećaj nekad u životu (isključujući poremećaje povezane s uzimanjem psihoaktivnih tvari), uz niske stope ozbiljnih mentalnih poremećaja u obje skupine (11 %). Počinitelji ubojstava žena imali su manju uče-

less affective dysregulation and often involves individuals diagnosed with dissocial or narcissistic personality disorder. Termination of the relationship is a common cause of homicide, and the risk of suicide is also present. Overcontrolled male perpetrators have a better level of functioning and minimal psychopathology, and can be diagnosed with dependent or schizoid personality disorder. A history of violence exists in a small number of cases, while unexpected outbursts of impulsive, often destructive behavior are present in terms of unconscious motivation (8). Vignola-Lévesque (18) classified perpetrators into abandoned partner, generally angry/aggressive partner, controlling violent partner and unstable dependent partner. She also pointed to the fact that the existence of alexithymia contributes to the actions of the perpetrators.

MENTAL DISORDERS IN INTIMATE PARTNER FEMICIDE PERPETRATORS

In terms of the psychological-psychiatric aspect of violence, it is implied that the act of violence is committed by individuals with mental disorders, however individuals with schizophrenia or similar disorders are most commonly not violent and instead pertain to the group of individuals with mental disorders in the diagnostic category of personality disorders, such as dissocial, borderline and paranoid personality disorder (19).

Intimate partner femicide perpetrators are usually less emotionally stable, that is, they display high neuroticism and low extraversion, they are prone to bizarreness, they are more aggressive or less empathetic, i.e. they have high psychoticism (20). In a study conducted in Sweden, Caman et al. (3) analyzed a total of 179 homicides perpetrated by men from 2007 to 2009, of which 26% were intimate partner femicides, and the results showed that one third of the perpetrators, regardless of the type of homicide, had been at some point in their lives diagnosed with a mental disorder (excluding disorders relating to psycho-

stalost poremećaja iz skupine korištenja psihoaktivnih tvari. „Ubojstvo-samoubojstvo" bilo je relativno često kod počinitelja femicida (20 %). Pavliček i sur. (6) su kod počinitelja obiteljskih ubojstava našli da se kod počinitelja koji su prije ili nakon kaznenog djela pokušali samoubojstvo nalazi znatan udio onih s dijagnosticiranim nekim oblikom duševne bolesti.

Počinitelji sa disocijalnim poremećajem ličnosti, koji su inače često zastupljeni kod nasilnih kaznenih djela, manje su učestali kod počinitelja ubojstva supružnika gdje je češće prisutan granični ili narcistični poremećaj ličnosti, depresivno disforični poremećaj (depresija), konzumacija alkohola ili droga (21,22). Strah od napuštenosti, odnosno prekida veze, može utjecati na emocionalnu nestabilnost te potencijalni razvoj depresivnosti kod osoba koje imaju predisponirajuće osobine ličnosti.

PSIHOTIČNI POREMEĆAJI

Posebnu pažnju u dijagnostičkoj i terapijskoj forenzičkoj evaluaciji treba obratiti postojanju psihotične ljubomore (23) koja je povezana s najvećim stupnjem opasnosti kod paranoidne psihoze i paranoidne shizofrenije (24). „Abnormalna" ljubomora može postojati kod osoba s poremećajem ličnosti, psihoorganski uvjetovanim poremećajima, psihogenim afektivnim reakcijama, zloporabom alkohola ili droga i sl., ali ne dostiže kvalitetu psihotičnog poremećaja. Psihotična (patološka, bolesna) ljubomora je stanje kod kojeg su prisutne sumanute ideje ljubomore. Posebno je važna ljubomora koja se može javiti kod ovisnika o alkoholu (24). Također, pojava uhođenja žrtve može biti u korelaciji s nasiljem nad ženama i, zajedno s fizičkim napadom, može se smatrati čimbenikom rizika za najteža kaznena djela (25). Paranoidne ideje koje dosežu razinu sumanutosti mogu biti rizik za nasilje, naročito

active substance abuse), while the rates of serious mental disorders in both groups were low (11%). There was a lower incidence of disorders from the psychoactive substance use group among the perpetrators of femicide. "Homicide-suicide" was relatively common among femicide perpetrators (20%). Among family homicide perpetrators, Pavliček et al. (6) found that a significant share of those who attempted suicide before or after the criminal offense was diagnosed with some form of mental illness.

Perpetrators with dissocial personality disorder, which are generally often among those committing violent crimes, were less common among spousal homicide perpetrators, where borderline or narcissistic personality disorder, depressive dysphoric disorder (depression), and alcohol or drug use were more commonly present (21, 22). Fear of abandonment, i.e. termination of the relationship, can affect emotional instability and potentially lead to depression in individuals with predisposing personality traits.

