Psihotropna polifarmacija u djece i adolescenata

/ Psychotropic Polypharmacy in Children and Adolescents

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Psihotropna polifarmacija (PP) definira se kao praksa propisivanja dvaju ili više psihotropnih lijekova za jedan ili više dijagnosticiranih psihijatrijskih poremećaja. Podatci o stopi PP u pedijatrijskoj populaciji pokazuju da je ova praksa u porastu. Baza dokaza o učinkovitosti PP u pedijatrijskoj psihijatrijskoj praksi je ograničena. Zbog složenosti etiologije i težine psihičkih poremećaja u djece primjena PP ponekad je neizbježna. U takvim slučajevima svaka kombinacija korištenih lijekova mora imati svoje etiološko i kliničko opravdanje, jer će samo tada PP biti korisna i opravdana, a ne pretjerana i opterećena nuspojavama. Ovaj pregledni rad donosi glavne spoznaje u ovom području s jasnim zaključkom da su potrebna visoko kvalitetna i longitudinalna istraživanja kako bi se odgovorilo na pitanja učinkovitosti i sigurnosti psihotropne polifarmacije u liječenju psihičkih poremećaja u djece i adolescenata. Do tada, stav prema kombiniranoj farmakoterapiji trebao bi biti konzervativan, a kombiniranje psihotropnih lijekova pažljivo praćeno zbog specifične zabrinutosti zbog rizika od povećanja nuspojava s polifarmacijom.

/ Psychotropic polypharmacy (PP) is defined as the practice of prescribing two or more medications for one or more diagnosed psychiatric disorders. Data on the rates of PP in pediatric population demonstrate that this practice is on the rise. The evidence base on the efficacy of psychotropic polypharmacy in pediatric psychiatric practice is limited. Due to the complexity of the etiology and severity of mental disorders in children, the use of PP is sometimes unavoidable. In such cases, each combination of drugs used must have its etiological and clinical justification because only then will PP be useful and justified, and not excessive and burdened with side effects.

This review brings the main findings in this area with a clear conclusion that more high quality and longitudinal studies are needed to answer the questions of the effectiveness and safety of psychotropic polypharmacy in the treatment of mental disorders in children and adolescents. Until then, the attitude to combination pharmacotherapy should be conservative, and combining psychotropic medications should be closely monitored due to the specific concern of the risks of the increase of adverse events with polypharmacy.

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UVOD

Psihotropna polifarmacija, definirana kao istodobna primjena dvaju ili više psihotropnih lijekova kod jednog pacijenta za jedan ili više dijagnosticiranih psihijatrijskih poremećaja, sve je učestalija suvremena praksa u kliničkoj psihijatriji (1, 2). U literaturi se koriste različiti pojmovi za primjenu dvaju ili više psihotropnih lijekova kod jednog bolesnika, kao što su *kofarmacija, kombinirana farmakoterapija, konkomitantna psihotropna medikacija, kombinirana psihotropna farmakoterapija* (3). Budući da u istraživanjima nema razlike između definicija, svi pojmovi će se u ovom pregledu razmatrati pod nazivom psihotropne polifarmacije (PP).

Definicija polifarmacije varira ovisno o mjerenim parametrima: duljini preklapajućih dana izloženosti i trajanju razdoblja procjene (4). Mjere ishoda uključuju dvije vrste polifarmacije: unutar iste skupine, npr. istodobna primjena dvaju ili više antipsihotika i međuklasna (unutar više skupina), npr. istodobna primjena antipsihotika i antidepresiva.

Prema Preskornu i Laceyu (5) postoji nekoliko razloga za polifarmaciju: za liječenje dviju patofiziološki različitih, ali komorbidnih bolesti u istog bolesnika; za sprječavanje štetnog učinka primarnog lijeka; za pružanje akutnog poboljšanja dok se čeka odgođeni učinak drugog lijeka (npr. korištenje lorazepama u akutnoj maniji dok se čeka početak antimaničnog učinka litija); za liječenje određenih faza bolesti (npr. dodavanje antidepresiva stabilizatoru raspoloženja kada bipolarni pacijent razvije depresivnu epizodu) te za pojačavanje ili povećanje učinkovitosti primarnog lijeka (npr. kombiniranje selektivnog inhibitora ponovne pohrane serotonina i drugog antidepresiva za liječenje bolesnika s velikim depresivnim poremećajem).

Kombiniranje psihotropnih lijekova može dovesti do mogućeg povećanja koristi, ali i rizika, osobito uzevši u obzir potencijal za interakcije psihotropnih lijekova. Zabrinutost u vezi s

INTRODUCTION

Psychotropic polypharmacy, defined as the concomitant use of two or more psychotropic drugs in a single patient for one or more diagnosed psychiatric disorders, is increasingly common contemporary practice in clinical psychiatry (1,2). Different terms for the use of two or more psychotropic drugs in a single patient are used in the literature such as *copharmacy, combined pharmacotherapy, concomitant psychotropic medication, combined psychotropic pharmacotherapy* (3). Since studies do not distinguish between the definitions, in this review all terms will be considered under the term of "psychotropic polypharmacy" (PP).

The definition of polypharmacy varies depending on the parameters measured: the length of overlapping days of exposure and the duration of the period assessed (4). The outcome measures include two types of polypharmacy: within class, e.g., two concomitant antipsychotics, and inter-class (multi-class), e.g., concomitant antipsychotic and antidepressant.

According to Preskorn and Lacey (5), there are several reasons for polypharmacy: to treat two pathophysiologically distinct but co-morbid illnesses in the same patient; to prevent an adverse effect produced by the primary drug; to provide acute amelioration while awaiting the delayed effect of another medication (e.g., using lorazepam in acute mania while waiting for the antimanic effects of lithium to exert themselves); to treat intervening phases of an illness (e.g., adding an antidepressant to a mood stabilizer when a bipolar patient develops a depressive episode); and to boost or augment the efficacy of the primary drug (e.g., combining a selective serotonin reuptake inhibitor and another antidepressant to treat a patient with major depression).

Combining psychotropic drugs may lead to possible increases in benefits, but also in risks, particularly given the potential for psychotropic drug interactions. Concerns about the use

upotrebom kombinacije psihotropnih lijekova odnosi se na potencijalnu kumulativnu toksičnost i povećanu osjetljivost na nuspojave, kao i na suradljivost kod primjene više lijekova i složenost doziranja (6).

Psihotropna polifarmacija u djece i adolescenata

Kombiniranje psihotropnih lijekova u liječenju psihijatrijskih poremećaja u djece i adolescenata je postalo sve učestalije u posljednja dva desetljeća (7,8). Čimbenici koji doprinose rastu pedijatrijske PP uključuju: 1. prevladavanje biologijskog modela u psihijatrijskoj praksi; 2. netočne pretpostavke o učinkovitosti kombinacija, 3. ograničena svijest kliničara o metaboličkim i neurološkim nuspojavama lijekova i 4. nedovoljno postupno ukidanje lijeka (9).

U nekim je situacijama kratkoročna polifarmacija očigledno prikladna ili čak neophodna. Na primjer, kada se pacijenta prebacuje s jednog psihotropnog lijeka na drugi većina kliničara odlučuje preklapati ili unakrsno titrirati ta dva lijeka, što rezultira namjerno kratkotrajnim razdobljem kombiniranog liječenja (4-6). Drugi kliničari, osobito u bolničkim uvjetima, često koriste antipsihotike druge generacije kao privremenu korisnu dodatnu terapiju stimulansima ili stabilizatorima raspoloženja u liječenju egzacerbacija mentalnih bolesti. U svakom od ovih slučajeva dugoročni cilj je i dalje monoterapija, ali kombinacije se koriste za postizanje kratkoročnih ciljeva kao što je smanjenje rizika pri zamjeni lijekova ili brže rješavanja akutnih simptoma. Iako empirijska podloga za kratkotrajnu primjenu psihotropnih kombinacija u pedijatrijskoj populaciji nije osobito snažna, obrazloženje je utemeljeno na kliničkom iskustvu i uključuje relativno kratko izlaganje rizicima kombinacija.

S druge strane, dugotrajna terapija održavanja psihotropnim kombinacijama u djece i adolescenata otvara daleko značajnija pitanja

of a combination of psychotropic drugs relate to potential cumulative toxicity and increased vulnerability to adverse events, as well as compliance in multiple drug administration and dosing complexity (6).

