Antidepresivi u starijih osoba

/ Antidepressants in the Elderly Population

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Depresija pripada u kronične poremećaje s najvećim stupnjem onesposobljenosti, a njezina učestalost raste s dobi. Nadalje, starije osobe oboljele od depresivnog poremećaja imaju brojna obilježja koja ih razlikuju od ostalih dobnih skupina, poput tjelesnih komorbiditeta zbog kojih uzimaju često brojne lijekove, ograničene pokretljivosti, dugotrajne boli, kognitivnog propadanja, socijalne izolacije, usamljenosti, a zbog starenja prisutne su i fiziološke promjene u gotovo svim organima. Antidepresivi su temeljna terapija depresivnog poremećaja u svakoj životnoj dobi. U mlađih odraslih osoba svi su antidepresivi podjednako učinkoviti. Međutim, učinak antidepresiva u starijih osoba je u osnovi slabiji, te se razlikuje između pojedinih antidepresiva. Starije su osobe iznimno osjetljive na nuspojave antidepresiva, kao i na farmakodinamske i farmakokinetske interakcije s drugim supstancijama. Stoga je za uspjeh liječenja ključan ciljan odabir antidepresiva, polagana titracija doze, te primjena najniže terapijske doze održavanja, uz pažljivo praćenje stanja bolesnika.

Liječenje depresije u starijoj dobi izazov je za kliničara. S obzirom na veliku heterogenost kliničke slike, te brojne tjelesne bolesti, potrebna su kvalitetna istraživanja pojedinih podskupina starijih osoba s depresijom. Individualni pristup iznimno je bitan u svakodnevnom liječenju ovih vrlo ranjivih bolesnika.

/ Depression is among the most disabling chronic disorders, and its prevalence appears to increase with age. Elderly depressed patients differ from younger adults with depression in many ways, such as the presence of multimorbidity, complex treatment regimens, reduced mobility, chronic pain, cognitive decline, social isolation and loneliness, and physiological changes in almost all organs. Antidepressants are the first-line treatment for depression in any age. While all antidepressants have similar efficacy in younger adults, elderly individuals might respond differently to particular ones. Elderly individuals are highly vulnerable to adverse events and to both pharmacodynamics and pharmacokinetic drug-drug interactions. Therefore, careful choice of antidepressant, slow dose-titration, and the lowest effective maintenance dose, with close monitoring for potential adversities, are essential.

Treatment of depression in older age is a major challenge. Given the substantial clinical heterogeneity of clinical presentations and comorbid conditions, more high-quality studies are needed in selected subpopulations, while an individualized approach remains a high priority.

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KLJUČNE RIJEČI / *KEY WORDS*:
Antidepresivi / *Antidepressants*
Farmakoterapija / *Pharmacotherapy*
Liječenje / *Treatment*
Starije osobe / *Elderly people*

TO LINK TO THIS ARTICLE:

UVOD

Depresivni poremećaj može se pojaviti u svakoj životnoj dobi, počevši od djetinjstva. Cilj ovog kratkog preglednog rada jest prikaz terapije antidepresivima u starijih osoba s depresivnim poremećajem. Na početku valja napomenuti da se postojeća literatura jako razlikuje prema dobnoj granici, kada počinje starija dob. Prema nekim autorima je to iznad 65 (1-3), ili iznad 60 (4-6) a prema nekima već iznad 55 godina (7,8). Nadalje, depresija koja se pojavi tek u starijoj životnoj dobi još se naziva i depresija starije životne dobi, ili depresija s kasnim početkom, dok se ona koja počinje u ranijoj dobi naziva i depresija s ranim početkom. Simptomi depresije nikako nisu dio procesa starenja, iako pojavnost depresije raste s dobi. Depresivni poremećaj prisutan je u 7 % osoba starije životne dobi (5). Međutim, u osoba starijih od 100 godina izmjerena je učestalost depresivnih simptoma od čak 32,2 % (9).

Postoji složeni i još uvijek nedovoljno poznat odnos između depresije, posebice one s kasnim početkom, i demencije, a posebice Alzheimerove bolesti. Čini se da je njihov odnos dvosmjeran, budući da depresija s jedne strane prethodi demenciji, a s druge strane može biti i njezina posljedica (6). U nedavnom preglednom radu prikazani su neki potencijalno povoljni učinci selektivnih inhibitora ponovne pohrane serotonina (SIPSS) na biološke pokazatelje Alzheimerove bolesti (6).