PSYCHOTIC DISORDERS

In diagnostic and therapeutic forensic evaluation, special attention should be paid to the existence of psychotic jealousy (23) which is associated with the highest degree of danger in cases of paranoid psychosis and paranoid schizophrenia (24). "Abnormal" jealousy can exist in individuals with personality disorders, psycho-organic disorders, psychogenic affective reactions, alcohol or drug abuse etc., but does not reach the quality of a psychotic disorder. Psychotic (pathologic, sick) jealousy, is a state of having delusional dimensions of jealousy. Particularly important is the jealousy that can manifest in alcohol addicts (24). Furthermore, stalking the victim may be correlated with violence against women and, in addition to physical assault, can be considered a risk factor for the most serious criminal offenses (25). Paranoid ideas reaching the level of delusion can be a risk factor for violence, particularly when they are comorbid with antisocial personality disorder (26).

kada su komorbidne s antisocijalnim poremećajem ličnosti (26).

U Engleskoj i Walesu oko 10 % počinitelja ubojstava imalo je simptome psihičkog poremećaja u vrijeme ubojstva. Od 1.180 počinitelja partnerskog ubojstva 20 % je imalo simptome psihičkog poremećaja u vrijeme djela, od toga 7 % simptome psihoze, a 13 % depresije, dok je 30 % počinitelja sa simptomima psihičkog poremećaja bilo u kontaktu sa službama za mentalno zdravlje u godini prije kaznenog djela (27).

U istraživanju provedenom na Odjelu za forenzičku psihijatriju Neuropsihijatrijske bolnice „Dr. Ivan Barbot" Popovača (28) na neubrojivim shizofrenim počiniteljima obiteljskog ubojstva vidi se da su češće žrtve bili roditelji i siblicidi. Kod osoba sa shizofrenim i sumanutim poremećajima česta je pri ubojstvu uporaba oštrih predmeta (29). Moguće je da su uobičajeni simptomi poremećaja iz spektra shizofrenije, kao što su paranoidne ideje povezane s općim nasiljem, ali ne nužno s nasiljem nad intimnim partnerima. Veći postotak počinitelja obiteljskog nasilja ima dijagnozu shizofrenije nego počinitelji ubojstva intimne partnerice (30). Dijagnoze shizofrenije, shizoafektivnog poremećaja, bipolarnog poremećaja i/ili depresije sa psihotičnim simptomima nisu bile ranije učestalo evidentirane u okviru psihijatrijskog praćenja prije kaznenog djela ubojstva (3).

Počinitelji obiteljskih ubojstava imali su znatno veće stope psihijatrijskih dijagnoza, dok su počinitelji parterskog ubojstva bili češće bez psihijatrijske dijagnoze. Počinitelji obiteljskih ubojstava koji su u skrbi stručnjaka mentalnog zdravlja imaju tendenciju dugotrajnijih problema mentalnog zdravlja i veće korištenje timova za mentalno zdravlje u zajednici i forenzičkih i skrbničkih usluga za mentalno zdravlje, dok su počinitelji partnerskog ubojstva imali povijest korištenja psihoaktivnih tvari, povijest ranijeg kažnjavanja, samoozljeđivanja i suicidalnih pokušaja (30).

Around 10% of homicide perpetrators in England and Wales presented symptoms of a mental disorder at the time of the homicide. Out of the 1180 intimate partner homicide perpetrators, 20% presented with symptoms of a mental disorder at the time of committing the crime, out of which 7% had symptoms of psychosis and 13% had symptoms of depression, while 30% of the perpetrators who displayed symptoms of a mental disorder had contact with mental health services in the year before committing the crime (27).

A study conducted at the Department of Forensic Psychiatry in the Neuropsychiatric Hospital "Dr. Ivan Barbot" in Popovača (28) addressing the mentally incompetent schizophrenic perpetrators of family homicide showed that more commonly parents were the victims, or the crime involved siblicide. Individuals with schizophrenic and delusional disorders often use sharp objects to commit homicide (29). It is possible that common symptoms of schizophrenia spectrum disorders, such as paranoid ideation, are associated with general violence, but not necessarily with intimate partner violence. A higher percentage of domestic violence perpetrators is diagnosed with schizophrenia when compared to perpetrators of intimate partner femicide (30). In the past, the diagnoses of schizophrenia, schizoaffective disorder, bipolar disorder and/or depression with psychotic symptoms were not frequently recorded in the course of psychiatric monitoring before the criminal offense of homicide (3).

The rates of psychiatric diagnoses were significantly higher among family homicide perpetrators, while the perpetrators of intimate partner homicide were more frequently without a psychiatric diagnosis. Family homicide perpetrators under the care of mental health professionals tend to suffer from long-term mental issues and utilize mental health teams within the community more frequently, as well as the forensic and mental health care services, while among the perpetrators of intimate partner homicide there was a history of psychoactive substance use, previous convictions, self-harm and suicide attempts (30).