Psychotropic polypharmacy in children and adolescents

Combining psychotropic drugs in treatment of psychiatric disorders in children and adolescents has become increasingly common over the past two decades (7,8). The factors that contribute to the growth of pediatric PP include: (1) predominance of the biological model in psychiatric practice; (2) invalid assumptions on efficacy of combinations, (3) limited professional awareness of metabolic and neurological adverse drug events, and (4) infrequent use of appropriate deprescribing (9).

In some situations, short-term polypharmacy is clearly appropriate or even necessary. For instance, when changing a patient from one psychotropic drug to another, most clinicians choose to overlap or cross-titrate the two, resulting in a purposely brief period of combination treatment (4–6). Other clinicians, especially in the inpatient setting, often use second-generation antipsychotics as temporarily useful adjuncts to stimulants or mood stabilizers in treating exacerbations of mental illness. In each of these instances, the long-term goal is still monotherapy, but combinations are used to achieve short-term goals, such as to reduce risks while switching medications or to promote a more rapid resolution of acute symptoms. Although the empirical base for short-term use of psychotropic combinations in the pediatric population is not particularly strong, the rationale is grounded in clinical experience and involves a relatively brief exposure to the risks of the combination.

On the other hand, long-term maintenance treatment with psychotropic combinations in children and adolescents raises far more signif-

o učinkovitosti, sigurnosti i troškovima liječenja (10). Kombinacija više lijekova može ponuditi prednosti za specifična klinička stanja kao što je uporaba stimulansa i alfa agonista za liječenje poremećaja deficita pažnje i hiperaktivnosti (*Attention Deficit Hyperactivity Disorder* - ADHD) (11) ili atomoksetina i niskih doza antipsihotika za komorbidni ADHD i Touretteov sindrom (10). Međutim, baza dokaza za konkomitantnu farmakoterapiju u pedijatrijskoj psihijatrijskoj praksi vrlo je ograničena, dok je rizik od štete značajan (10,12). Istodobna uporaba psihotropnih lijekova povećava rizik od interakcija među lijekovima, dodatnih nuspojava na lijekove i može stvoriti krug korištenja jednog lijeka radi liječenja nuspojava drugog.

Prevalencija polifarmacije opada s povećanjem strogosti kriterija preklapanja (12). Na temelju kriterija 14-dnevnog preklapanja više od jedne četvrtine (28,8 %) djece i adolescenata primilo je psihotropnu polifarmaciju; od ovih pacijenata, 72,7 % je koristilo kombinacije najmanje 60 dana, a 61,3 % uzimalo je kombinacije 90 dana ili dulje.

Stope pedijatrijske PP-a razlikuju se u različitim terapijskim okruženjima (3). Istraživanja su pokazala da čak oko trećina djece kojoj je propisana psihofarmakološka terapija u ambulantnim uvjetima prima više od jednog psihotropnog lijeka te da je PP češća u dječaka, adolescenata, djece smještene u udomiteljstvu i djece s komorbidnim psihičkim poremećajima (12,13). Retrospektivna kohortna studija pokazala je da je 38 % mladih koji su uzimali psihotropne lijekove tijekom najmanje 90 dana dobilo dva ili više psihotropna lijeka (13). Djeca liječena u javnim zdravstvenim službama, djeca u udomiteljstvu, djeca koja su doživjela traumu i djeca s intelektualnim teškoćama ranjivija su za visoke stope konkomitantne psihotropne medikacije (10,12,14,15).

Stope PP su veće u stacionarnim psihijatrijskim ustanovama od ambulantnih ustanova. Podatci

icant questions about efficacy, safety, and costs (10). The combination of multiple medications may offer benefits for specific clinical conditions, such as the use of a stimulant and alpha agonist for the treatment of attention deficit hyperactivity disorder (ADHD) (11), or atomoxetine and low doses of antipsychotics for comorbid of ADHD and Tourette's syndrome (10). However, the evidence base for concomitant pharmacotherapy in pediatric psychiatric practice is limited while risk for harm is significant (10,12). The use of concomitant psychotropics increases the risk of drug-drug interactions and additive drug adverse reactions, and may create a cycle of using one drug to treat the adverse effects of another.

The prevalence of polypharmacy decreases with increasing stringency of the overlap criteria (12). On the basis of the 14-day overlap criterion, more than one-quarter (28.8%) of children and adolescents received psychotropic polypharmacy; of these patients, 72.7% had been using the combinations for at least 60 days and 61.3% took the combinations for 90 days or longer.

The rates of pediatric PP differ among various treatmet settings (3). Research has shown that as many as about one third of children prescribed psychopharmacological therapy in outpatient setting received more than one psychotropic drug and that PP is more common in boys, adolescents, children placed in foster care and children with comorbid mental disorders (12,13). A retrospective cohort study found that 38% of youth on psychotropic medication for at least 90 days were prescribed two or more psychotropic medications (13). Children treated in public health care services, in foster care, those who have experienced trauma, and those with intellectual disability were found to be vulnerable to high rates of concomitant psychotropic medication (10, 12, 14, 15).

PP rates are higher in psychiatric inpatient facilities than in outpatient facilities. Data from

iz Finske pokazuju da je 36 % hospitaliziranih pacijenata koji su primali psihotropne lijekove imalo propisano više od jednog lijeka (16). Connor i sur. (17) su otkrili da je 76 % mladih primljenih na bolničko liječenje bilo na psihotropnim lijekovima, a 40 % na više od jednog psihotropnog lijeka. Druga studija iz Indije izvijestila je o stopi PP u 52 % djece i adolescenata koji se liječe u stacionarnim uvjetima (18), dok je u ranijoj studiji povijest PP pronađena u 60,3 % djece i adolescenata. Nedavna studija koja je ispitivala stope istodobne uporabe psihotropnih lijekova u 21 ustanovi za stacionarno psihijatrijsko liječenje pokazala je da je 86,9 % mladih primalo 2 ili više različitih psihotropnih lijekova tijekom najmanje 60 dana, 64,6 % je primalo 3 ili više različitih psihotropnih lijekova tijekom najmanje 60 dana. Za djecu koja su primala 3 ili više različitih skupina lijekova, 55,7 % je primalo ove lijekove tijekom 90 ili više dana (20). Prediktori antipsihotične polifarmacije u mladih kod otpusta iz psihijatrijskih stacionara bili su prijam zbog nasilja ili agresije, dijagnoza intelektualnih teškoća, psihotičnog poremećaja ili neurorazvojnog poremećaja, veći broj ranijih hospitalizacija i dulja hospitalizacija (16,18,20).

Vrsta i broj psihijatrijskih dijagnoza utječu na prevalenciju i trajanje PP u djece i adolescenata. Dijagnoze koje predviđaju psihotropnu polifarmaciju kod mladih uključuju neurorazvojne poremećaje (intelektualne poteškoće, poremećaji s tikovima i razvojni poremećaji), poremećaje ponašanja (poremećaj deficita pažnje i hiperaktivnosti, poremećaj s prkošenjem i suprodstavljanjem, poremećaj ophođenja), poremećaje kontrole impulsa (intermitentni eksplozivni poremećaj), psihotične poremećaje, depresiju, anksioznost i bipolarni poremećaj (12,13,16,19-21). Mladi bolesnici s teškim poremećajima rezistentni na monoterapiju i djeca s višestrukim dijagnozama mentalnih poremećaja vjerojatnije će primiti psihotropnu polifarmaciju (13,16,21).

Finland show that 36% of hospitalized patients receiving psychotropic medication were prescribed more than one drug (16). Connor *et al.* (17) found that 76% of the youths admitted to a residential treatment center were on psychotropics, with 40% on more than one psychotropic medication. Another study from India reported a rate of PP in 52% of child and adolescent inpatients (18), while in an earlier study a history of PP was found for 60.3% of children and adolescents. A recent study that examined the rates of concomitant psychotropic use in 21 psychiatric residential treatment facilities showed that 86.9% of youth received 2 or more different psychotropics for at least 60 days, 64.6% received 3 or more different psychotropics for at least 60 days. For children receiving 3 or more different classes of medication, 55.7% received these medications for 90 days or longer (20). Predictors of antipsychotic polypharmacy in youth at discharge from psychiatric inpatient units were admission for violence or aggression, diagnoses of intellectual disability, psychotic disorders, or neurodevelopmental disorders, a greater number of previous admissions, and longer hospitalization (16,18,20).