Starije osobe s depresivnim poremećajem imaju drukčija obilježja od mlađih bolesnika. Na primjer, često su smanjene pokretljivosti, imaju kroničnu bol, vrlo su krhki, često u fazi žalovanja, slabijeg socioekonomskog statusa nakon umirovljenja, te također socijalno izolirani i usamljeni (5). Starenje organizma popraćeno je brojnim fiziološkim promjenama, poput gubitka neurona, smanjenja protoka u moždanim arterijama, redukcije količine P glikoproteina, kao i sklonosti nastanku hipotenzije (10).

Starije osobe s depresijom vrlo često imaju brojne tjelesne komorbiditete u sklopu kojih uzimaju razne lijekove. Stoga je polifarmacija česta, a s njom

INTRODUCTION

Depression might occur at any age, starting from childhood. The topic of this article is depression in the elderly, late-life depression or geriatric depression. However, the age of onset of “older age” in the population is not clearly defined. It refers to the presence of depressive disorder in individuals of over 65 (1-3), 60 (4-6), or even over 55 (7,8) years of age. If patients experienced their first depressive episode in this age, they are considered to have late-onset depression, and if they had depressive episodes previously, they had early-onset depression. While depression is not an essential part of ageing, the prevalence of depression appears to increase with age. Unipolar depression was found to affect 7% of the world’s older population (5). However, the prevalence of depressive symptoms in individuals older than 100 years was 32.2% (9).

The relationship between depression, particularly the late-onset one, and dementia of Alzheimer type (DAT) is complex. There is evidence that depression in older age is both a risk factor and a consequence of dementia (6). The potential beneficial effects of SSRIs on pathophysiological biomarkers of DAT has been recently reviewed (6).

Older patients with depression differ substantially from younger age groups. They face additional issues such as reduced mobility, chronic pain, frailty, bereavement, drop in socioeconomic status with retirement, and isolation or loneliness (5). Ageing is also characterized by a number of physiological changes, including loss of neurons, decline in cerebral blood flow, reduction of P-glycoprotein levels, and higher tendency for orthostatic hypotension (10).

Depression in this age group is also characterized by the presence of medical comorbidities, requiring the use of different medications and frequently coexisting cognitive dysfunction.

i mogućnost interakcija lijekova. U starijoj dobi je, razumije se, česta i kognitivna disfunkcija.

PRIMJENA ANTIDEPRESIVA U STARIJOJ ŽIVOTNOJ DOBI

Antidepresivi su temelj liječenja depresije. U najvećoj mrežnoj meta-analizi do sada, u osoba starijih od 18 godina svi su antidepresivi bili učinkovitiji od placeba u liječenju akutne epizode, iako su među njima utvrđene razlike u učinkovitosti (11). Međutim, druga je meta-analiza, koja je obuhvatila samo istraživanja antidepresiva u starijoj dobi, pokazala da mnogi antidepresivi nisu imali veći učinak nego placebo, ali su kvetiapin i duloksetin, te također mirtazapin, escitalopram, imipramin, agomelatin i vortioksetin, bili učinkoviti u ovoj populaciji (12). Ovakvi rezultati pokazuju da je liječenje depresije u starijoj dobi poseban izazov. Na primjer, čak polovica starijih osoba s depresijom nije imala dobar odgovor na prvi primijenjeni lijek (3). Međutim, i ove činjenice treba uzeti s oprezom. Spomenuta meta-analiza je analizirala deset puta manji broj istraživanja (12) nego meta-analiza koja je obuhvatila dvostruko slijepa istraživanja u odrasloj dobi (11). Naime, starija životna dob je isključni kriterij u većini istraživanja antidepresiva. Ipak, najzanimljivije jest da je kvetiapin, koji uopće nije odobren kao monoterapija depresije, bio najučinkovitiji lijek, kako u odgovoru na antidepresive, tako i u postizanju remisije kod starijih osoba s depresijom (12). No ne znamo je li kvetiapin u monoterapiji ovako učinkovit i u mlađih osoba s depresijom, jer nije bio uključen u ranije spomenutu meta-analizu (11). Valja pritom napomenuti da su meta-analize uključile samo dvostruko slijepa istraživanja (11,12), te je pitanje mogu li se njihovi rezultati primijeniti i na čitavu populaciju starijih osoba s depresijom. Naime, uključni kriteriji za ovakva istraživanja su vrlo strogi, te pacijenti sa somatskim multimorbiditetima, posebice s nereguliranim tjelesnim simptomima, ne mogu biti uključe-

Therefore, polypharmacy is common, as are drug-drug interactions, while the sensitivity to adverse reactions is increased.