ALKOHOL I DROGE KAO KRIMINOGENI FAKTORI

Štetna uporaba ili ovisnost o alkoholu često pridonosi partnerskom nasilju i femicidu (31). Korištenje psihoaktivnih tvari i poremećaj ličnosti kao osnovne ili komorbidne dijagnoze povećavaju rizik za počinjenje nasilja u svim dijagnostičkim kategorijama (32). Alkohol je od ranije poznat kao kriminogeni faktor koji doprinosi počinjenju nasilnih kaznenih djela, posebice fatalnom između intimnih partnera (33–35) te su prevencija alkoholizma i adekvatan tretman ovisnika o alkoholu važan element posredne prevencije ubojstava intimnih partnera. Na važnost utjecaja alkohola te važnost preventivnih programa ukazuju i druga istraživanja. Počinitelji koji koriste alkohol imaju osam puta češću vjerojatnost da će zlostavljati svoje partnere i dva puta veću vjerojatnost da će ubiti partnera (36).

Korištenje droga (amfetamina, opijata, heroina, kokaina) također je rizik za nasilje kao i kombinacija droga s alkoholom. Konzumacija kokaina je rizik za nasilje pa tako i ozbiljno nasilje u odnosu na partnericu. Osim što može potaknuti nasilje farmakološkim učincima, može pomoći oslobađanju agresije kod osoba s poremećajem ličnosti, naročito kod disocijalne ličnosti (21).

DEPRESIJA I RIZICI ZA NASILJE

Doprinos depresivnosti na počinjenje ubojstva posebno je značajan kao rizik za počinjenje ubojstva-samoubojstva. Pokazalo se da su takvi počinitelji obično stariji te da su i ranije iskazivali prijetnje ili pokušaje samoubojstva, uz anamnezu zlostavljanja u djetinjstvu (37) pa se suicidalne ideje moraju smatrati važnim čimbenikom rizika za bračna ubojstva. Fazel navodi da su kod počinitelja u depresivnim podskupinama s anamnezom ranijih nasilnih zločina i zloporabe supstancija ili samoozljeđi-

ALCOHOL AND DRUGS AS CRIMINOGENIC FACTORS

Harmful use of alcohol or alcohol addiction often contribute to the occurrence of intimate partner violence and femicide (31). Psychoactive substance use and personality disorder as the primary or comorbid diagnoses increase the risk of committing violence in all diagnostic categories (32). Alcohol has long been known as a criminogenic factor which contributes to the commission of criminal offenses, especially fatal among intimate partners (33-35), therefore the prevention of alcoholism and adequate treatment of alcohol addicts represent important elements in the indirect prevention of intimate partner homicide. Other studies have also pointed to the importance of alcohol effects and its preventive programs. Perpetrators who consume alcohol are eight times more likely to abuse their partners and two times more likely to murder their partners (36).

Drug use (amphetamines, opiates, heroin, cocaine) also represents a risk factor for violence, as well as combining drugs with alcohol. Cocaine consumption is a risk factor for violence, also including serious violence against one's female partner. In addition to potentially inducing violence through pharmacological effects, it can also help release aggression in individuals with personality disorders, especially in case of dissocial personality disorder (21).

DEPRESSION AND RISK OF VIOLENCE

The contribution of depression to homicide is particularly significant as a risk factor for committing homicide-suicide. It has been shown that such perpetrators are usually older and have a history of threats or attempted suicide, along with a history of childhood abuse (37), therefore suicidal ideation must be considered as an important risk factor for marital homicide. Fazel reports that among perpetrators in the depressive subgroups with a history of previous violent crimes and substance abuse or self-harm, violent crime rates are higher

vanja, stope nasilnih zločina veće od 15 % tijekom otprilike 3 godine praćenja, dok je kod muškaraca s dijagnozom shizofrenije to događa u oko 10 % (38). Depresivnost i suicidalne ideje mogu biti rizični faktor za počinjenje ubojstava i samoubojstava.

UBOJSTVO-SAMOUBOJSTVO

Barbieri i sur. (39) opisuju da je ubojstvo-samoubojstvo „dvostruka smrt" s kriminološkog stanovišta te da može biti pokazatelj jake emotivne veze između ubojice i njegove žrtve, straha od izdaje i gubitka objekta. Kod ubojstva-samoubojstva počinitelj ubija najmanje jednu žrtvu i tada učini suicid, u većini slučajeva odmah nakon ubojstva. Počinitelji su uglavnom muškarci, u braku, izvanbračnoj zajednici ili nedavno rastavljeni od svoje partnerice, a žrtva je obično sadašnja ili bivša partnerica (40,41). Osim što se najčešće dešavaju u obitelji (91 %) i unutar para (60 %), mogu obuhvatiti djecu (21 %) ili roditelje (5 %) počinitelja (42). U istraživanju Malphurs i Cohen (43) vidi se da su četvrtinu počinjenih ubojstava-samoubojstava počinile osobe u dobi od 55 godina i starije.