The type and number of psychiatric diagnoses influence the prevalence and duration of PP in children and adolescents. Diagnoses predictive of psychotropic polypharmacy in youth include neurodevelopmental disorders (intellectual disabilities, tic disorders and developmental disorders), disruptive behavioral disorders (attention-deficit hyperactivity disorder, oppositional defiant disorder, conduct disorder), impulse control disorders (intermittent explosive disorder), psychotic disorders, depression, anxiety and bipolar disorder (12,13,16,19-21). Young patients with severe disorders, resistance to monotherapy and children with multiple mental health diagnoses were more likely to receive psychotropic polypharmacy (13,16,21).

Among children receiving long-term psychotropic polypharmacy, a vast majority receive com-

Velika većina djece koja uzimaju PP dugotrajno primaju kombinacije psihotropnih lijekova iz različitih terapijskih skupina. Najčešće korištene kombinacije su stimulansi s antipsihoticima, antidepresivima ili alfa agonistima, a slijede antipsihotici u kombinaciji s antidepresivima ili stabilizatorima raspoloženja (3,9,10).

Postoje neke dobro istražene kombinacije lijekova (11,22,23). Ova su ispitivanja, međutim, pratila pacijente tijekom ograničenog razdoblja (šest do osam tjedana). Dugoročna učinkovitost i sigurnost ovih kombinacija lijekova ostaju nepoznati. S obzirom na to da nema podataka kliničkih ispitivanja ni opservacijskih studija koji bi razjasnili učinkovitost, sigurnost i podnošljivost dugotrajnog liječenja kombinacijama psihofarmaka u pedijatrijskoj populaciji, dugotrajna kombinirana terapija održavanja otvara daleko značajnija pitanja u usporedbi s kratkotrajnim kombiniranim liječenjem (3,9,10,20,24).

Ozbiljno zabrinjava da farmakokinetske i farmakodinamske interakcije mogu dovesti do brojnih nuspojava u djece koja istodobno uzimaju više psihotropnih lijekova (10,20). Primjena atipičnih antipsihotika ili antipsihotika druge generacije (ADG) uz antidepresive može rezultirati razvojem dijabetesa melitusa - tipa 2 (25). Štoviše, zabilježene su niske stope metaboličkog praćenja u populaciji mladih koji su primali psihotropnu polifarmaciju (9). Pokazalo se da kombinacija selektivnog inhibitora ponovne pohrane serotonina (SIPPS) i ADG u dugotrajnoj istodobnoj primjeni uzrokuje blokadu enzima P-450 uzrokovanu kompetitivnom inhibicijom enzima (26) i može dovesti do serotoninskog sindroma ili do toksičnih razina antipsihotika. Nuspojave PP mogu se teško razlikovati od novih ponašajnih simptoma i voditi prema novim lijekovima (9). Drugi razlog za zabrinutost je nepoznati utjecaj dugoročnih učinaka PP na strukturu i funkciju mozga u razvoju (27).

binations of psychotropic drugs from different therapeutic classes. The most commonly used combinations are stimulants with antipsychotics, antidepressants or alpha agonists, followed by antipsychotics combined with antidepressants or mood stabilizers (3,9,10).

There are some well-researched uses of medication combinations (11,22,23). These trials, however, followed patients for a limited period of time (six to eight weeks). The long-term efficacy and safety of these drug combinations remain unknown. Considering that there are no data from either clinical trials or observational studies to clarify the efficacy, safety, and tolerability of long-term treatment with psychotropic combinations in the pediatric population, long-term maintenance combination treatment raises far more significant questions compared with short-term combination treatment (3,9,10,20,24).

Of serious concern is that pharmacokinetic and pharmacodynamic interactions can lead to a number of side effects in children taking multiple psychotropic drugs simultaneously (10, 20). The use of atypical antipsychotics in addition to antidepressants may result in the development of type 2 diabetes mellitus (25). Moreover, low rates of metabolic screening in youth population receiving psychotropic polypharmacy have been reported (9). The combination of a selective serotonin reuptake inhibitor (SSRI) and a second generation antipsychotic (SGA) in long-term concomitant regimens has been shown to produce blockade of P-450 enzymes caused by competitive inhibition of enzymes (26) and could lead to a serotonin syndrome or to toxic levels of an antipsychotic. Adverse events from PP may be difficult to distinguish from new behavioral symptoms and lead to more medications (9). Another concern is the unknown impact of long-term effects of PP on the brain structure and function in development (27).

Many children receiving combination psychopharmacotherapy do not receive psychosocial

Mnoga djeca koja primaju kombiniranu psihofarmakoterapiju ne primaju psihosocijalne intervencije za koje postoje dokazi o učinkovitosti i koje su vrlo često uključene u smjernice za liječenje različitih psihičkih poremećaja u djetinjstvu i adolescenciji kao prva linija liječenja (13,28).

Unatoč sve većoj upotrebi PP u djece i adolescenata postoji vrlo malo dokaza iz kontroliranih kliničkih ispitivanja koji bi pružali smjernice za kliničare (9,10,20,24). Stoga se PP u liječenju psihijatrijskih poremećaja u djece i adolescenata uglavnom temelji više na iskustvu nego na dokazima (10). PP može biti optimalna terapijska intervencija kod neke djece, uključujući situacije pacijenata s rezidualnim simptomima koji su na monoterapiji, s prisutnim komorbidnim stanjima, potencijalne sinergističke učinke za određene skupine simptoma ili mehanizama djelovanja, profilaksu ili rješavanje nuspojava (9,20).

Ovaj rad prikazuje trenutna saznanja o PP u pedijatrijskoj populaciji od 18 godina. Žurna potreba za osiguranjem podataka o učinkovitosti i sigurnosti kronične izloženosti istovremenoj primjeni dvaju ili više psihotropnih lijekova temelji se na zabrinutosti zbog rastuće prevalencije u kontekstu ograničenih informacija o učinkovitosti i sigurnosti, pa čak i za monoterapiju u djece.

Psihotropna polifarmacija u liječenju poremećaja deficita pažnje i hiperaktivnosti (ADHD) ili hiperkinetskog poremećaja u djece i adolescenata

Poremećaj deficita pažnje i hiperaktivnosti (ADHD) ili hiperkinetski poremećaj čest je neurorazvojni poremećaj u djece i adolescenata koji utječe na više aspekata života pojedinca te obiteljsko, socijalno i školsko funkcioniranje (29). ADHD se može liječiti farmakološkim i nefarmakološkim terapijama uključujući sa-

interventions for which there is evidence of efficacy and which are included in the guidelines for the treatment of various mental disorders in childhood and adolescence very often as first-line therapy (13,28).

Despite the increasing use of PP in children and adolescents, there is very little evidence from controlled clinical trials to provide guidance for clinicians (9,10,20,24). Thus, PP in treating psychiatric disorders in children and adolescents is mostly based on experience rather than evidence (10). PP can be the optimal therapeutic intervention in some children, including situations with residual symptoms on monotherapy, presence of comorbid conditions, potential synergistic effects from targeting different symptom clusters or mechanisms of action, or prophylaxis for or management of adverse effects (9,20).

This paper provides the current state of knowledge regarding PP in pediatric population under the age of 18 years. The urgent need to provide data regarding the effectiveness and safety of chronic exposure to concurrent psychotropics is based upon the concern about the rising prevalence in the context of limited efficacy and safety information even for monotherapy of psychotropics in children.

Psychotropic polypharmacy in the treatment of attention-deficit/hyperactivity disorder (ADHD) or hyperkinetic disorder in children and adolescents

Attention-deficit/hyperactivity disorder (ADHD) or hyperkinetic disorder is a common neurodevelopmental disorder in children and adolescents which affects multiple aspects of an individual's life and family as well as social and academic functioning (29). ADHD can be treated using pharmacologic and non-pharmacologic therapies, including counseling and behavioral and environmental modification strategies. Every

vjetovanje, bihevioralnu terapiju, strategije modifikacije okoline. Svaki od ovih tretmana se pokazao učinkovitim; međutim, kombinacija različitih metoda liječenja pokazala se najučinkovitijom (29,30).

Farmakološka terapija ADHD-a može uključivati upotrebu stimulansa i ne-stimulansa ili kombinaciju različitih modaliteta liječenja (29-31). Liječnici bi trebali slijediti postupni pristup u odabiru i prilagodbi lijekova za liječenje ADHD-a, usko surađujući s obiteljima, skrbnicima te drugim medicinskim i obrazovnim stručnjacima kako bi zajedno izradili prikladne planove liječenja.

Stimulansi s produljenim oslobađanjem (engl. *extended release* - ER) prva su linija farmakološkog liječenja ADHD-a (29-31). Ako jedan stimulans (bilo metilfenidat ili amfetamin) ne djeluje u najvišoj prikladnoj dozi, liječnik bi trebao razmisliti o isprobavanju drugog stimulansa (29-31).