TREATMENT OF DEPRESSION IN THE ELDERLY

Antidepressants are the cornerstone for the treatment of depression. In the most comprehensive network meta-analysis to date in individuals older than 18 years, all antidepressants had higher acute response rates compared to placebo, although some differences were demonstrated across different agents (11). However, the other meta-analysis, conducted specifically on elderly patients, demonstrated that many antidepressants did not outperform placebo, whereas quetiapine and duloxetine, followed by mirtazapine, escitalopram, imipramine, agomelatine, and vortioxetine, were the most efficacious (12). Those findings suggest that the treatment of depression in elderly individuals is a particular challenge. For example, half of the elderly individuals had no response to the first-line agent (3). However, those conclusions should be drawn with caution, given that the former study analysed almost 10 times more trials (11) than the latter (12). This is because elderly patients were excluded from many trials. The most striking finding is that quetiapine, which has no improved indication as monotherapy in major depression, was the most effective drug in terms of achieving both response and remission during acute treatment of depression in elderly patients (12). While both aforementioned large meta-analyses focused on randomized-controlled trials (11, 12), those data, particularly regarding older patients, might not be applicable to all patients. Participants with multiple comorbidities, especially unstable medical conditions requiring complex drug regimens, are usually excluded from such

ni. A upravo je takvih bolesnika s depresijom mnogo u svakodnevnoj praksi. Zato u literaturi nema mnogo dokaza o učinku antidepresiva u depresivnih bolesnika starije životne dobi, koji se također liječe i zbog brojnih tjelesnih bolesti (7), te dobivaju višestruke kombinacije lijekova.

U svakom slučaju, terapiju antidepresivom u osoba starije životne dobi treba započeti s polovicom doze antidepresiva kojom započinje liječenje u odrasloj dobi (1), s pažljivom titracijom do minimalne učinkovite doze. Na primjer, nedavna meta-analiza dvostruko slijepih studija primjene SIPPSa u osoba starijih od 18 godina pokazala je da porast okupiranosti serotoninskog transportera ovim lijekovima za više od 80 % ne dovodi do daljnjeg povećanja učinka (13). Iako rezultati u osoba starije dobi nisu posebno analizirani, zapažen je nagli porast odustajanja od terapije zbog nuspojava, kako se doza SIPPSa povećavala (13).

Bez obzira na potencijalnu lošiju učinkovitost, te ostala navedena ograničenja, antidepresivi su prva linija liječenja u starijih osoba s depresijom (14), baš kao i u mlađih osoba, iako je u starijih osoba potreban dodatan oprez. Prema uputama o lijeku neki se antidepresivi u starijih osoba preporučuju primjenjivati u nižim dozama. Upute o titraciji, dozama održavanja te maksimalnim dopuštenim dozama antidepresiva u starijih osoba prikazuje tablica 1.

Međutim, u vrlo starih osoba, ili onih s brojnim tjelesnim bolestima, preporučuju se još niže početne doze, doze održavanja, te maksimalne doze (7). Duloksetin i venlafaksin smatraju se relativno sigurnim lijekovima što se tiče produženja QTc intervala i nastanka aritmija (17).

Starije su osobe posebice osjetljive na razvoj nuspojava, kako antidepresiva, tako i drugih lijekova. Stoga se mogu očekivati i farmakodinamske interakcije među različitim supstancijama. Neke od farmakodinamskih interakcija prikazuje tablica 2.

Napominjemo da tablica 2 ne prikazuje sve farmakodinamske interakcije, nego samo one koje

trials. Therefore, treatment of depression in individuals with unstable or severe medical comorbidities is not supported by evidence because such patients are often excluded from clinical trials (7).