Počinitelji koji su počinili samoubojstvo nakon ubojstva češće to čine nakon dovršenih zločina nego pri pokušaju ubojstva te kada je ubijeno više žrtava (6). Istraživanje Larchet i sur. (42) pokazalo je da je manje vjerojatno da će počinitelji obiteljskih ubojstava-samoubojstava biti pod utjecajem alkohola, biti od ranije poznati policiji i imati anamnezu o psihijatrijskom, liječenju od onih koji nisu počinili samoubojstvo nakon ubojstva, a najčešće se koristi vatreno oružje.

RASPRAVA

U prevenciji kaznenih djela ubojstva intimne partnerice trebalo bi obratiti pažnju na prepoznavanje rizika počinjenja nasilja kod osoba s

than 15% in the period of approximately 3 years of monitoring, whereas in men diagnosed with schizophrenia this occurs in about 10% of cases (38). Depression and suicidal ideations can be a risk factor for committing homicides and suicides.

HOMICIDE-SUICIDE

Barbieri et al. (39) observed that homicide-suicide is a "double death" from a criminological point of view, and can be an indicator of a strong emotional connection between the murderer and his victim, a fear of betrayal and loss of the object. In cases of homicide-suicide, the perpetrator murders at least one victim and then commits suicide, in most cases immediately after the crime. The perpetrators are generally men, either married, cohabitating or recently divorced from their partner, while the victim is usually the current or former partner (40, 41). The crimes mostly occur within the family (91%) and between a couple (60%), but can also include children (21%) or parents (5%) of the perpetrator (42). In a study conducted by Malphurs and Cohen (43) it was evident that one quarter of the homicides-suicides was committed by individuals 55 years old or older.

The perpetrators who commit suicide after homicide more often do so after having completed the crimes rather than while attempting homicide, as well as in cases when multiple victims have been killed (6). In a study conducted by Larchet et al., it was observed (42) that perpetrators of family homicide-suicide are less likely to be under the influence of alcohol, to be previously known to the police or to have a history of psychiatric treatment as compared to those who did not commit suicide after homicide, while firearms are the most frequently used weapon.

DISCUSSION

In the prevention of intimate partner femicides, attention should be paid to identifying the risk of violence in individuals with a history of treatment for alcohol or drug problems, self-harm or

anamnezom liječenja zbog problema s alkoholom ili drogama, samoozljeđivanja ili pokušaja samoubojstva te ranijim kažnjavanjem. Posebnop forenzičko značenje za nasilno ponašanje mogu imati granične, narcistične i antisocijalne karakteristike ličnosti (44), uz postojanje konzumacije alkohola ili droga, no da li će se nasilje dogoditi ovisi o međusobnoj interakciji predisponirajućih osobina i precipitirajućih čimbenika.

Počinjenje ubojstva intimne partnerice često je kulminacija dugotrajnog nasilja, a u svrhu prepoznavanja rizika mogu se koristiti ljestvice za procjenu rizika opasnosti kao što su *Spousal Assault Risk Assessment Guide* (SARA), *Historical Clinical and Risk Management* 20 (HCR-20) (45), *Short-Term Assessment of Risk and Treatability* (START) (46), *Danger Assessment Revised 20-item* (DA-R20) (47), *Severe Intimate Violence Partner Risk Prediction Scale* (SIVPAS) (48). Prethodno nasilje te ranija prekršajna ili kaznena kažnjavanost za partnersko nasilje faktori su rizika za počinjenja i težih kaznenih djela (49). Stoga je važna interdisciplinarna suradnja i prepoznavanje rizika od svih službi uključenih u zaštitu od nasilja (50). Važni faktori su i vrsta odnosa između žrtve i počinitelja te obiteljska dinamika, dok na razini zajednice čimbenici rizika uključuju kulturu i njezina prevladavajuća uvjerenja o nasilju, prethodne preventivne kampanje i pravne definicije i zakonske mjere prema počiniteljima (51).

ZAKLJUČAK

Rizični faktori za počinjenje najtežih kaznenih djela prema intimnoj partnerici su osim ranije počinjenog partnerskog nasilja osobine ličnosti počinitelja, problem sa konzumacijom alkohola i/ili droga, dostupnost vatrenog oružja, narušena partnerska dinamika uz neprihvaćanje raskida partnerske veze, prijetnje ubojstvom ili samoubojstvom te poteškoće mentalnog zdravlja. U cilju što bolje prevencije potrebna

suicide attempts, as well as those with previous convictions. Borderline, narcissistic and antisocial personality traits (44) can be of special forensic significance in terms of violent behavior, along with the existence of alcohol or drug consumption, however, whether violence will occur depends on the mutual interaction of predisposing traits and precipitating factors.

