PRIMENA INTRANAZALNOG ESKETAMINA U TRETMANU TERAPO-REZISTENTNE DEPRESIJE: PRIKAZ SLUČAJA

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CASE REPORT

USE OF INTRANASAL ESKETAMINE IN THE TREATMENT OF TREATMENT-RESISTANT DEPRESSION: A CASE REPORT

Stefan Jerotić[1,2], Joko Poleksić[3], Maja Ivković[1,2], Milan Latas[1,2]

[1] Univerzitetski klinički centar Srbije, Klinika za psihijatriju, Beograd, Srbija

[2] Univerzitet u Beogradu, Medicinski fakultet, Beograd, Srbija

[3] Univerzitet u Beogradu, Medicinski fakultet, Institut za anatomiju „Niko Miljanić", Beograd, Srbija

[1] *University Clinical Center of Serbia, Clinic for Psychiatry, Belgrade, Serbia*

[2] *University of Belgrade, Faculty of Medicine, Belgrade, Serbia*

[3] *University of Belgrade, Faculty of Medicine, Institute of Anatomy "Niko Miljanić", Belgrade, Serbia*

SAŽETAK

Uvod: Terapo-rezistentna depresija (TRD) je pojam koji označava depresivnu epizodu u okviru koje nije došlo terapijskog odgovora na primenu dva antidepresiva. Farmakološke strategije lečenja TRD uključuju složen postupak, sa mogućnostima primene više različitih psihofarmaka i u osnovi podrazumevaju: (1) zamenu/optimizaciju doze antidepresiva, ili (2) augmentaciju antidepresivne terapije. U okviru strategije augmentacije, značajno mesto zauzimaju NMDA antagonisti, u koje se ubraja i intranazalni esketamin. Dosadašnja istraživanja ukazuju da aplikacija intranazalnog esketamina kao augmentacionog agensa predstavlja efikasnu farmakološku strategiju u tretmanu TRD.

Prikaz slučaja: U ovom radu prikazujemo uspešnu primenu intranazalnog esketamina u koadministraciji sa inhibitorom ponovnog preuzimanja serotonina/noradrenalina (SNRI antidepresiva) kod pacijenta sa TRD.

Zaključak: Neophodna su dalja istraživanja u cilju boljeg razumevanja mehanizma delovanja, načina doziranja, kao i dugoročnih ishoda i bezbednosnog profila ovog pristupa.

Ključne reči: depresija, terapo-rezistentna depresija, farmakološko lečenje, intranazalni esketamin

ABSTRACT

Introduction: Treatment-resistant depression (TRD) refers to a depressive episode that has not responded to treatment with two antidepressants. Pharmacological strategies for treating TRD involve a complex process, which includes several options for the use of different psychopharmaceuticals, fundamentally consisting of: (1) substituting/optimizing the dose of antidepressants, or (2) augmenting antidepressant therapy. Within the augmentation strategy, NMDA antagonists, including intranasal esketamine, play a significant role. Current research suggests that the application of intranasal esketamine as an augmentation agent is an effective pharmacological strategy in the treatment of TRD.

Case report: In this paper, we present the successful application of intranasal esketamine in co-administration with a serotonin/norepinephrine reuptake inhibitor (SNRI antidepressant) in a patient with TRD.

Conclusion: Further research is necessary to better understand the mechanisms of action, dosing modalities, as well as the long-term outcomes and safety profile of this approach.

Keywords: depression, treatment-resistant depression, pharmacological treatment, intranasal esketamine

Autor za korespondenciju:
Stefan Jerotić
Klinika za psihijatriju, Univerzitetski klinički centar Srbije
Pasterova 2, 11000 Beograd, Srbija
Elektronska adresa: stefan.jerotic@gmail.com

Corresponding author:
Stefan Jerotić
Clinic for Psychiatry, University Clinical Center of Serbia
2 Pasterova Street, 11000 Belgrade, Serbia
E-mail: stefan.jerotic@gmail.com

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UVOD

Depresija predstavlja jedan od vodećih uzroka pada kvaliteta života i ima značajan udeo u globalnom ekonomskom opterećenju bolestima. Procenjuje se da depresija pogađa više od 300 miliona ljudi, širom sveta [1]. Poslednja epidemiološka istraživanja na teritoriji Republike Srbije, na reprezentativnom uzorku populacije ukazuju da verovatna prevalencija depresije iznosi 5.7% [2], što je u skladu sa prevalencijom velikog depresivnog poremećaja u drugim državama sveta [3].