The starting dose should be half of the initial adult dose (1) and be titrated until the patient responds. A recent meta-analysis of double-blind trials for individuals with MDD aged 18 years or older reported that increases in transporter occupancy above 80% by SIPSS did not improve treatment efficacy (13). While the latter study did not separately address older individuals, dropouts due to adverse effects increased steeply throughout the dosing range (13).

Regardless of those limitations, antidepressants are the first-line treatment in elderly patients with depression (14), which is similar to depression in younger individuals. However, in the age group of the elderly, particular vigilance is needed. According to the prescribing information, some antidepressants require dosing restrictions, careful initial dose titration, and monitoring, as shown in Table 1.

However, very old patients or those with medical comorbidities need even lower initial, maintenance, and maximum dosages of antidepressants (7).

Duloxetine and venlafaxine are considered relatively safe in respect to QTc prolongation and arrhythmias (17)

Elderly patients might be particularly sensitive to adverse effects of antidepressants, as well as those of other drugs. Some pharmacodynamic interactions which might occur between antidepressants and other drugs are shown in Table 2.

Elderly individuals are more vulnerable to side effects, which might occur in lower doses. For example, it was reported that about 8% of elderly individuals on SSRIs or venlafaxine

TABLICA 1. Preporuke o doziranju antidepresiva u starijih osoba
TABLE 1. Dosing recommendations for antidepressants in elderly patients

Antidepresivi / Antidepressants	Maksimalna dnevna doza u odraslih osoba (mg) / Maximum daily dose in adults (mg)	Maksimalna dnevna doza u starijih osoba (mg) / Maximum daily dose in the elderly (mg)	Sigurnost primjene / Safety considerations
SIPPS / SSRI			Povećan rizik hiponatremije i padova / Potential hyponatremia and increased risk of falls
Citalopram / Citalopram	40	20	Produženje QTc intervala ovisno o dozi / Dose-dependent QTc prolongation
Escitalopram / Escitalopram	20	10	Produženje QTc intervala ovisno o dozi / Dose-dependent QTc prolongation
Fluoksetin / Fluoxetine	60	40	
Fluvoksamin / Fluvoxamine	300	Nema ograničenja / No restrictions	Polaganija titracija doze i pažljiva opservacija / Slower dose titration and caution
Paroksetin / Paroxetine	50-60	40	Mogućnost antikolinergičkih nuspojava / Potential anticholinergic side effects
Sertralin / Sertraline	200	Nema ograničenja, no preporučuje se oprez / No restrictions, but caution is advised	
SNRI / SNRI			
Duloksetin / Duloxetine	120	Nema ograničenja, no preporučuje se oprez / No restrictions, but caution is advised	
Venlafaksin / Venlafaxine	375	Nema ograničenja, no preporučuje se oprez / No restrictions, but caution is advised	Preporučuje se najniža učinkovita doza / Lowest effective dose is recommended
Ostali antidepresivi / Other antidepressants			
Agomelatin / Agomelatine	50	Nema ograničenja doze do dobi od 75 godina / No dosing restrictions up to the age of 75 years	Ne preporučuje se starijima od 75 godina, jer nema dovoljno podataka / Not recommended in patients older than 75 years due to the lack of data
Amitriptilin / Amitriptyline	150-200 300 mg u hospitaliziranih bolesnika / 300 for inpatients	Polagana titracija, polovicom uobičajene doze / Slow dose titration; half of the usual dose is recommended	Mogućnost antikolinergičkih nuspojava i hipotenzije / Potential anticholinergic side effects and hypotension
Bupropion / Bupropion	300	Nema ograničenja / No restrictions	
Maprotilin / Maprotiline	150	75	Mogućnost antikolinergičkih nuspojava / Potential anticholinergic side effects
Mirtazapin / Mirtazapine	45	Nema ograničenja / No restrictions	
Moklobemid / Moclobemide	600	Nema ograničenja / No restrictions	
Reboksetin / Reboxetine	12	Najviša doza u kliničkim istraživanjima: 4 mg / Maximum dose in clinical trials: 4 mg	Ne preporučuje se u starijih osoba zbog nedovoljno podataka / Not recommended in elderly patients due to the lack of data
Sulpirid / Sulpiride	400	Nema ograničenja / No restrictions	Starije su osobe ↑ osjetljive na ekstrapiramidne nuspojave, sedaciju i hipotenziju / Elderly people are more sensitive to extrapyramidal side effects, sedation, and hypotension
Tianeptin / Tianeptine	37,5	Osobe s tjelesnom težinom<55 kg smiju primati najviše 12,5 mg2 x/dan / Patients with body weight <55 kg should receive maximum 12.5 mg b.i.d.	
Trazodon / Trazodone	300 600 mg u hospitaliziranih osoba / 600 for inpatients	Početna dnevna doza ne smije biti>100 mg, dok pojedine doze održavanja ne smiju biti više od 100 mg / Initial daily dose should not be >100 mg, while separate doses should not exceed 100 mg	Moguća sedacija i hipotenzija / Potential sedation and hypotension
Vortioksetin / Vortioxetine	20	Početna dnevna doza je 5 mg; oprez s dnevnim dozama iznad 10 mg / Starting dose should be 5 mg daily; caution with doses >10 mg daily	