Za djecu koja ne podnose stimulanse ili koja ne postižu zadovoljavajuće smanjenje simptoma, središnji alfa agonisti i atomoksetin su učinkoviti i relativno dobro podnošljivi kao alternativa ili kao lijekovi za pojačanje učinka (29-31). Alfa agonist ili atomoksetin može se propisati kao monoterapija ili u slučajevima djelomičnog odgovora na stimulans, ER klonidin i gvanfacin odobreni su od Američke agencije za hranu i lijekove (*Food and Drug Administration* - FDA) kao dodatak stimulansima. Međutim, liječenje kombinacijom stimulansa i alfa agonista bez ranijeg nepotpunog odgovora na stimulans nije rezultiralo boljim liječenjem simptoma ADHD-a u usporedbi sa samim stimulansom. Trenutni podatci podupiru kombinirano liječenje rezidualnih simptoma ili pacijenata s djelomičnim odgovorom na stimulanse, ali ne na početku liječenja zbog očekivanih sinergističkih učinaka različitih mehanizama djelovanja (11).

Sustavni pregled kombinacije psihostimulansa i atomoksetina u djece s ADHD-om pokazuje

type of treatment has been shown to be effective; however, a combination of treatment methods has been shown to be most effective (29,30).

The pharmacologic therapy of ADHD may include the use of stimulant and non-stimulant medications, or a combination of different treatment modalities (29-31). Medical practitioners should follow a stepwise approach in the selection and adjustment of medications to treat ADHD, while working closely with families, caregivers, and other medical and educational professionals to form appropriate treatment plans.

Extended release (ER) stimulant medications are first line in pharmacologic management of ADHD (29-31). If one stimulant medication (either methylphenidate or amphetamine) does not work at the highest appropriate dose, a medical practitioner should then consider trying the other stimulant medication (29-31).

For children who are unable to tolerate stimulants or who do not achieve satisfactory symptom management, central alpha agonists and atomoxetine are effective and generally well-tolerated alternative or augmentative agents (29-31). An alpha agonist or atomoxetine may be prescribed as monotherapy or, in cases of partial stimulant response, ER clonidine and guanfacine are also approved by the US Food and Drug Administration (FDA) as augmentative to stimulant medication. However, treatment with a combination of a stimulant and an alpha-agonist without previous incomplete response to a stimulant did not result in the superior management of ADHD symptoms compared with the stimulant alone. Current data support combination treatment for residual symptoms or only partial response to stimulants, but not at treatment outset for anticipated synergistic effects from different mechanisms of action (11).

A systematic review of the combination of psychostimulants and atomoxetine in children with ADHD shows that evidence for efficacy

da su dokazi o učinkovitosti ograničeni zbog malog broja studija i ispitanika, heterogenosti dizajna studija i nekih prednosti za pojedinačne pacijente kod kojih monoterapija nije bila uspješna, iako bez jakih dokaza (32).

Podatci randomiziranih kontroliranih studija (RKS) otkrivaju da kombinacija stimulansa i valproata ili risperidona dovodi do veće koristi u odnosu na monoterapiju stimulansima za komorbidnu agresiju i ometajuće ponašanje, s najvećim empirijskim dokazima za risperidon (22,33,34). Sve su studije koristile niske doze risperidona (srednja doza <2 mg/dan za sve studije) koja je u istraživanjima shizofrenije nazvana „ultra-niska doza" (35). Unatoč niskim dozama i često kratkom trajanju ispitivanja, u ispitivanjima risperidona uočeno je značajno povećanje prolaktina i povećanje tjelesne težine (36). Štoviše, u sustavnom pregledu primjene psihostimulansa i antipsihotika u djece s ADHD-om i poremećajima ponašanja nisu pronađeni dokazi za veću učinkovitost kombinirane psihofarmakoterapije u usporedbi s monoterapijom psihostimulansima (36). Kombinirana terapija antipsihoticima i stimulansima preporučuje se prema nekim smjernicama, ali samo kao treća linija liječenja, nakon monoterapije stimulansima i stimulansa u kombinaciji s bihevioralnim intervencijama za liječenje agresije u bolesnika s ADHD-om (29,30).

Otvorene studije i podatci RKS koji kombiniraju SIPPS s lijekovima za ADHD za liječenje komorbidne anksioznosti i depresije podržavaju sigurnost, ali ne i učinkovitost ovih kombinacija (37,38). Ograničene studije o ovoj kombinaciji veliki su jaz između baze dokaza i kliničke prakse, budući da se ovi lijekovi obično propisuju zajedno u kliničkoj praksi (39).

ADHD se također može pojaviti zajedno s poremećajima iz autističnog spektra i drugim neurorazvojnim poremećajima kao što su fetalni alkoholni sindrom, Touretteov sindrom, trisomija 21 ili drugi genetski sindromi (29). Općenito, načelo u liječenju djeteta ili adolescenta s

is limited due to the small number of studies and subjects, heterogeneity of study design, and some benefits for individual patients in whom monotherapy has not been successful, although without strong evidence (32).

Randomized-controlled trials (RCT) data find that combination stimulant and divalproex or risperidone leads to incremental benefit beyond stimulant monotherapy for comorbid aggression and disruptive behavior, with the greatest empirical support for risperidone (22,33,34). All studies used low-dose risperidone (mean dose <2 mg/day for all studies), which has been termed „ultra-low dose" in schizophrenia research (35). Despite low doses and often short study duration, significant prolactin elevation and weight gain were observed in risperidone trials (36). Moreover, in a systematic review of the use of psychostimulants and antipsychotics in children with ADHD and behavioral disorders no evidence was found for greater efficacy of combined psychopharmacotherapy compared to psychostimulant monotherapy (36). Antipsychotic and stimulant combination therapy is recommended by some guidelines, but only as a third-line treatment following stimulant monotherapy and stimulants combined with behavioral interventions to treat aggression in patients with ADHD (29,30).

Open-label studies and RCT data combining SSRIs with ADHD medication for management of comorbid anxiety and depression supports safety but not efficacy of these combinations (37, 38). The limited studies on this combination constitute a large gap between evidence base and clinical practice, as these medications are commonly co-prescribed in clinical practice (39).

ADHD can also co-occur with autism spectrum disorders and other neurodevelopmental disorders such as fetal alcohol syndrome, Tourette syndrome, trisomy 21, or other genetic syndromes (29). A general principle in treating a child or adolescent with ADHD and comorbid mental health or medical disorders is to treat the

ADHD-om i komorbidnim poremećajem mentalnog zdravlja ili drugim medicinskim poremećajima je prvo liječenje primarne dijagnoze ili najhitnijeg, onesposobljavajućeg problema s odobrenim lijekovima (29-31).

U Hrvatskoj psihostimulansi nisu financirani od osnovnog zdravstvenog osiguranja za pacijente u javnim zdravstvenim ustanovama (40). Pacijenti koji si mogu omogućiti privatno plaćanje imaju pristup psihostimulansima. U teškim slučajevima ADHD-a s komorbidnom agresijom, ako je indicirana farmakoterapija, liječnici moraju primijeniti antipsihotike „*off-label*".

Psihotropna polifarmacija u liječenju poremećaja iz spektra autizma u djece i adolescenata

Poremećaj iz spektra autizma (PAS) je složen neurorazvojni poremećaj karakteriziran trajnim oštećenjima u recipročnoj socijalnoj komunikaciji i socijalnim interakcijama uz prisutnost ograničenih, ponavljajućih obrazaca ponašanja, interesa ili aktivnosti (41). Bihevioralne intervencije, kao što je Primijenjena analiza ponašanja (*Applied Behavior Analysis* - ABA), terapija je temeljena na dokazima za djecu s PAS-om i trebala bi biti prva linija liječenja (42). Iako su tehnike ABA glavni oslonac u liječenju, one su skupe i dugotrajne, zahtijevaju educirane terapeute za njihovo provođenje i nisu uvijek dostupne ili odobrene od zdravstvenog osiguranja. Farmakoterapija se široko koristi, ali samo su dva lijeka iz skupine ADG odobrena od strane FDA za liječenje razdražljivosti kod PAS-a - risperidon i aripiprazol (43).