Intimate partner femicide is often a culmination of long-term violence, and hazard risk assessment scales that can be used for the purpose of risk identification include *Spousal Assault Risk Assessment Guide* (SARA), *Historical Clinical and Risk Management* 20 (HCR-20) (45), *Short-Term Assessment of Risk and Treatability* (START) (46), *Danger Assessment Revised 20-item* (DA-R20) (47), *Severe Intimate Violence Partner Risk Prediction Scale* (SIVPAS) (48). Previous acts of violence and earlier misdemeanor or criminal convictions for intimate partner violence represent risk factors for the occurrence of more serious criminal offenses (49). Interdisciplinary cooperation and risk identification by all services involved in the protection against violence are, therefore, very important (50). The type of relationship between the victim and the perpetrator, as well as the family dynamics, are important factors as well, while risk factors at the community level include the culture and its prevailing beliefs about violence, previous preventive campaigns and legal definitions, as well as legal measures against perpetrators (51).

CONCLUSION

In addition to previous acts of intimate partner violence, risk factors for the commission of the most serious criminal offenses against female intimate partners also include the personality traits of the perpetrator, alcohol/drugs consumption issues, availability of firearms, disrupted partner dynamics and refusal to accept the termination of the intimate partner relationship, homicide or suicide threats and mental health difficulties. In order to achieve the best possible prevention, interdisciplinary cooperation of all services involved in

je interdisciplinarna suradnja svih služби koje sudjeluju u zaštiti od partnerskog nasilja, procjena rizika i otkrivanje rizičnog ponašanja, liječenje psihičkih poremećaja te sankcioniranje počinitelja i praćenje psihosocijalnim i drugim zaštitnim i sigurnosnim mjerama liječenja. Kako bi se prevenirale posljedice nasilja i smanjila vjerojatnost najtežih kaznenih djela važna je edukacija profesionalaca koji dolaze u kontakt s mogućim počiniteljima nasilja i teških kaznenih djela proizašlih iz partnerskog nasilja, edukacija, zaštita i pružanje terapijskih intervencija žrtvama te edukacija javnosti, uz informacije o dostupnim službama ako postoji nasilje ili prijetnja od počinjenja nasilja.

the protection against intimate partner violence is necessary, in addition to risk assessment and detection of risky behavior, treatment of mental disorders and sanctioning of perpetrators, and monitoring by means of psychosocial and other protective and safety measures of treatment. In order to prevent the possible consequences of violence and reduce the likelihood of the most serious criminal offenses, it is important to educate professionals coming into contact with the possible perpetrators of intimate partner violence and serious criminal offenses, as well as to educate and protect the victims, and provide them with therapeutic interventions, in addition to educating the public and publishing information on the available services in case of violence or threats of violence.

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Kongresi u 2025. godini
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19th International Conference of Gerontology and Geriatric Psychiatry
Dubai, 30 – 31. siječnja 2025.
https://waset.org/gerontology-and-geriatric-psychiatry-conference-in-january-2025-in-dubai

American Psychoanalytic Association National Meeting
San Francisco, 4 – 9. veljače 2025.
https://apsa.org/meetings-events/

International Conference on Clinical Child Psychiatry, Behavioral and Mental Health
Toronto, 14 – 15. veljače 2025.
https://www.iierd.org/events/index. php?id=2707271

42nd Global Psychiatry and Mental Health Conference
Pariz, 17 – 18. veljače 2025.
https://globalhealth.org/event/42nd-global-psychiatry-and-mental-health-conference/

3rd Annual Meeting on Neuroscience & Psychiatry
Dubai, 17 – 18. veljače 2025.
https://psychiatry.averconferences.com/

6th International Brain Stimulation Conference
Kobe, 23 – 26. veljače 2025.
https://neurosoft.com/en/events/6th-international-brain-stimulation-conference-2025

Mayo Clinic Psychiatry Clinical Updates
Lahaina, 24 – 28. veljače 2025.
https://10times.com/e1d4-12d3-ggxk-x

ECNP Workshop on Applied Neuroscience
Nica, 20 – 23. ožujka 2025.
https://www.ecnp.eu/early-career-scientists/workshop

Cognitive Neuroscience Society Annual Meeting
Boston, 29. ožujka – 1. travnja 2025.
https://www.cogneurosociety.org/annual-meeting/

Annual Anxiety and Depression Conference
Las Vegas, 3 – 6. travnja 2025.
https://adaa.org/calendar/adaa-2025-conference

33rd European Congress of Psychiatry
Madrid, 5 – 8. travnja 2025.
https://epa-congress.org/