Farmakološki tretman akutne faze depresivnog poremećaja (raniji naziv unipolarna depresija) je opsežno proučavan godinama unazad, što je rezultovalo objavljivanjem preporuka u sprovođenju tretmana, odnosno preporučenoj upotrebi psihofarmaka prve i druge linije [4,5]. Uprkos višestrukoj primeni uobičajeno preporučene antidepresivne terapije, u dovoljnoj dozi i dovoljno dugom vremenskom periodu, kod značajnog broja pacijenata ne dolazi do terapijskog odgovora [6]. Procenjuje se da nakon primene dva antidepresiva prve linije, taj broj čini oko 30% svih pacijenata [7]. Imajući u vidu da je takvu depresivnu epizodu "teže lečiti", definisan je pojam "terapo-rezistentne depresije" (TRD) koji se intenzivno proučava u poslednje dve decenije [6,8]. Iako i dalje ne postoji jasan konsenzus o tačnoj definiciji TRD, Evropska medicinska agencija (EMA) [9] i Američka uprava za hranu i lekove (FDA) [10] označavaju TRD na sledeći način: odsustvo terapijskog odgovora na dva ili više antidepresivna tretmana u dovoljnoj dozi, dovoljno dug vremenski period uz pridržavanje (adherencu) propisanim tretmanom.

Farmakološke strategije lečenja TRD uključuju složen postupak, sa mogućnostima primene različitih psihofarmaka koji u osnovi podrazumevaju: (1) zamenu ili optimizaciju doze antidepresiva ili (2) augmentaciju. Augmentacija podrazumeva koadministraciju leka iz grupe antipsihotika, stabilizatora raspoloženja ili NMDA antagonista, zajedno sa primenom antidepresiva. Detaljan pregled farmakoloških strategija lečenja TRD, sa visokim stepenom dokaza, smo pružili na drugom mestu, na koju upućujemo zainteresovanog čitaoca [11]. U okviru strategije augmentacije, relativno novi farmakoterapijski pristup čini upotreba NMDA antagonista. Esketamin je S-enantiomer racemske smeše ketamina i ima visok afinitet za NMDA receptore u pravcu antagonizacije [12]. Intranazalni oblik esketamina je odobren za upotrebu od strane FDA 2019., a od strane EMA 2020. godine [13]. Prvobitna klinička istraživanja su pokazala da primena intranazalnog esketamina u TRD, dovodi do značajnog terapijskog efekta nakon 28 dana [14]. Dodatno, niz meta-analitičkih studija je potvrdio efikasnost primene intranazalnog esketamina kod TRD [15,16].

INTRODUCTION

Depression is one of the leading causes of decreased quality of life and significantly contributes to the global economic burden of diseases. It is estimated that depression affects more than 300 million people worldwide [1]. Recent epidemiological studies in the Republic of Serbia, conducted on a representative sample of the population, indicate that the likely prevalence of depression is 5.7% [2], which aligns with the prevalence of major depressive disorder in other countries [3].

The pharmacological treatment of the acute phase of depressive disorder (formerly known as unipolar depression) has been extensively studied over the years, resulting in the publication of treatment recommendations and the suggested use of first and second-line psychopharmacological agents [4,5]. Despite the multiple applications of commonly recommended antidepressant therapy, administered at adequate doses and for sufficient durations, a significant number of patients do not achieve a therapeutic response [6]. It is estimated that after the use of two first-line antidepressants, this number accounts for about 30% of all patients [7]. Given that such depressive episodes are "difficult to treat," the concept of "treatment-resistant depression" (TRD) has been defined and intensively studied over the past two decades [6,8]. Although there is still no clear consensus on the exact definition of TRD, the European Medicines Agency (EMA) [9] and the United States Food and Drug Administration (FDA) [10] describe TRD as the absence of a therapeutic response to two or more antidepressant treatments at adequate doses and for sufficient durations, with adherence to the prescribed treatment regimen.

Pharmacological strategies for treating TRD involve complex procedures, with possibilities including the use of various psychopharmacological agents that essentially involve: (1) replacement or optimization of the antidepressant dose or (2) augmentation. Augmentation involves the co-administration of a drug from the group of antipsychotics, mood stabilizers, or NMDA antagonists, along with the use of antidepressants. A detailed review of pharmacological strategies for treating TRD, with a high level of evidence, is provided elsewhere, to which we refer the interested reader [11]. Within the augmentation strategy, a relatively new pharmacotherapeutic approach involves the use of NMDA antagonists. Esketamine is the S-enantiomer of the racemic mixture of ketamine and has a high affinity for NMDA receptors, acting as an antagonist [12]. The intranasal form of esketamine was approved for use by the FDA in 2019 and by the EMA in 2020 [13]. Initial clinical studies have shown that the application of intranasal esketamine in TRD leads to significant

Povodom potencijalnih neželjenih efekata esketamina, dosadašnji podaci ukazuju da se najčešće javljaju na dan aplikacije i da su prolazni, a uključuju pojave poput vrtoglavice, pospanosti, parestezije, disgeuzije, glavobolje, anksioznost i disocijativne simptome [14,17].

U nastavku ovog rada iznosimo prikaz slučaja pacijenta sa TRD koji je tretiran intranazalnim esketaminom. Pristup pacijentovoj medicinskoj dokumentaciji za potrebe ovog prikaza slučaja odobren je od strane Etičkog odbora Univerzitetskog kliničkog centra Srbije, broj 1141/7. Pacijent je upoznat sa svim aspektima istraživanja, uključujući ciljeve, potencijalne rizike i koristi, te je nakon toga dao svoju pismenu saglasnost, potpisom informisanog pristanka.