Istraživanja pokazuju rastuću stopu upotrebe psihotropnih lijekova među djecom i mladima s PAS-om (44,45). Prijavljene stope psihofarmakoterapije kreću se od 27 % do 83 %, s PP-om u rasponu od 10 % do više od 50 % (46). U 15 % djece s PAS-om PP je uključivala više od 3 skupine lijekova.

primary diagnosis or most urgent or impairing problem with approved medication first (29-31).

In Croatia, psychostimulants are not reimbursed by public health insurance in public health services for treatment of ADHD (40). Those who can afford to pay privately can access psychostimulants. Clinicians must resort to the use of anti-psychotics off-label in severe cases of ADHD with comorbid aggression if pharmacotherapy is indicated.

Psychotropic polypharmacy in the treatment of autism spectrum disorders in children and adolescents

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder characterized by persistent impairments in reciprocal social communication and social interactions along with the presence of restricted, repetitive patterns of behaviors, interests, or activities (41). Behavioral intervention, such as Applied Behavior Analysis (ABA), is evidence-based practice for children with ASD and should be the first-line treatment (42). Although ABA techniques are the mainstay of treatment, they are expensive and time consuming, require trained therapists for their provision, and are not always available or reimbursable by health insurers. Pharmacotherapy is widely used, however, only two drugs from the class of SGA have been approved by the FDA for the treatment of irritability of ASD, risperidone and aripiprazole (43).

Research shows increasing rates of psychotropic use among children and youths with ASD (44,45). Reported rates of psychopharmacotherapy range from 27% to 83%, with PP ranging from 10% to more than 50% (46). In 15% of children with ASD, PP included more than 3 classes of medications.

Both older age and psychiatric comorbidity are associated with higher prevalences of psycho-

Starija dob i psihijatrijski komorbiditet povezani su s većom prevalencijom psihofarmakoterapije i PP (46,47). Međutim, PP je također značajna među mlađim dobnim skupinama (33 % djece u dobi od 2 do 10 godina i 10 % djece od 0 do 1 godine) za koje je zabrinutost oko sigurnosti njihove primjene veća, jer su dokazi o koristi još oskudniji (46).

Uobičajene kombinacije skupina psihotropnih lijekova u bolesnika s PAS-om uključuju antipsihotike i lijekove za ADHD, antipsihotike i antidepresive, antidepresive i lijekove za ADHD, te sve tri skupine (antipsihotici, antidepresivi i lijekovi za ADHD) (46). Kombinirano farmakološko liječenje usmjereno je na liječenje pridruženih simptoma (kao što je iritabilnost) ili komorbidnih psihijatrijskih stanja (npr. ADHD, poremećaj s prkošenjem i suprotstavljanjem, psihotični poremećaji, anksioznost i poremećaji raspoloženja), koji su česti u bolesnika s PAS-om (44,46). Međutim, dokazi istraživanja koji podupiru PP u djece s PAS-om su malobrojni. Porast propisivanja stimulansa tijekom vremena može odražavati sve veće prepoznavanje komorbidnog ADHD-a (i njegove perzistencije) kod mladih ljudi s PAS-om (43). Osim toga, kliničari su spremniji propisati metilfenidat nakon dokaza iz naturalističke studije da je dugoročno učinkovit kod mladih ljudi s PAS-om i komorbidnim ADHD-om, čak i u kombinaciji s drugim psihotropnim lijekovima (48). Iako postoje neki dokazi za primjenu antipsihotika i lijekova za ADHD u mladih bolesnika s PAS-om, korištenje antidepresiva treba biti ograničeno na pojedine slučajeve (44).

Djeca PAS-om osjetljivija su na nuspojave psihotropnih lijekova (49). Mnoga djeca s PAS-om ne mogu adekvatno verbalno izraziti svoje nuspojave. Umjesto toga, oni svoju nelagodu izražavaju na druge načine, često svojim ponašanjem i/ili pogoršanjem ionako zahtjevnog ponašanja što može rezultirati višestrukim propisivanjem lijekova (49).

pharmacotherapy and PP (46,47). However, PP is also significant among the younger age groups (33% of children aged 2–10 years and 10% of 0- to 1-year-olds) for whom safety concerns are increased as evidence of benefit is even more sparse (46).

Common combinations of psychotropic drug classes in patients with ASD include antipsychotics and ADHD medications, antipsychotics and antidepressants, antidepressants and ADHD medications, and all 3 classes (antipsychotics, antidepressants, and ADHD medications) (46). Combined pharmacological treatments are directed at the treatment of associated symptoms (such as irritability) or coexisting psychiatric conditions (e.g. ADHD, oppositional disorder, psychotic disorders, anxiety and mood disorders), which are frequent in patients with ASD (44,46).

However, research evidence to support PP in children with ASD is scarce. The increase in prescribing of stimulants over time may reflect the increasing recognition of co-morbid ADHD (and its persistence) in young people with ASDs (43). In addition, clinicians are more willing to prescribe methylphenidate following evidence from a naturalistic study that it is effective long-term in young people with ASD and co-morbid ADHD even in association with other psychotropic drugs (48). While there is some evidence for the use of antipsychotics and ADHD medication in young patients with ASD, the use of antidepressants should be limited to selected cases (44).

Children with ASD are more sensitive to the side effects of psychotropic medications (49). Many children with ASD are unable to effectively communicate their side effect symptoms verbally. Instead, they express their discomfort in other ways, often through their behaviour and/or a worsening of challenging behaviours which may result in multiple medication prescriptions (49).

Dječji i adolescentni psihijatri u Hrvatskoj propisuju antipsihotike kod djece i adolescenata s PAS-om onda kada je prisutna značajna iritabilnost i/ili agresivnost koja ne reagira na druge mogućnosti liječenja (50).

Psihotropna polifarmacija u liječenju anksioznih poremećaja u djece i adolescenata

Anksiozni poremećaji u djece i adolescenata učinkovito se liječe psihoterapijom, a antidepresivi su indicirani za umjerene i teške anksiozne poremećaje (51). Tri lijeka iz skupine selektivnih inhibitora ponovne pohrane serotonina (SIPPS) odobrena su od FDA za liječenje opsesivno-kompulzivnog poremećaja (OKP) kod djece: sertalin (od 6 godina), fluoksetin (od 7 godina) i fluvoksamin (od 8 godina) (51). Duloksetin, selektivni inhibitor serotonina i noradrenalina (SIPPSN), jedini je antidepresiv koji je dobio odobrenje FDA za liječenje generaliziranog anksioznog poremećaja u djece i adolescenata (52). Istraživanja ne podržavaju upotrebu SIPPS u liječenju simptoma posttraumatskog stresnog poremećaja u djece i adolescenata (53).

Studije trendova propisivanja upućuju na povećanje upotrebe PP-a koja uključuje antidepresive u posljednjih nekoliko godina (40,54,55). U nedavnoj nacionalnoj studiji u Koreji većina primjene za antidepresive kod djece i adolescenata uključivala je istodobnu primjenu drugih psihotropnih lijekova (60,5 %) poput antipsihotika, lijekova za ADHD i benzodiazepina/zolpidema koji su korišteni u 26,7 %, 24,4 % odnosno 26,3 % pacijenata (54). Dva ili više antidepresiva kombinirana su u 8,4 % slučajeva. Populacijska studija o distribuciji antidepresiva među mladim osobama u Švedskoj pokazala je da je kod djece i adolescenata bio najveći porast polifarmacije od tri ili više skupina psihotropnih lijekova između 2006. i 2013. godine (55). Anksiolitici, hipnotici i sedativi činili su

Child and adolescent psychiatrists in Croatia prescribe antipsychotics in children and adolescents with ASD when significant irritability and /or aggression is present nonresponsive to other treatment options (50).

Psychotropic polypharmacy in the treatment of anxiety disorders in children and adolescents

The anxiety disorders in children and adolescents are effectively treated and psychotherapy and antidepressants are indicated for moderate and severe anxiety disorders (51). Three drugs from the selective serotonin reuptake inhibitors (SSRI) class are FDA-approved for the treatment of obsessive-compulsive disorder (OCD) in children: sertaline (from 6 years), fluoxetine (from 7 years) and fluvoxamine (from 8 years) (51). *Duloxetine,* selective serotonin norepinephrine inhibitor (SNRI), is the only antidepressant that has received FDA approval for the treatment of GAD in children and adolescents (52). Research does not support the use of SSRIs in the treatment of symptoms of posttraumatic stress disorder in children and adolescents (53).