SIPPS = Selektivni inhibitor ponovne pohrane serotonina / SSRI = Selective serotonin reuptake inhibitor
SNRI = Selektivni inhibitor ponovne pohrane noradrenalina / SNRI = Selective noradrenaline reuptake inhibitor
(Prema Kok i Reynolds, 2017;Beyeri Johnson, 2018;www.halmed.hr, 2019;Nevels i sur., 2016) / (According to Kok and Reynolds, 2017; Beyer and Johnson, 2018; www.halmed.hr, 2019; Nevelset et al., 2016)

TABLICA 2. Farmakodinamske interakcije antidepresiva i ostalih lijekova
TABLE 2. Pharmacodynamic interactions between antidepressants and other drugs

Antidepresivi / Antidepressants	Interakcije s: / Interaction with	Vrsta farmakodinamske interakcije / Pharmacodynamic interaction
SIPPS / SSRI	Antikoagulansima / Anticoagulants Antitrombocitnim lijekovima / Anti-platelet drugs Nesteroidnim antireumaticima / Non-steroid anti-inflammatory drugs	↑ Rizik krvarenja / ↑ Risk of bleeding
SIPPS / SSRIs SNRI / SNRIs TCA / TCAs	Diuretici / Diuretics ??? / Kidney disease	Hiponatremija / Hyponatremia
TCA / TCAs Paroksetin / Paroxetine	Klozapin / Clozapine Olanzapin / Olanzapine Kvetiapin / Quetiapine Biperiden / Biperiden	Antikolinergičke nuspojave / Anticholinergic effects

SIPPS = Selektivni inhibitori ponovne pohrane serotonina / SSRI = Selective serotonin reuptake inhibitor
??? / SSRIs = Selective serotonin reuptake inhibitors
SNRI = Selektivni inhibitori ponovne pohrane noradrenalina / SNRIs = Selective noradrenaline reuptake inhibitors
TCA = Triciklički antidepresivi / TCAs = Tricyclic antidepressants
(Prema Trifirò i Spina, 2011; Nevelsi sur., 2016;Sultana i sur., 2015) / (According to Trifirò and Spina, 2011; Nevelset et al., 2016; Sultana et al., 2015)

su najbolje utvrđene. U starijih osoba nuspojave lijekova se javljaju već kod nižih doza nego u mlađih osoba. Na primjer, u oko 8 % starijih osoba koje dobivaju SIPPS ili venlafaksin, zapažena je hiponatremija, kao posljedica sindroma neadekvatne sekrecije antidiuretskog hormona (1). Međutim, brojne se nuspojave mogu spriječiti propisivanjem najnižih učinkovitih doza, te pažljivim izbjegavanjem farmakodinamskih i farmakokinetskih nuspojava (17). Općenito, SIPPS i SNRI se smatraju terapijom prvog izbora u starijih osoba s depresijom (14). Također se individualna terapija smatra modernim standardom liječenja, što posebice dolazi do izražaja u starijoj životnoj dobi. Tako izbor antidepresiva može ovisiti i o nuspojavi koju želimo izbjeći. Prema meta-analizi, mirtazapin i amitriptilin bili su povezani s manje mučnine, maprotilin i mianserin s rjeđom nesanicom, a tianeptin s manje vrtoglavice, u usporedbi s ostalim antidepresivima (12). Trazodon može poboljšati kvalitetu spavanja. Antidepresivi koji jako povećavaju serotonergičku aktivnost mogu povećati vjerojatnost fraktura u starijih osoba (17). Osim navedenih nuspojava preporuka je da, ako ne dođe do početnog terapijskog odgovora na kraju drugog tjedna terapije, treba ili promijeniti antidepresiv, ili dodati drugi lijek, posebice u osoba koje imaju i druge potencijalne pokazatelje lošeg odgovora na terapiju (14).