PRIKAZ SLUČAJA

Pacijent starosti 64 godine se javio na Kliniku za psihijatriju Univerzitetskog kliničkog centra Srbije (KZP UKCS) početkom 2022. godine usled tegoba u vidu neraspoloženja, bezvoljnosti, nedostatka energije, doživljaja napetosti, anksiozno-ruminativnih tendencija po egzistencijalnom osnovu (heteroanamnestički neproporcionalne u odnosu na povod), povlačenja iz društvenog života, smanjene potrebe za komuniciranjem sa porodicom i prijateljima, izbegavanja aktivnosti koje su ranije dovodile do zadovoljstva. Navedene tegobe su bile prisutne oko 2 meseca u izraženom obliku i dovele su do značajnog pada u funkcionisanju u svim životnim domenima. Nakon ambulantne kliničke eksploracije pacijent je hospitalizovan i u nastavku stacionarno eksplorisan. Utvrđeno je da su se prve smetnje javile oko 5 godina unazad, kada je započeto ambulantno lečenje u regionalnom zdravstvenom centru. Od 2018. godine pacijent je imao tri diskretne epizode depresivnog poremećaja koje su bile karakterisane prethodno navedenim smetnjama. Iz lične anamneze, od značaja je, da je pacijent srednje stručne spreme, sa ukupnim radnim stažom u iznosu od 43 godine. Bez poznatih alergija na lekove. Evidentiran je pozitivan porodični hereditet na nelečeni etilizam (drugi stepen srodstva). Osim navedenog, nije uočen porodični hereditet na afektivne, niti na bilo koje druge psihijatrijske poremećaje.

Pre prve hospitalizacije, primenjivani farmakoterapijski protokoli su podrazumevali upotrebu fluoksetina (40 mg max dosis) koji je u različtim vremenskim periodima augmentisan mirtazapinom (15 mg max dosis), olanzapinom (5 mg max dosis), uz primenu sulpirida (50 mg max dosis) i benzodijazepina. Na prijemu na hospitalno lečenje, u psihičkom statusu, pacijent je bio svestan i ispravno orijentisan u svim modalitetima psihijatrijske eksploracije. Psihičkim statusom dominiralo je depresivno raspoloženje i anhedonija, bez deluzio-

improvements in therapeutic effect after 28 days [14]. Additionally, a series of meta-analytic studies have confirmed the efficacy of intranasal esketamine in TRD [15,16].

Regarding potential side effects of esketamine, current data indicate that they most commonly occur on the day of application and are transient, including symptoms such as dizziness, drowsiness, paresthesia, dysgeusia, headache, anxiety, and dissociative symptoms [14,17].

In this paper, we present a case report of a patient with TRD who was treated with intranasal esketamine. Access to the patient's medical records for the purposes of this case report was approved by the Ethics Committee of the University Clinical Center of Serbia, number 1141/7. The patient was informed of all aspects of the research, including the objectives, potential risks, and benefits, and subsequently provided written consent by signing an informed consent form.

CASE REPORT

A 64-year-old patient presented to the Psychiatry Clinic of the University Clinical Center of Serbia (UCCS) in early 2022 due to symptoms such as low mood, lack of motivation, low energy, sense of tension, anxiety-ruminative tendencies on an existential basis (heteroanamnestically disproportionate to the cause), withdrawal from social life, reduced need for communication with family and friends, and avoidance of activities that previously led to satisfaction. The mentioned symptoms were present for approximately 2 months in a pronounced form and led to a significant decline in functioning across all areas of life. Following outpatient clinical evaluation, the patient was hospitalized and subsequently explored in an inpatient setting. It was determined that the initial issues appeared around 5 years ago when outpatient treatment began at a regional health center. Since 2018, the patient has had three discrete episodes of depressive disorder characterized by the previously mentioned symptoms. From the personal medical history, it is notable that the patient has a secondary education level and a total of 43 years of work experience. There are no known drug allergies. A positive family history of untreated alcoholism (second-degree relatives) has been recorded. Aside from this, no family history of affective or other psychiatric disorders has been observed.

Before the first hospitalization, pharmacotherapy protocols included the use of fluoxetine (40 mg max dose), which was augmented at different times with mirtazapine (15 mg max dose), olanzapine (5 mg max dose), sulpiride (50 mg max dose), and benzodiazepines. Upon admission for inpatient treatment, the

nih elemenata u sadržaju mišljenja i perceptivnih obmana. Nagonski dinamizmi su bili kompromitovani u vidu hipoapeticije i socijalne restkrikcije, dok je u voljnoj sferi bila prisutna hipobulija. Neurološki i somatski status po svim sistemima organa nisu pokazivali nikakve osobitosti. Vitalni i antropometrijski parametri su bili u fiziološkim okvirima.