Prescribing trend studies suggest an increase in the use of PP involving antidepressants in recent years (40, 54, 55). In a recent nationwide study in Korea, a majority of antidepressant use in children and adolescents included concomitant psychotropic medication (60.5%) with antipsychotics, ADHD medications, and benzodiazepines/zolpidem used in 26.7%, 24.4%, and 26.3% of patients, respectively (54). Two or more antidepressants were combined in 8.4% of cases. Population-based study of antidepressant dispensations among young individuals in Sweden found that children and adolescents experienced the largest increase in polypharmacy of three or more psychotropic drug classes between 2006 and 2013 (55). Anxiolytics, hypnotics, and sedatives comprised the most com-

najčešću dodatnu skupinu psihotropnih lijekova među mladim osobama kojima su propisani antidepresivi.

Primjena PP s antidepresivima u liječenju pedijatrijskih anksioznih poremećaja potaknuta je kliničkim čimbenicima kao što su težina poremećaja i česti komorbiditeti s drugim psihijatrijskim i medicinskim stanjima (40,51). Neki lijekovi kao što su buspiron, benzodiazepini, psihostimulansi, drugi SIPPS, ADG i triciklički antidepresivi predloženi su kao pojačanje SIPPS ili SIPPSN za liječenje dječjih anksioznih poremećaja; međutim, postoji vrlo malo ili nimalo dokaza koji podržavaju ove strategije (51).

Budući da mnogi pedijatrijski bolesnici s OKP-om ne uspijevaju postići remisiju i imaju rezidualne simptome nakon liječenja antidepresivima u obliku monoterapije, kliničari često koriste strategije PP-a (40). Ograničeni trenutni dokazi podupiru pojačavanje učinka SIPPS s ADG u pedijatrijskom OKP-u rezistentnom na liječenje (58). U pedijatrijskih su bolesnika SIPPS i ADG povezani s dugotrajnim povećanjem tjelesne težine i/ili povećanim metaboličkim rizikom (10,20,25), što zahtijeva odgovarajuće praćenje tjelesne težine i metaboličkih poremećaja u bolesnika na polifarmaciji s ove dvije skupine lijekova. Također, postoje neki dokazi za korištenje klomipramina kao strategije pojačavanja učinka SIPPS u ovoj populaciji, iako potencijalni rizik od kardiovaskularnih nuspojava zahtijeva pomno praćenje bolesnika na ovoj kombinaciji (58). Značajan stupanj PP u mladih pacijenata koji primaju antidepresive zahtijeva pažljivo praćenje i daljnja istraživanja potencijalnih koristi i šteta (40,55).

U Hrvatskoj je utvrđena veća stopa „*off-label*" propisivanja antidepresiva mladima nego u drugim razvijenim zemljama (59). Fluvoksamin je bio najpropisivaniji antidepresiv za liječenje anksioznih poremećaja u djece i adolescenata, kako za OKP, tako i za anksiozne poremećaje koji ne uključuju OKP.

mon additional CNS drug class among young persons who were prescribed antidepressants.

The use of PP with antidepressants in treatment of paediatric anxiety disorders is prompted by clinical factors such as the severity of the disorder and frequent co-morbidity with other psychiatric and medical conditions (40,51). Some drugs such as buspirone, benzodiazepines, psychostimulants, other SSRIs, SGA and tricyclic antidepressants have been proposed as augmentation of SSRIs or SNRIs for the treatment of pediatric anxiety disorders. However, there is very little or no evidence to support these strategies (51).

Because many paediatric patients with OCD fail to achieve remission and present with residual symptoms after treatment with antidepressants as monotherapy, clinicians often use PP strategies (40). The limited current evidence supports augmentation of SSRIs with second generation antipsychotics (SGA) in treatment-resistant paediatric OCD (58). In paediatric patients, SSRIs and SGAs have been associated with long-term weight gain and/or increased metabolic risk (10,20,25), which calls for appropriate monitoring of weight and metabolic disturbances in patients on polypharmacy with both drug classes. There is also some evidence for the use of clomipramine as augmentation strategy for SSRIs in this population although the potential risk of cardiovascular AEs calls for close monitoring of patients on the combination (58). The substantial degree of PP in young patients receiving antidepressants requires careful monitoring and further research into potential benefits and harms (40, 55).

A higher off-label rate of antidepressant prescriptions to young people has been found in Croatia that in other developed countries (59). Fluvoxamine was the most prescribed antidepressant for the treatment of anxiety disorders in children and adolescents, both for OCD and non-OCD anxiety disorders.

Psihotropna polifarmacija u liječenju depresije u djece i adolescenata

Mogućnosti liječenja depresije u djece i adolescenata razlikuju se ovisno o težini poremećaja. Blaga do umjerena depresija može se liječiti psihoedukacijom i psihoterapijom, a teže depresivne epizode zahtijevaju primjenu farmakoterapije (60). Antidepresivi se smatraju prvom linijom liječenja za umjerenu do tešku depresiju kod koje nije došlo do odgovora na adekvatno liječenje psihoterapijom (60,61). Lijekovi ne bi trebali biti jedini oblik liječenja depresivnih pedijatrijskih bolesnika, već ih treba koristiti u kombinaciji s psihoterapijom.

SIPPS su antidepresivi prve linije za djecu i adolescente s dijagnozom depresije (60,61). Fluoksetin je odobren od FDA za djecu od 8 godina i stariju, a escitalopram za dob od 12 godina i više. Dvije nedavne meta-analize zabilježile su mali terapijski učinak za sve antidepresive, dok se fluoksetin pokazao jedinim antidepresivom koji ima statistički značajan učinak u odnosu na placebo za učinkovitost liječenja depresije (62,63). Triciklički antidepresivi (TA) i venlafaksin nisu se pokazali učinkovitima (61).

Studija *Treatment of Adolescent Depression Study* (TADS) je utvrdila da je kombinirano liječenje (fluoksetin i kognitivno-bihevioralna terapija - KBT) superiornije u odnosu na monoterapiju fluoksetinom i KBT-om na kraju 12-tjedne akutne faze (64) s koristima liječenja koje su nastavljene za depresiju i suicidalnost tijekom jednogodišnjeg praćenja (65).

Studija *Treatment of Resistant Depression in Adolescents* (TORDIA) ispitivala je upotrebu drugog SIPPS ili venlafaksina s KBT-om ili bez KBT-a u adolescenata koji nisu imali odgovor na prvi SIPPS (66). Slično ispitivanju TADS, stope odgovora pokazale su da je kombinirano liječenje bolje od monoterapije lijekovima (54,8 % naspram 40,5 %). Nije uočena razlika u stopama odgovora na liječenje drugim SSRI-

Psychotropic polypharmacy in the treatment of depression in children and adolescents

Treatment options for depression in children and adolescents vary by the severity of the disorder. Mild-to-moderate depression may be managed with psychoeducation and psychotherapy, and more severe depressive episodes require pharmacotherapy (60). Antidepressant medications are considered first-line treatment for moderate-to-severe depression or depression that has not responded to an adequate trial of psychotherapy (60,61). Medications should not be the only form of treatment for depressed pediatric patients, but used in combination with psychotherapy.

SSRIs are the first-line antidepressant agents for children and adolescents diagnosed with depression (60,61). Fluoxetine is approved by the FDA for children 8 years of age and older, and escitalopram is approved for ages 12 years and older. Two recent meta-analyses have noted a small therapeutic effect for all antidepressants with fluoxetine being the only antidepressant to have a statistically significant effect over placebo on efficacy for the treatment of depression (62,63). Tricyclic antidepressants (TCAs) and venlafaxine have not proved to be efficacious for paediatric depression (61).

The Treatment of Adolescent Depression Study (TADS) has found that combination treatment (fluoxetine and cognitive-behavioral therapy - CBT) has been superior to fluoxetine monotherapy and CBT at the end of the 12-week acute phase (64) with benefits of treatment continued for depression and suicide measures at 1-year follow-up (65).

The Treatment of Resistant Depression in Adolescents (TORDIA) study examined the use of a second SSRI or venlafaxine with or without CBT in adolescents who failed to respond to an initial SSRI (66). Similar to the TADS trial, response rates demonstrated that combination treatment was superior to medication mono-

om u odnosu na venlafaksin. Osim toga, nije uočena značajna razlika u nuspojavama između skupina.

Iako se općenito dobro podnose, SIPPS se povezuju s povećanim rizikom od bihevioralne aktivacije i pogoršanje suicidalnih ideacija kod pedijatrijskih bolesnika s depresijom (67). Godine 2004. FDA je izdala upozorenje "crna kutija" (engl. *black box warning*) kako bi istaknula potencijalne rizike antidepresiva kod pojedinaca u dobi do 18 godina (61). Slična upozorenja u Europi izdala je Europska agencija za lijekove 2005. (68).