would develop hyponatremia related to the syndrome of inappropriate secretion of the antidiuretic hormone (SIADS) (1). Many potential adverse events might be prevented by both prescribing the lowest effective antidepressant dose and avoiding potential PD and PK interactions (17).

In general, SSRI/SNRIs are considered the first-line treatment for the depression in the elderly (14). However, individual treatment is crucial, especially in the elderly population. The choice on antidepressants might also depend on the avoidance of potential adverse events. According to a recent network meta-analysis of side effects, mirtazapine and amitriptyline were associated with less nausea, maprotiline and mianserine with less insomnia, and tianeptine with less dizziness, compared to some other antidepressants (12). Trazodone might improve sleep quality. Antidepressants with high serotonin activity are associated with the risk of fractures in elderly (17). In patients with poor response to a chosen antidepressant at week 2, a switch to another drug or the augmentation of the current regimen is recommended, particularly in those with predictors of treatment resistance (14).

Given that elderly patients with depression frequently receive polypharmacy, drug-drug

S obzirom na čestu polifarmaciju u starijih osoba kod uvođenja antidepresiva bitno je uvijek razmotriti moguće interakcije s ostalim lijekovima. Većina ovih interakcija se odvija putem enzima citokroma P 450 (CYP 450). Antidepresivi mogu biti supstrati i/ili inhibitori nekoliko skupina ovih enzima, kao što je prikazano u tablici 3.

interactions also need to be considered when choosing antidepressants. The majority of those interactions occur via cytochrome P 450 (CYP 450) enzymes. Antidepressants are substrates for those enzymes, and some of them are also inhibitors of several CYP450 isoenzymes, which is shown in Table 3.

TABLICA 3. Antidepresivi kao supstrati i/ili inhibitori CYP 450 enzima
TABLE 3. Antidepressants as substrates and inhibitors for enzymes CYP 450

Skupina CYP450 / CYP450	Supstrati / Substrates	Inhibitori / Inhibitors	Induktori / Inducers
1A2	**Agomelatin / Agomelatine** **Duloksetin / Duloxetine** **Mirtazapin / Mirtazapine** Klozapin / Clozapine Olanzapin / Olanzapine Teofilin / Theophylline	**Fluvoksamin / Fluvoxamine** Ciprofloksacin / Ciprofloxacin Norfloksacin / Norfloxacin	Omeprazol / Omeprazole Rifampicin / Rifampicin Gospina trava / St. John's wort Karbamazepin / Carbamazepine Ritonavir / Ritonavir
CYP2C9	Varfarin / Warfarin Losartan / Losartan **Fluoksetin (↓) / Fluoxetine (↓)** **Sertralin (↓) / Sertraline (↓)**	Amjodaron / Amiodarone Fluvastatin / Fluvastatin Lovastatin / Lovastatin Tiklopidin / Ticlopidine **Fluoksetin (↓) / Fluoxetine (↓)** **Fluvoksamin (↓) / Fluvoxamine (↓)** **Paroksetin (↓) / Paroxetine (↓)** **Sertralin (↓) / Sertraline (↓)**	Gospina trava / St. John's wort
CYP2C19	**Amitriptilin / Amitriptyline** **Citalopram / Citalopram** **Escitalopram / Escitalopram** **Moklobemid / Moclobemide** Klopidrogel / Clopidogrel Omeprazol / Omeprazole	**Fluoksetin / Fluoxetine** **Fluvoksamin / Fluvoxamine** **Moklobemid / Moclobemide** Tiklopidin / Ticlopidine	Karbamazepin / Carbamazepine Fenitoin / Phenytoin Fenobarbiton / Phenobarbitone Gospina trava / St. John's wort
CYP2D6	**Duloksetin / Duloxetine** **Venlafaksin / Venlafaxine** **Vortioksetin / Vortioxetine** **Maprotilin / Maprotiline** **Mirtazapin / Mirtazapine** **Sertralin / Sertraline** Antipsihotici (flufenazin, haloperidol, risperidon) / Antipsychotics (fluphenazine, haloperidol, risperidone) Metadon / Methadone Antiaritmici (flekainid) / Antiarrhythmics (flecainide) Tramadol / Tramadol Beta-blokatori (nebivolol, metoprolol, propranolol) / Beta-blockers (nebivolol, metoprolol, propranolol)	**Fluoksetin / Fluoxetine** **Paroksetin / Paroxetine** Amjodaron / Amiodarone Kinidin / Quinidine Ritonavir / Ritonavir Tiklopidin / Ticlopidine	
CYP3A4	**Kvetiapin / Quetiapine** **Mirtazapin / Mirtazapine** **Trazodon / Trazodone** Antipsihotici (aripiprazol, brekspiprazol, kariprazin) / Antipsychotics (aripiprazole, brexpiprazole, cariprazine) Statini / Statins Makrolidi... / Macrolides...	Diltiazem / Diltiazem Eritromicin / Erythromycin Inhibitori protein kinaze / Protein kinase inhibitors Indinavir / Indinavir Itrakonazol / Itraconazole Ketokonazol / Ketoconazole Verapamil / Verapamil **Fluoksetin / Fluoxetine** **Fluvoksamin / Fluvoxamine** **Sertralin (↑ doze) / Sertraline (↑ doses)**	Karbamazepin / Carbamazepine Fenitoin / Phenytoin Fenobarbiton / Phenobarbitone Gospina trava / St. John's Worth Rifampicin / Rifampicin Glukokortikoidi / Glucocorticoids