U toku hospitalizacije izvršeno je psihološko testiranje koje je ukazalo na visokoprosečnu inteligenciju, sa padom u psihomotornoj brzini, domenima pažnje i koncentracije, uz očuvan test realnosti. Uočeni su povišeni indikatori anksioznosti, napetosti i depresivnosti – bihejvioralna apatija, nedostatak inicijative, hroničan umor, slaba koncentracija i nersapoloženje. Nisu uočeni indikatori psihotičnosti ili poremećaja ličnosti. Laboratorijske i hormonske pretrage, uključujući i hormone štitaste žlezde nisu pokazali značajna odstupanja izvan referentnih vrednosti. CT endokranijuma nije pokazao nijedan specifičan patološki supstrat. Uspostavljena je dijagnoza povratnog velikog depresivnog poremećaja. Nakon primenjenih radno-okupacionih, suportivno-psihoterapijskih mera, pacijent je otpušten u inicijalnoj remisiji uz primenu farmakoterapije mirtazapinom 30 mg/dan, duloksetinom 30 mg/dan i pregabalinom 150 mg/dan.

Nedelju dana po otpustu sa hospitalnog lečenja pacijent je funkcionisao zadovoljavajuće, a zatim je usledio delimični povratak tegoba, dominantno u vidu psihomotorne usporenosti, smanjenja volje za obavljanje svakodnevnih aktivnosti, doživljaja napetosti u stomaku i pojave inicijalne insomnije. U toku intenzivnog ambulantnog praćenja, farmakoterapija je modifikovana u pravcu povećanja doze duloksetina do 120 mg/dan i pregabalina do 300 mg/dan, uz krakotrajnu primenu zolpidema 10 mg/dan. Terapijski protokol je augmentisan primenom aripiprazola do 5 mg/dan.

Usled odsustva terapijskog odgovora na do tada primenjene mere, realizovana je druga hospitalizacija na KZP UKCS tokom 2023. godine. Tokom navedene hospitalizacije, simptomatologija iz depresivog spektra je bila prisutna u istom obimu i intenzitetu kao i tokom prve hospitalizacije, bez uočavanja novih elemenata u kliničkoj slici. Pacijent je otpušten sa hospitalnog lečenja, bez primene terapijskih vikenda radi testiranja funkcionalnosti u zajednici zbog organzacionih ograničenja koje su na snazi od početka kovid pandemije. Farmakoterapija na otpustu je uključivala bupropion 150 mg/dan, aripiprazol 7.5 mg/dan, mirtazapin 30 mg/dan i pregabalin 150 mg/dan.

U toku daljeg praćenja, pacijent nije ostvario zadovoljavajuću funkcionalnost. Takođe, primena intenzivnih mera bihejvioralne aktivacije tokom ambulantnog lečenja nije dovela do značajnijeg terapijskog efekta,

patient's mental status was conscious and properly oriented in all modalities of psychiatric exploration. The mental status was dominated by depressive mood and anhedonia, without delusional elements in thought content or perceptual disturbances. Drive dynamics were compromised in the form of hypoappetite and social restriction, while hypobulia was present in the volitional sphere. Neurological and somatic status across all organ systems showed no particularities. Vital and anthropometric parameters were within physiological ranges.

During hospitalization, psychological testing indicated above-average intelligence with a decline in psychomotor speed, attention, and concentration domains, while reality testing remained intact. Elevated indicators of anxiety, tension, and depression were observed, including behavioral apathy, lack of initiative, chronic fatigue, poor concentration, and low mood. No indicators of psychosis or personality disorders were noted. Laboratory and hormonal tests, including thyroid hormones, showed no significant deviations from reference values. Cranial CT did not reveal any specific pathological substrates. A diagnosis of recurrent major depressive disorder was established. After applying occupational, supportive, and psychotherapeutic measures, the patient was discharged in initial remission with pharmacotherapy including mirtazapine 30 mg/day, duloxetine 30 mg/day, and pregabalin 150 mg/day.

One week after discharge from inpatient treatment, the patient functioned satisfactorily, followed by a partial return of symptoms, mainly psychomotor slowing, reduced will to perform daily activities, abdominal tension, and initial insomnia. During intensive outpatient follow-up, the pharmacotherapy was modified, increasing duloxetine to 120 mg/day and pregabalin to 300 mg/day, with short-term zolpidem 10 mg/day. The therapeutic protocol was augmented with aripiprazole up to 5 mg/day.

Due to the absence of a therapeutic response to the measures applied so far, a second hospitalization was carried out at the KZP UKCS during 2023. During this hospitalization, depressive spectrum symptoms were present to the same extent and intensity as during the first hospitalization, with no new elements observed in the clinical picture. The patient was discharged without preliminary therapeutic weekend dischargesdue to organizational constraints in place since the beginning of the pandemic of COVID-19. Pharmacotherapy at discharge included bupropion 150 mg/day, aripiprazole 7.5 mg/day, mirtazapine 30 mg/day, and pregabalin 150 mg/day.