Ostale SIPPS, SIPPSN i druge antidepresive, poput mirtazapina i bupropiona treba propisivati, ali s oprezom zbog nedostatka dostupnih čvrstih i visokokvalitetnih dokaza (61).

PP je u pedijatrijskih bolesnika s velikim depresivnim poremećajem doživjela značajan porast (69) te je uporaba antidepresiva u kombinaciji s drugim psihofarmakološkim lijekovima također značajno porasla posljednjih godina postajući uobičajena praksa (9,40). Polifarmacija s antidepresivima koristi se za liječenje depresije s psihotičnim simptomima, terapijski rezistentne depresije ili komorbidnih poremećaja kao što su OKP i ADHD, iako većina kliničkih smjernica eksplicitno priznaje nedostatak empirijske podloge za takve preporuke i potrebu za daljnjim istraživanjima (30,36,39,60,70).

Iako je moguća alternativa za terapijski rezistentne slučajeve, nisu prijavljene studije koje bi procjenjivale kombiniranu upotrebu dvaju skupina antidepresiva za liječenje pedijatrijske depresije (70). Samo su dvije manje serije slučajeva izvijestile o istodobnoj primjenu SIPPS i ADG za liječenje rezidualnih simptoma ili terapijski rezistentne depresije (71,72). Do danas većina kliničkih smjernica ne preporučuje pojačavanje učinka SIPPS s ADG za pedijatrijske bolesnike s terapijski rezistentnom depresijom uglavnom uzimajući u obzir potencijalne sigur-

therapy (54.8% vs 40.5%). No difference in response rates was observed between a second SSRI versus venlafaxine. In addition, no significant difference in adverse effects between any treatment group was observed.

Although generally well tolerated, SSRIs have been associated with an increased risk of behavioural activation and worsening of suicidal ideation in paediatric depression patients (67). In 2004, the US Food and Drug Administration (FDA) issued a "black box" warning to highlight potential risks of antidepressants in individuals aged up to 18 years (61). Similar warnings were issued in Europe by the European Medicines Agency in 2005 (68).

Other SSRIs, serotonin norepinephrine reuptake inhibitors (SNRIs) and other antidepressants, such as mirtazapine and bupropion, should be prescribed but with caution because of the paucity of robust and high-quality evidence that is available (61).

PP in paediatric patients with major depressive disorder has also experienced a substantial increase (69) and the use of antidepressants in combination with other psychopharmacological treatments has also markedly grown in recent years, becoming a common practice (9,40). Polypharmacy with antidepressants is used for the treatment of depression with psychotic features, treatment resistant depression or comorbid disorders such as OCD and ADHD, although most clinical guidelines explicitly acknowledge the lack of empirical support for such recommendations and the need for further research on polypharmacy (30,36,39,60,70).

Although a possible alternative for treatment-resistant cases, no studies assessing the combined use of two antidepressant classes for the treatment of paediatric depression have been reported (70). Only two small case series have reported the concomitant use of SGAs and SSRIs for the management of residual symptoms or treatment-resistant depression (71,72). To date, most clinical guidelines do not recommend augmentation of

nosne probleme povezane s dugotrajnim liječenjem ADG (10,20,25).

Pojačavanje učinka antidepresiva (SIPPS ili venlafaksina) sa stabilizatorom raspoloženja (valproat, topiramat, litij, ADG) u adolescentnoj depresiji rezistentnoj na liječenje tijekom 12 tjedana povezano je s većom vjerojatnošću odgovora na liječenje i remisije (73). Međutim, ne postoje randomizirana kontrolirana klinička ispitivanja strategija pojačavanja u terapijski rezistentnoj depresiji kod adolescenata, ali moguće je slijediti podatke za odrasle koji pokazuju učinkovitost pojačavanja učinaka antidepresiva mirtazapinom, bupropionom, ADG, litijem ili tiroksinom (74).

Tri studije su otkrile povoljan učinak dodavanja litija tricikličkim antidepresivima (75,76) ili venlafaksinu (77). Međutim, te su studije procijenile dodavanje litija skupinama antidepresiva koje se same po sebi nisu pokazale učinkovitima za liječenje depresije u djece, kao što su triciklički antidepresivi (61), dok potencijalni neželjeni učinci litija u tim populacijama mogu ograničiti njegovu primjenu (78).

Podatci za liječenje depresije u mladih antidepresivima u Hrvatskoj pokazuju da dječji i adolescentni psihijatri nisu pomno pratili dostupne dokaze o učinkovitosti i sigurnosti (59). Sertralin je bio najpropisivaniji antidepresiv za liječenje velikog depresivnog poremećaja u retrospektivnoj studiji, a slijede ga fluvoksamin i tianeptin. Za trenutne trendove u propisivanju antidepresiva za djecu i adolescente u Hrvatskoj mogu biti odgovorni čimbenici koji se odnose na nacionalni sustav zaštite mentalnog zdravlja.

Psihotropna polifarmacija u liječenju bipolarnog poremećaja u djece i adolescenata

Liječenje bipolarnog poremećaja (BP) u djece i adolescenata treba uključivati psihofarmakoterapiju u kombinaciji s psihosocijalnim inter-

SSRIs with SGAs for paediatric patients with treatment resistant depression mainly considering potential safety concerns associated with long-term treatment with SGAs (10,20,25).

Augmentation of antidepressants (SSRI or venlafaxine) with a mood stabilizer (divalproate, topiramate, lithium, atypical antipsychotic) in adolescent TRD over 12 weeks was associated with a higher likelihood of response and remission (73). However, there are no randomized controlled clinical trials of augmentation strategies in TRD in adolescents, and it is possible to follow adult data showing the efficacy of antidepressant augmentation with mirtazepine, bupropion, atypical antipsychotics, lithium, or thyroxine (74).

Three studies have detected a beneficial effect of the addition of lithium to TCAs (75,76) or venlafaxine (77). However, those studies assessed the addition of lithium to antidepressant classes that have not proved to be efficacious per se for the treatment of paediatric depression such as tricyclic antidepressants (61) and potential AEs of lithium in these populations may limit its application (78).

Data for antidepressant treatment of depression in youth in Croatia indicate that child and adolescent psychiatrists did not follow available effectiveness and safety evidence closely (59). Sertraline was the most prescribed antidepressant for the treatment of major depressive disorder in a retrospective study, followed by fluvoxamine and tianeptine. Factors relating to national mental health care system may account for the current trends in the prescription of antidepressant drugs for children and adolescents in Croatia.

Psychotropic polypharmacy in the treatment of bipolar disorder in children and adolescents

Treatment of bipolar disorder (BD) in children and adolescents should include psychopharmacotherapy in combination with psychosocial interventions (79).

vencijama (79). Lijekovi koje je odobrila FDA za akutnu maničnu epizodu u pedijatrijskom BP-u uključuju aripiprazol, asenapin, risperidon ili kvetiapin za bolesnike u dobi od ≥10 godina i litij ili olanzapin za adolescente u dobi od 12 ili 13 do 18 godina (80). Nijedan stabilizator raspoloženja (karbamazepin, lamotrigin ili valproat) trenutno nije odobren od FDA za bilo koju fazu juvenilnog BP-a (79). Unatoč niskim stopama odgovora u dvije RKS, duga povijest uporabe među odraslim osobama s BP-om, u kombinaciji s pozitivnim nalazima u otvorenim studijama, razlog su za razmatranje valproata kao opcije za mlade koji ne reagiraju na odobrene lijekove ili ih ne toleriraju (81).

PP je potrebna u više od polovice djece i adolescenata s BP-om u akutnoj maniji zbog nedostatka odgovora na jedan antipsihotik ili stabilizator raspoloženja (80). Kombinacija stabilizatora raspoloženja (82,83) ili kombinacija stabilizatora raspoloženja i ADG (84,85) može povećati odgovor kod pedijatrijskog BP-a kao što je prikazano u otvorenim studijama. Randomizirana kontrolirana studija je pokazala da je uporaba kvetiapina kao dodatne terapije valproatu učinkovitija u liječenju bipolarne manije u adolescenata od monoterapije valproatom (86).

