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.

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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.

Priredila Andrijana Šantić, dr.med. veljača 2024,. prema Voineskos D, Daskalakis ZJ, Blumberger DM. Management of Treatment-Resistant Depression: Challenges and Strategies. Neuropsychiatr Dis Treat 2020 Jan;Volume 16:221–34.n/Compiled by Andrijana Šantić, MD, February 2024, based on Voineskos D, Daskalakis ZJ, Blumberger DM. Management of Treatment-Resistant Depression: Challenges and Strategies. Neuropsychiatr Dis Treat 2020 Jan;Volume 16:221–34.

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 mozgu 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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