In the course of further follow-up, the patient did not achieve satisfactory functionality. Additional-

te je krajem 2023. godine usledila i treća hospitalizacija. Tokom ove hospitalizacije, pored suportivnih i radno-okupacionih mera pacijent je tretiran venlafaksinom 300 mg/dan, naizmenično augmentisan kvetijapinom 100 mg/dan i litijumom 300 mg/dan, uz primenu pregabalina 225 mg/dan. Rezultati ponovnog psihološkog testiranja nisu pokazali odstupanja od prethodnog testiranja tokom prve hospitalizacije. Detaljnom analizom celokupnog toka bolesti i formulacijom slučaja u svim relevantnim bio-psiho-socijalnim dimenzijama, utvrđeno je da pacijent ima terapo-rezistentnu depresiju, imajući u vidu da su primenjeni višestruki antidepresivi u dovoljno dugom vremenskom periodu, u dovoljnim dozama, uz očuvanu komplijansu koja je verifikovana tokom hospitalnog lečenja, a u ambulantnim uslovima i auto- i heteroanamnestički.

Usled svega navedenog, a nakon konzilijarnog sagledavanja, sa pacijentom je započeto praćenje uz primenu intranazalnog esketamina. Osnovni antidepresiv je bio venlafaksin 300 mg/dan, koji je primenjivan u kontinuitetu.

Faza indukcije je sprovođena od 1. do 4. nedelje, dva puta nedeljno, aplikacijom intranazalnog esketamina u dozi od 2x28 mg, u okviru ustanove. Lek je aplikovan od strane edukovanog medicinskog osoblja, uz kontinuiran nadzor i praćenje vitalnih parametara.

Faza održavanja je sprovođena od 5. do 9. nedelje, jednom nedeljeno, aplikacijom intranzalnog esketamina u dozi od 2x28 mg, u istim okolnositma.

Neposredno pre svake aplikacije, u okviru faze održavanja i u okviru faze indukcije, sprovođeno je psihometrijsko testiranje MADRS skalom, instrumentom koji je klinički standard za procenu simptoma depresije i koji je validiran na srpskoj populaciji [18].

Sedamnaestog dana primene (druga polovina treće nedelje), uočen je terapijski odgovor (50% redukcije simptomatologije), verifikovan MADRS skalom. Kretanje ukupnog intenziteta simptoma tokom vremena je prikazano na grafikonu 1. Intenzitet simptoma po pojedinim stavkama (prijavljena tuga, očigledna tuga, unutrašnja napetost, skraćeno spavanje, smanjen apetit, otežana koncentracija, klonulost, nesposobnost osećanja, pesimističke misli, suicidalne misli) je prikazan u Tabeli 1.

Prilikom prvih nekoliko aplikacija, pacijent je osetio kratkotrajno, prolazno trnjenje u proksimalnim i distalnim delovima ekstremiteta. Osim navedenog, nije bilo pojave vrtoglavice, disocijacije, mučnine, gavobolje, somnolencije, disgeuzije, povraćanja, kao niti drugih prijavljenih neželjenih efekata, koji bi opredelili pacijenta za prekid primene intranazalnog esketamina. Vrednosti krvnog pritiska, pre i nakon primene intranazalnog esketamina, nisu odstupale od fizioloških vrednosti i prikazane su na grafikonu 2.

ly, the application of intensive behavioral activation measures during outpatient treatment did not lead to significant therapeutic effects, leading to a third hospitalization at the end of 2023. During this hospitalization, alongside supportive and occupational measures, the patient was treated with venlafaxine 300 mg/day, alternately augmented with quetiapine 100 mg/day and lithium 300 mg/day, along with pregabalin 225 mg/day. Results of repeated psychological testing showed no deviations from previous testing during the first hospitalization. A detailed analysis of the entire disease course and case formulation in all relevant bio-psycho-social dimensions determined that the patient has treatment-resistant depression, given the use of multiple antidepressants over a sufficient duration and dosage, with verified compliance during inpatient treatment and corroborated by self- and heteroanamnesis in outpatient settings.

In light of the above, and following a team medical review, the patient was started on follow-up with intranasal esketamine. The primary antidepressant was venlafaxine 300 mg/day, administered continuously.