International Neuroscience Winter Conference
Sölden, 6 – 10. travnja 2025.
https://www.swc.ucl.ac.uk/winterneuroscienceconference/index.html

39th International Conference on Mental Health and Psychiatry
Amsterdam, 7 – 8. travnja 2025.
https://psychiatriccongress.europeannualconferences.com/

31ˢᵗ International Symposium on Controversies in Psychiatry
Barcelona, 10 – 11. travnja 2025.
https://www.controversiasbarcelona.org/

2ⁿᵈ World Congress on Psychology & Behavioral Sciences
Pariz, 22 – 24. travnja 2025.
https://frigateconferences.com/psychology

Society for Sex Therapy and Research 50ᵗʰ Annual Meeting
Filadelfija, 24 – 27. travnja 2025.
https://sstarnet.org/abstracts

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Washington, 10. svibnja 2025.
https://conferencealerts.co.in/event/2906381

37ᵗʰ International Conference on Mental Health
Pariz, 14. – 15. svibnja 2025.
https:/ mentalhealth. neurologyconference.com/abstract-submission.php

Annual Meeting of the American Psychiatric Association
Los Angeles, 17 – 21. svibnja 2025.
https://www.psychiatry.org/psychiatrists/meetings/annual-meeting

16ᵗʰ Conference on Cognitive Science
Dubrovnik, 21 – 25. svibnja 2025.
https://ducog.cecog.eu/

19ᵗʰ International Conference on Psychology
Atena, 26 – 29. svibnja 2025.
https://www.atiner.gr/psychology

EACLIPT Conference
Frankfurt, 28 – 30. svibnja 2025.
https://www.eaclipt.org/post/eaclipt2025

64ᵗʰ International Neuropsychiatric Congress
Pula, 29. svibnja – 1. lipnja 2025.
https://www.pula-cong.com/

18ᵗʰ ESTSS Conference
Tbilisi, 12 – 15. lipnja 2025.
https://estss.org/18th-european-society-for-traumatic-stress-studies-conference-tbilisi-12-15-june-2025/

36ᵗʰ World Congress Collegium Internationale Neuro-Psychopharmacologicum
Melburn, 15 – 18. lipnja 2025.
https://cinp2025.org/

FENS Regional Meeting
Oslo, 16 – 19. lipnja 2025.
https://frm2025oslo.no/conference-venue

11ᵗʰ Congress of the European Academy of Neurology
Helsinki, 21 – 24. lipnja 2025.
https://www.ean.org/congress2025

Royal College of Psychiatrists International Congress
Newport, 23 – 26. lipnja 2025.
https://www.rcpsych.ac.uk/events/congress

9ᵗʰ International Conference on Neuroscience and Cognitive Brain Information
Atena, 6 – 10. srpnja 2025.
https://www.thinkmind.org/library/BRAININFO

Alzheimer's Association International Conference
Toronto, 27 – 31. srpnja 2025.
https://aaic.alz.org/

19ᵗʰ International Conference on Alzheimer's disease and Dementia
Berlin, 4 – 5. kolovoza 2025.
https://alzheimersdisease.neuroconferences.com/

39ᵗʰ Annual Conference of the European Health Psychology Society
Groningen, 25 – 29. kolovoza 2025.
https://2025.ehps.net/

55ᵗʰ EABCT Congress
Glazgov, 3 – 6. rujna 2025.
https://eabct2025.org/

6ᵗʰ EPATH Conference
Hamburg, 4 – 6. rujna 2025.
https://epath.eu/save-the-date-6th-epath-conference/

World Sleep
Singapur, 5 – 10. rujna 2025.
https://worldsleepcongress.com/

ISTSS 41ᵗʰ Annual Meeting
Baltimore, 17 – 20. rujna 2025.
https://istss.org/

20. hrvatski psihijatrijski dani
Pula, 1. – 4. listopada 2025.

https://www.20psihdani.org/

25ᵗʰ World Congress of Psychiatry
Prag, 5 – 8. listopada 2025.
https://2025.wcp-congress.com/

38ᵗʰ ECNP Congress
Amsterdam, 11 – 14. listopada 2025.
https://www.ecnp.eu/congress2025/ECNPcongress

Annual Meeting of American Academy of Child and Adolescent Psychiatry
Chicago, 20 – 25. listopada 2025.
https://www.aacap.org/aacap/CME_and_Meetings/Future_Annual_Meetings

46th STAR Conference
Bayonne, 29. – 31. listopada 2025.
https://star-society.org/next-star-conferences/

32. godišnja konferencija hrvatskih psihologa
Split, 5. – 8. studenoga 2025.