(Prema Mannheimer i sur., 2008; Spina i de Leon, 2014; Spina i sur., 2016; Šagud i sur.,2017; Piña i sur., 2018; Goodlet i sur., 2019) / (According to Mannheimer *et al.*, 2008; Spina and de Leon, 2014; Spina *et al.*, 2016; Šagud *et al.*, 2017; Piña et al., 2018; Goodlet *et al.*, 2019)

ZAKLJUČAK

Depresivni poremećaj u starijoj dobi je često težak i onesposobljavajući, te se svakako treba liječiti. S obzirom na vrlo velik raspon dobi ove populacije, koji obuhvaća više od 40 godina, depresivni poremećaj uključuje osobe u različitim životnim razdobljima. Stoga osobe na donjoj granici ovog raspona mogu još uvijek biti radno aktivne, dok ostale mogu biti desetljećima umirovljene. Stoga mogu postojati i značajne razlike u životnim navikama, komorbiditetu i kognitivnim sposobnostima. Naziv „starije osobe" obuhvaća vrlo raznoliku populaciju, te sadrži vjerojatno nekoliko vrlo različitih kategorija. Još uvijek nemamo dovoljno podataka o učinkovitosti i podnošljivosti antidepresiva u starijoj populaciji. Za sada, dok još nemamo pouzdanih bioloških pokazatelja, izbor antidepresiva se temelji na vodećim simptomima kod pojedine osobe, prisutnosti tjelesnih bolesti, nuspojavama koje želimo izbjeći, te ostaloj terapiji koju bolesnik dobiva. Individualni pristup, uz uporabu najniže učinkovite doze, principi su moderne psihofarmakologije, a od ključne su važnosti u osobito ranjivoj populaciji starijih bolesnika s depresivnim poremećajem.

CONCLUSION

Major depression in the old age is potentially dangerous and disabling, and should be treated. Given the wide range of the term "elderly people", which encompasses more than 40 years, it includes individuals in different life phases. For example, some of them might still be employed at the lower age-limits, while others might be retired for decades. They might differ significantly in terms of life habits, comorbidity, and cognition. Therefore, the term "elderly" is not a uniform construct, and needs to be re-defined and probably divided into several categories. More data is needed regarding the efficacy and safety of antidepressants in the elderly population. So far, and in the absence of reliable biomarkers, the choice of antidepressants is based on the leading symptoms of depression, the presence of somatic comorbidities, and concomitant treatment. An individualized treatment approach and the use of the lowest effective dose is a rule in modern psychopharmacology, but appears to be essential in the extremely vulnerable population of elderly patients with depression.

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