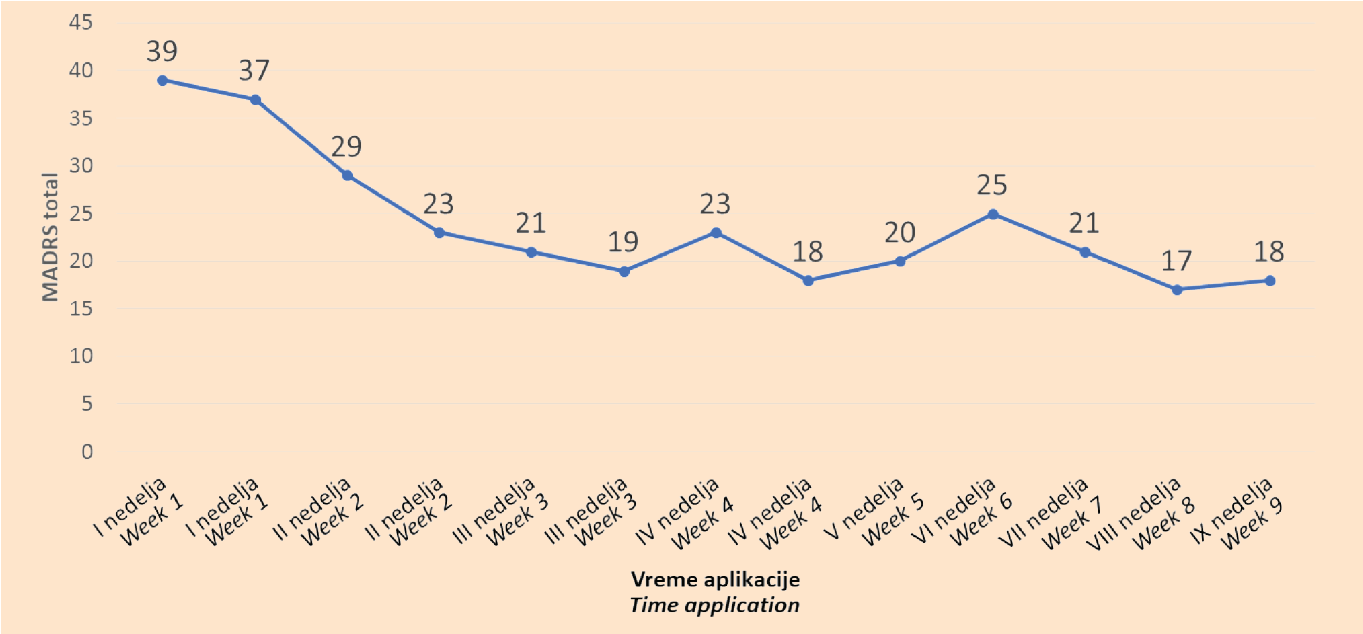
The induction phase was conducted from week 1 to week 4, twice a week, with intranasal esketamine 2x28 mg administered within the facility. The medication was administered by trained medical staff, with continuous monitoring and vital parameter tracking.

The maintenance phase was conducted from week 5 to week 9, once a week, with intranasal esketamine 2x28 mg, under the same conditions.

Immediately before each application, during both the maintenance and induction phases, psychometric testing using the MADRS scale, a clinical standard for assessing depression symptoms validated in the Serbian population, was conducted.

On the seventeenth day of application (second half of the third week), a therapeutic response (50% reduction in symptoms) was observed, verified by the MADRS scale. The progression of overall symptom intensity over time is shown in Graph 1. Symptom intensity for specific items (reported sadness, apparent sadness, inner tension, reduced sleep, decreased appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, suicidal thoughts) is presented in Table 1.

During the first few applications, the patient experienced short-term, transient tingling in the proximal and distal parts of the extremities. Apart from this, there were no occurrences of dizziness, dissociation, nausea, headache, somnolence, dysgeusia, vomiting, or any other reported side effects that would lead the patient to discontinue intranasal esketamine. Blood pressure values before and after the application of in-



Napomena: MADRS skala primenjena na dan ambulantnog pregleda, neposredno pred primenu intranazalnog esketamina. U toku prve 4 nedelje, pacijent je ambulantno pregledan uz primenu terapije dva puta nedeljno u rasponu od 3 dana. U toku aplikacije dva puta nedeljno, prikazani su sukcesivni dolasci, sa leva na desno, odnosno: I nedelja vizita 1, potom I nedelja vizita 2, itd. Opseg skorova MADRS skale je 0-60, viši skor ukazuje na izraženiji intenzitet simptoma.

Note: The item scores range from 0-6, with higher scores indicating greater symptom intensity. The MADRS scale was applied on the day of the outpatient examination, immediately before the administration of intranasal esketamine. During the first 4 weeks, the patient was examined twice a week, with a 3-day interval between therapy sessions. For the twice-weekly applications, the successive visits are presented from left to right, i.e., Week 1, Visit 1, then Week 1, Visit 2, etc.

Grafikon 1. Intenzitet ukupnih simptoma depresije na MADRS skali tokom vremena

Figure 1. Intensity of depressive symptoms total scores on the MADRS scale over time