Neuroscience 2025
San Diego, 15 – 19. studenoga 2025.
https://www.sfn.org/meetings/neuroscience-2025

Predmetno i autorsko kazalo za volumen 52/2024

PREDMETNO KAZALO

AUTORSKO KAZALO

Upute
autorima

Instructions
to authors

O časopisu

Socijalna psihijatrija je recenzirani časopis koji je namijenjen objavljivanju radova iz područja socijalne psihijatrije, ali i iz kliničke psihijatrije i psihologije, biologijske psihijatrije, psihoterapije, forenzičke psihijatrije, ratne psihijatrije, alkohologije i drugih ovisnosti, zaštite mentalnog zdravlja osoba s intelektualnim teškoćama i razvojnim poremećajima, epidemiologije, deontologije, organizacije psihijatrijske službe. Praktički nema područja psihijatrije iz kojeg do sada nije objavljen pregledni ili stručni rad.

Svi radovi trebaju biti pisani na hrvatskom i engleskom jeziku.

Svi zaprimljeni radovi prolaze kroz isti proces recenzije pod uvjetom da zadovoljavaju i prate kriterije opisane u Uputama za autore i ne izlaze iz okvira rada časopisa.

Uredništvo ne preuzima odgovornost za gledišta u radu - to ostaje isključivom odgovornošću autora.

Časopis objavljuje sljedeće vrste članaka: uvodnike, izvorne znanstvene, stručne i pregledne radove, prikaze bolesnika, lijekova i metoda, kratka priopćenja, osvrte, novosti, prikaze knjiga, pisma uredništvu i druge priloge iz područja socijalne psihijatrije i srodnih struka.

Iznimno Uredništvo časopisa može prihvatiti i drugu vrstu rada (prigodni rad, rad iz povijesti struke i sl.), ako ga ocijeni korisnim za čitateljstvo.

Tijekom cijelog redakcijskog postupka, *Socijalna psihijatrija* slijedi sve smjernice Odbora za etiku objavljivanja (*Committee of publication ethics* – COPE), detaljnjije na: https://publicationethics.org/files/Code%20of%20Conduct_2.pdf, kao i preporuke ponašanja, izvještavanja, uređivanja i objavljivanja znanstvenih radova u časopisima medicinske tematike koje objavio Međunarodni odbor urednika medicinskih časopisa (*International Committee of Medical Journal Editors* – ICMJE), detaljnije na: http://www.icmje.org/journals-following-the-icmje-recommendations/.

Urednici časopisa *Socijalna psihijatrija* također su obvezni osigurati integritet i promicati inovativne izvore podataka temeljenih na dokazima, kako bi održali kvalitetu i osigurali utjecaj objavljenih radova u časopisu, a sukladno načelima iznesenim u Sarajevskoj deklaraciji o integritetu i vidljivosti (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5209927/).

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Svaki rad zaprimljen u Uredništvu časopisa *Socijalna psihijatrija* pregledava glavni urednik. Ako rad ne zadovoljava kriterije opisane u Uputama za autore, glavni urednik časopisa rad vraća autoru. Radovi koji zadovoljavaju uvjete bit će upućeni na recenziju.

Recenzija

Radovi koji su pisani prema Uputama za autore, šalju se na recenziju.

Časopis *Socijalna psihijatrija* recenzentima savjetuje da se pridržavaju uputa u Uputama za recenzente koje su dostupne na mrežnim stranicama Časopisa.

Aim & Scope

Socijalna psihijatrija is a peer-reviewed journal intended for publication of manuscripts from the fields of social psychiatry, clinical psychiatry and psychology, biopsychology, psychotherapy, forensic psychiatry, war psychiatry, alcoholism and other addictions, mental health protection among persons with intellectual and developing disabilities, epidemiology, deontology and psychiatric service organisations.

All manuscripts must be written in the Croatian and English language.

All manuscripts undergo the same review process if they follow the scope of the Journal and fulfil the conditions according to the Author guidelines.

The Editorial board will not take the responsibility for the viewpoint of the Author's manuscript – it remains the exclusive responsibility of an Author.

Socijalna psihijatrija publishes the following types of articles: editorials, original scientific papers, professional papers, review's, case reports, reports on drugs and methods of treatment, short announcements, annotations, news, book review's, letters to the editor, and other papers in the field of social psychiatry.

Exceptionally, the Editorial board can accept other kinds of paper (social psychiatry event paper, social psychiatry history-related paper, etc.).

During the whole peer-reviewed process, the *Socijalna psihijatrija* journal follows the Committee of publication ethics (COPE) guidelines (https://publicationethics.org/files/Code%20of%20Conduct_2.pdf) as well as the "Recommendations for the conduct, reporting editing, and publication of scholarly work in medical journals" set by the International Committee of Medical Journal Editors (ICMJE - http://www.icmje.org/journals-following-the-icmje-recommendations/).

Editors at the *Socijalna psihijatrija* journal pay close attention to the integrity and visibility of scholarly publications as stated in Sarajevo Declaration (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5209927/).