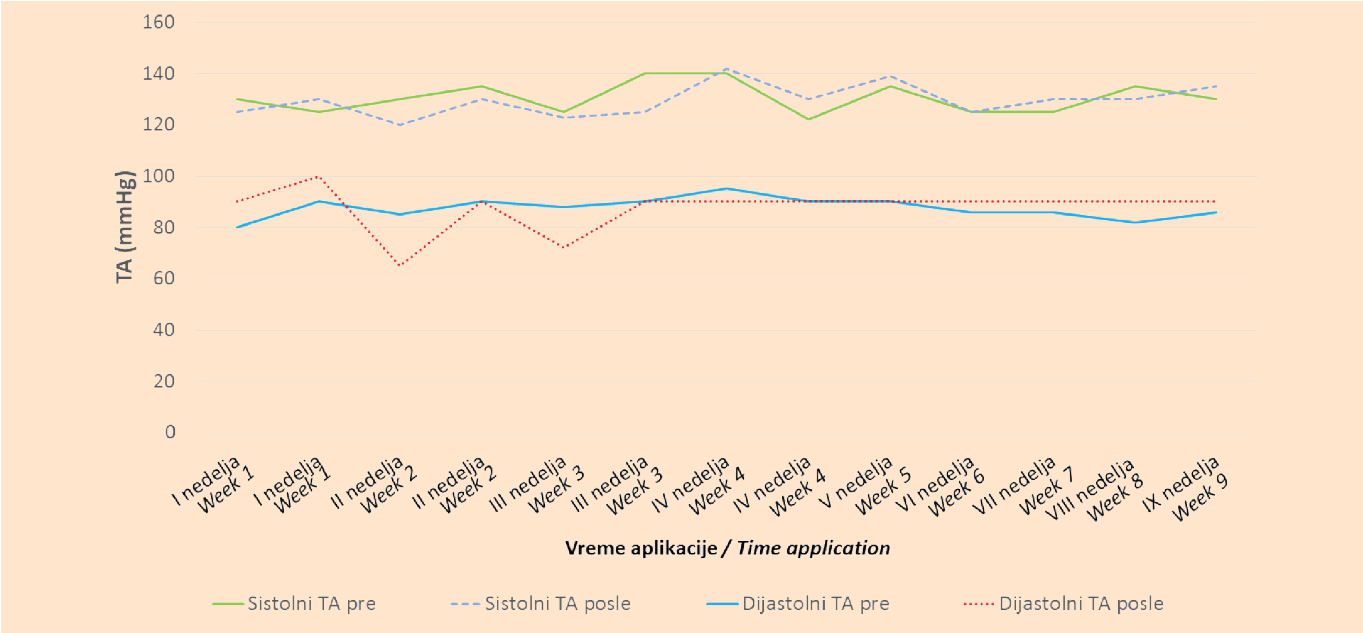
Tabela 1. Intenzitet simptoma po MADRS stavkama

Table 1. Symptom intensity according to MADRS items

	Broj nedelje (prikazane sukcesivno) / *Week number (displayed consecutively)*												
MADRS stavka / MADRS items	**I**	**I**	**II**	**II**	**III**	**III**	**IV**	**IV**	**V**	**VI**	**VII**	**VIII**	**IX**
Prijavljena tuga / *Reported sadness*	5	5	4	3	2	2	3	2	3	3	3	2	2
Očigledna tuga / *Obvious sadness*	5	4	2	2	1	1	2	1	1	3	3	2	2
Unutrašnja napetost / *Internal tension*	3	2	2	2	2	1	2	2	2	4	0	2	2
Skraćeno spavanje / *Reduced sleep*	3	3	4	2	3	3	4	2	2	2	0	0	0
Smanjen apetit / *Reduced appetite*	6	6	4	4	4	4	4	4	4	4	4	4	4
Otežana koncentracija / *Impaired concentration*	1	1	0	0	0	0	0	0	0	0	1	0	0
Klonulost / *Listlessness*	5	5	4	3	3	2	3	2	2	2	3	2	3
Nesposobnost osećanja / *Inability to feel*	6	6	5	3	3	3	2	2	2	2	3	2	2
Pesimističke misli / *Pessimistic thoughts*	3	3	3	3	2	2	2	2	3	4	3	2	2
Suicidalne misli / *Suicidal thoughts*	2	2	1	1	1	1	1	1	1	1	1	1	1

Napomena: Skorovi na stavkama su u opsegu 0-6, viši skor ukazuje na izraženiji intenzitet simptoma. MADRS skala primenjena na dan ambulantnog pregleda, neposredno pred primenu intranazalnog esketamina. U toku prve 4 nedelje, pacijent je ambulantno pregledan uz primenu terapije dva puta nedeljno u rasponu od 3 dana. U toku aplikacije dva puta nedeljno, prikazani su sukcesivni dolasci, sa leva na desno, odnosno: I nedelja vizita 1, potom I nedelja vizita 2, itd..

Note: The item scores range from 0-6, with higher scores indicating greater symptom intensity. The MADRS scale was applied on the day of the outpatient examination, immediately before the administration of intranasal esketamine. During the first 4 weeks, the patient was examined twice a week, with a 3-day interval between therapy sessions. For the twice-weekly applications, the successive visits are presented from left to right, i.e., Week 1, Visit 1, then Week 1, Visit 2, etc.



Napomena: U toku prve četiri nedelje pacijent je dva puta nedeljno, u rasponu od 3 dana ambulantno pregledan, uz primenu terapije. U toku aplikacije dva puta nedeljno, prikazani su sukcesivni dolasci, sa leva na desno, odnosno: I nedelja vizita 1, potom I nedelja vizita 2, itd..

Note: During the first four weeks, the patient was examined on an outpatient basis twice a week, spaced 3 days apart, with therapy administered. During the twice-weekly applications, successive visits are shown from left to right, i.e., Week 1 Visit 1, then Week 1 Visit 2, etc.

Grafikon 2. Vrednosti sistolnog i dijastolnog krvnog pritiska, pre i neposredno nakon aplikacije intranazalnog esketamina

Figure 2. Values of systolic and diastolic blood pressure, before and after the application of intranasal esketamine

Klinički, tokom primene venlafaksina, 300 mg/dan u kombinaciji sa primenom intranazalnog esketamina, u toku faze indukcije evidentirana je značajna redukcija simptomatologije i poboljšanje funkcionanosti u svim životnim dimenzijama, koja se održavala i nadalje.

DISKUSIJA

Odsustvo terapijskog odgovora kod velikog depresivnog poremećaja i pojava TRD predstavljaju značajan izazov za kliničku praksu. Na osnovu dosadašnjih pokazatelja, procenjuje se da, širom sveta, preko 100 miliona ljudi ispunjava kriterijme za TRD [6]. Dodatno, TRD karakteriše značajno povećanje suicidalne ideacije, pokušanog i realizovanog suicida u odnosu na nerezistentnu depresiju [19].

Iako brojne međunarodne smernice preporučuju strategije koje se mogu primeniti u TRD, i dalje nema podataka o jasnom postupanju prilikom pojave TRD (koji psihofarmak, koliko dugo). Drugim rečima, internacionalne smernice ne sugirešu tačne korake u smislu zamene/augmentacije psihofarmaka. Uprkos tome, na osnovu dokaza iz više pozitivnih randomizovanih kontrolisanih studija, kao i podataka iz meta-analiza, primena esketamina se poslednjih godina gotovo univerzalno preporučuje [20–22]. Pored demonstrirane efikasnosti u redukciji simptoma u TRD, podaci iz literature ukazuju na efikasnost u redukciji suicidalnosti, kao i brz terapijski odgovor [6].

tranasal esketamine did not deviate from physiological values and are shown in Graph 2.

Clinically, during the administration of venlafaxine, 300 mg/day in combination with intranasal esketamine, significant reduction in symptoms and improvement in functionality across all life dimensions were recorded during the induction phase and continued thereafter.

DISCUSSION

The absence of therapeutic response in major depressive disorder and the emergence of TRD represent significant challenges for clinical practice. Based on current indicators, it is estimated that over 100 million people worldwide meet the criteria for TRD [6]. Additionally, TRD is characterized by a significant increase in suicidal ideation, attempted, and completed suicides compared to non-resistant depression [19].

Although numerous international guidelines recommend strategies that can be applied in TRD, there are still no clear protocols for dealing with TRD (which psychopharmacologic, how long). In other words, international guidelines do not suggest exact steps in terms of replacing/augmenting psychopharmacological treatments. Nevertheless, based on evidence from multiple positive randomized controlled trials, as well as data from meta-analyses, the use of esketamine has been almost universally recommended in recent years

U skladu sa navedenim podacima je i naše iskustvo sa pacijentom koji je imao epizodu velikog depresivnog poremećaja, bez terapijskog odgovora na niz primenjenih psihofarmaka koji se smatraju terapijom "prvog reda", kao i višestruke augmentacione agense za koje postoji visok nivo dokaza, prema rezultatima randomizovanih kontrolisanih studija. U ovom slučaju, ostvaren je brz terapijski efekat, sa odgovorom (preko 50% redukcije simptoma) koji je evidentiran 17. dana od započinjanja terapije intranazalnim esketaminom, u koadministraciji sa SNRI – venlafaksin 300 mg/dan. Navedeno je potvrđeno padom skora na MADRS sa 39 (nivo teške depresivne epizode) na početku tretmana, na skor 18 (nivo blage depresivne epizode) u poslednjoj tački praćenja, tokom IX nedelje. Značajnije poteškoće u domenu podnošljivosti leka, nisu bile prisutne.

Sumarno, ovom radu smo prikazali uspešnu primenu intranazalnog esketamina u koadministraciji sa SNRI antidepresivom kod pacijenta sa TRD. Naglašavamo važnost budućih istraživanja u cilju boljeg razumevanja mehanizama delovanja, načina doziranja, kao i dugoročnih ishoda i bezbednosni profil ovog pristupa.

Sukob interesa: Nije prijavljen.

[20–22]. In addition to demonstrated efficacy in reducing symptoms in TRD, literature data indicate its effectiveness in reducing suicidality and providing a rapid therapeutic response [6].

Our experience with a patient who had an episode of major depressive disorder, without a therapeutic response to a series of applied psychopharmacological treatments considered "first-line" therapy, as well as multiple augmentation agents with a high level of evidence from randomized controlled trials, aligns with these findings. In this case, a rapid therapeutic effect was achieved, with a response (over 50% reduction in symptoms) observed on the 17th day of starting intranasal esketamine therapy, in co-administration with the SNRI venlafaxine 300 mg/day. This was confirmed by a decrease in the MADRS score from 39 (level of severe depressive episode) at the start of treatment to a score of 18 (level of mild depressive episode) at the last follow-up point during week IX. No significant difficulties in terms of drug tolerability were present.

In summary, this paper presents the successful use of intranasal esketamine in co-administration with an SNRI antidepressant in a patient with TRD. We emphasize the importance of future research to better understand the mechanisms of action, dosing methods, as well as long-term outcomes and safety profiles of this approach.

Conflict of interest: None declared.

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