Editorial board

Each received manuscript is evaluated by the Editor-in-Chief. The manuscripts that do not meet the main criteria listed in the Author guidelines are returned to the Author. Manuscripts that are qualified are processed further.

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Manuscripts that meet the scope of the Journal and are prepared according to the Author guidelines are sent to peer-review.

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Etički kodeks

Podrazumijeva se da su svi autori radova suglasni o publikaciji i da nijedan dio rada nije prije publikacije u *Socijalnoj psihijatriji* već bio objavljen u drugom časopisu te da nije u postupku objavljivanja u drugom časopisu.

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Rad i svi prilozi dostavljaju se isključivo u elektroničkom obliku. Preporučena duljina teksta iznosi do 20 kartica (1 kartica sadrži 1800 znakova s razmacima). Tekstove treba pisati u Wordu, fontom postavljenim za stil Normal, bez isticanja unutar teksta, osim riječi koje trebaju biti u boldu ili italiku. Naslove treba pisati istim fontom kao osnovni tekst (stil Normal), u poseban redak, a hijerarhiju naslova može se označiti brojevima (npr. 1., 1.1., 1.1.1. itd.).

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The translation or language editing of the manuscript from Croatian to English (and *vice versa*) is funded by authors.

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Manuscripts, figures and tables should be submitted in electronic form. Normally, manuscripts should be no longer than 20 standard pages (one standard page is 1800 keystrokes – characters with spaces). Texts should be written in Microsoft Word, in a continuous font and style: the one set under the Normal style, with no additional font effects used other than words that should be in bold or italic. Tittles should be written in the same font as the rest of the text (Normal style) in a separate row, and title hierarchy should be shown using numbers (e.g. 1., 1.1., 1.1.1., etc.).

There should be a title, name and surname, address, town, state and e-mail indicated for the corresponding author.

The title page should contain: the full and shortened title of the article, full names and full surnames of all authors of the article, and the institution they work for. All the authors should also provide an ORCID ID (please check the following website: https://orcid.org/register). The article should have a summary not exceeding 200 words. The summary should briefly describe the topic and aim, the methods, main results,

Cilj je kratak opis što se namjerava istraživati, tj. što je svrha istraživanja.

Metode se prikazuju tako da se čitatelju omogući ponavljanje opisanog istraživanja. Metode poznate iz literature ne opisuju se, već se navode izvorni literaturni podatci. Ako se navode lijekovi, rabe se njihova generička imena (u zagradi se može navesti njihovo tvorničko ime).

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The Introduction section is a short and clear overview; it briefly mention Authors involved with the research of the paper.

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Repeated citing of a manuscript should be marked by the same number as when it is mentioned for the first time.

Quotation marks should be used when citing another text. This mode of citation should only be used when the information cannot be properly reformulated or summarized (e.g. when referring to a definition).

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1. Authors

In case the manuscript has six or fewer Authors, all of them should be listed. Should the manuscript have more than six Authors, the first six should be listed and the rest of them marked with the abbreviation *et al.* or i sur. First list the surname and then the initials of the first name(s). Multiple initials for the same person should be written without spaces.

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Titles and subtitles are copied from the original and separated by a colon. Only the first word of the title and name are written in capital letters.

3. Journal title

Journal titles are shortened according to the MEDLINE system (a list of abbreviations is available at: http://www.ncbi.nlm.nih.gov/nlmcatalog/journals). The title of the journal is not shortened if fit is not found in the abovementioned shortcut list.

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Mimica N. Delirij. U: Begić D, Jukić V, Medved V. (ur.). Psihijatrija. Zagreb: Medicinska naklada, 2015, str. 84-86.

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Cook A, Spinazzola J, Ford J, Lanktree C, Blaustein M, Cloitre M, DeRosa R, Hubbard R, Kagen R, Liautaud J, Mallah K, Olafson E,van der Kolk B. Complex trauma in children and adolescents. Psych Ann 2005; 35(5): 390-398. Preuzeto 14. listopada 2017. shttps://doi.org/10.3928/00485713-20050501-05.

4. Numerical journal data

The data that can be found in the original or in any of the bibliographic database should be written in Arabic numerals, in the following order: year, volume, issue, part, supplement, pages. Issue number is entered in parentheses and it is required to enter it starting from 1. In case the issue of the Journal cannot be recognized (e.g. when the issues are bonded), that data may be omitted. The page numbers are written from first to last.

E. g.

Kingdon DG, Aschroft K, Bhandari B, Gleeson S,Warikoo N, Symons Metal. Schizophrenia and borderline personality disorder: similarities and differences in the experience of auditory hallucinations, paranoia and childhood trauma. J Nerv Ment Dis 2010; 10(6): 399-403.

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Book issue is indicated by the ordinary number and the abbreviation "Ed". In case the book has more than one volume, use the abbreviation "Vol".

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