Podatci o akutnom liječenju bipolarne depresije kod pedijatrijskih pacijenata su vrlo ograničeni i kompliciranim iznimno visokim stopama placebo odgovora u RKS (60). Lurasidon je odobren 2018. za liječenje velike depresivne epizode kod BP-I u maloljetnika u dobi od 10 do 17 godina i trenutno se preporučuje kao lijek prve linije za liječenje akutne bipolarne depresije u adolescenciji (87). Zbog rizika od manije izazvane antidepresivima u mladih s BP-om, antidepresive treba koristiti s oprezom u BP-I i BP II, te u kombinaciji s lijekovima za stabilizaciju raspoloženja (88). Kombinaciju olanzapina i fluoksetina odobrila je FDA za liječenje bipolarne depresije u dobnoj skupini od 10 do 17 godina na temelju pozitivnih podataka iz RKS (89);

FDA-approved options for an acute manic episode in pediatric BD include aripiprazole, asenapine, risperidone, or quetiapine for patients aged ≥10 years, and lithium or olanzapine for adolescents aged 12 or 13 to 18 years (80). No mood-stabilizing drug (carbamazepine, lamotrigine, or valproate) is currently FDA-approved for any phase of juvenile BD (79). Despite low response rates in two RCTs, a long history of use among adults with BD, combined with positive findings in open label studies are grounds for considering divalproex as an option for youth who do not respond to or tolerate approved medications (81).

PP is required in more than half of children and adolescents with BD in acute mania due to a lack of response to a single antipsychotic or mood stabilizer (80). Combination of mood stabilizers (82,83) or a combination of mood stabilizers and SGA (84,85) may increase the response in pediatric BD as shown in open-label studies. A randomized controlled trial demonstrated that the use of quetiapine as adjunctive therapy to divalproate was more effective in treating bipolar mania in adolescents than divalproate monotherapy (86).

The data on acute management of bipolar depression in paediatric patients are very limited and complicated by extremely high placebo-response rates in RCTs (60). Lurasidone was approved in 2018 for treatment of major depressive episodes in BD-I disorder in juveniles aged 10–17 years and is currently recommended as a first-line treatment of acute bipolar depression in youth (87). Due to the risks of antidepressant-induced mania in youth with BD, antidepressants should be used with caution in BD-I and BD-II, and in combination with mood-stabilizing medication (88). The combination of olanzapine and fluoxetine was approved by the FDA for the treatment of bipolar depression in the age group 10 to 17 years based on positive data from a RCT (89); however, there are concerns regarding olanzapine metabolic side-ef-

međutim, postoji zabrinutost zbog metaboličkihj nuspojava olanzapina. Unatoč ograničenim podatcima u djece i mladih, litij, lamotrigin i kvetiapin preporučeni su za bipolarnu depresiju zbog mnogo dokaza iz studija kod odraslih te u kombinaciji sa značajnim kliničkim iskustvom (90).

U trenutnoj kliničkoj praksi terapija održavanje ili dugotrajno liječenje juvenilnog BP-a s namjerom profilakse često uključuje *off-label* uporabu antipsihotika i stabilizatora raspoloženja zbog vrlo ograničenih podataka iz istraživanja (91). Trenutne smjernice za dugotrajno liječenje pedijatrijskog BP-a preporučuju stabilizatore raspoloženja (karbamazepin, lamotrigin, litij i valproat) i antipsihotike druge generacije (olanzapin, kvetiapin i risperidon) kao lijekove prve linije i njihove kombinacije kao drugu liniju liječenja (79 -81).

Studija u djece i adolescenata s BP-om tip I pokazala je pozitivan učinak dodatne terapije lamotriginom sa stabilizatorom raspoloženja ili antipsihotikom u terapiji održavanja tijekom 36 tjedana u usporedbi s placebom (92). Nedavna meta-analiza pokazala je da su kombinirani tretmani (lamotrigin, litij ili valproat, obično s ADG) dali superiorne rezultate u odnosu na rezultate prikupljene u ispitivanjima monoterapije (91). Međutim, dostupni podatci ne podupiru jednoznačno ranu primjenu kombiniranog liječenja, a nekoliko međunarodnih stručnih smjernica preporučuje početak liječenja juvenilnog BP-a pojedinačnim lijekovima i razmatranje kombinacija lijekova samo kada monoterapija nije uspješna (79-81).

BP u populaciji djece i adolescenata prati visoka stopa komorbidnih psihijatrijskih stanja. ADHD i granični poremećaj osobnosti su posebni dijagnostički izazovi (93). Preporuke su da se bipolarni simptomi najprije liječe stabilizatorima raspoloženja i/ili ADG kako bi se stabiliziralo raspoloženje prije razmatranja liječenja simptoma ADHD-a (79-81). Psihostifects. Despite limited data in children and youth, lithium, lamotrigine and quetiapine were recommended for bipolar depression due to the abundance of evidence from adult studies combined with substantial clinical experience (90).

In current clinical practice, maintenance or long-term treatment of juvenile BD with prophylactic purpose often involves the off-label use of antipsychotics and mood stabilizers due to very limited research data (91). Current guidelines for long-term treatment of pediatric BD recommend mood-stabilizers (carbamazepine, lamotrigine, lithium, and valproate) and atypical antipsychotics (olanzapine, quetiapine, and risperidone) as first-line treatments and their combinations as second-line regimens (79-81).

A study in children and adolescents with type I BP showed a positive effect of adjunctive lamotrigine therapy with a mood stabilizer or antipsychotic in maintenance therapy for 36 weeks compared to placebo (92). A recent meta-analysis showed that combination treatments (lamotrigine, lithium, or valproate, usually with an SGA) yielded superior results to outcomes pooled across the monotherapy trials (91). However, the available data do not unequivocally support early use of combined treatments, and several international expert guidelines recommend starting treatment of juvenile BD with single drugs and considering drug combinations only when monotherapy has failed (79-81).

BD in children and adolescent population is accompanied by a high rate of comorbid psychiatric conditions. ADHD and borderline personality disorder constitute particular diagnostic challenges (93). Recommendations are to treat bipolar symptoms first with mood stabilizers and/or SGAs to stabilize mood before considering treatment for ADHD symptoms (79-81). Psychostimulants, atomoxetine and bupropion add-ons to mood-stabilizing treatments have been reported to be efficacious in improving ADHD symptoms in young patients with BP

mulansi, atomoksetin i bupropion kao dodatci lijekovima za stabilizaciju raspoloženja pokazali su se učinkovitima u poboljšanju simptoma ADHD-a u mladih pacijenata s BP-om (81). Iako psihostimulansi, kao i antidepresivi, imaju određeni rizik za izazivanje manije u bolesnika s BP-om, ne postoji točna procjena rizika s terapijom ili bez terapije stabilizatorom raspoloženja (94).

Djeci i adolescentima na izvanbolničkom i stacionarnom psihijatrijskom liječenju u Hrvatskoj koji ispoljavaju disregulaciju u ponašanju s izraženim afektivnim simptomima najčešće se dijagnosticiraju mješoviti poremećaj osjećaja i ponašanja (F 92) te se psihofarmakološka terapija primjenjuje samo kada psihoterapija nije dovoljna. Stoga se čini da dječji i adolescentni psihijatri u Hrvatskoj nisu usvojili konceptualizaciju deficita kontrole impulsa i emocionalne nestabilnosti u djece i adolescenata kao BP i liječenje ovih simptoma ponajprije psihofarmakološkom terapijom kao u Sjevernoj Americi. Dijagnoza pedijatrijskog BP-a u Hrvatskoj postavlja se vrlo oprezno, a liječenje lijekovima uključuje ADG (50) te kombinaciju ADG i antidepresiva (59).

Psihotropna polifarmacija u liječenju ranog nastupa shizofrenije i psihotičnih poremećaja u djece i adolescenata

Psihični poremećaji uključuju u prvom redu shizofreniju, ali i shizoafektivni poremećaj, shizofreniformni i sumanuti poremećaj. Različiti psihotični poremećaji pogađaju otprilike 1,6 do 1,9 na 100 000 djece i adolescenata (96). Shizofrenija koja počinje prije 18. godine života poznata je kao shizofrenija s ranim početkom (SRP) (97). Shizofrenija u većine bolesnika počinje u dobi od 15. do 30. godine. Mogućnosti liječenja shizofrenije uključuju antipsihotike, psihoedukaciju, psihosocijalne intervencije,

(81). Although psychostimulants, as well as antidepressants, have a certain risk for inducing mania in patients with BD, there are no accurate risk estimation with or without mood stabilizer therapy (94).

Children and adolescents in outpatient and inpatient psychiatric treatment in Croatia exhibit behavioral dysregulation with pronounced affective symptoms are most often diagnosed with mixed emotional and behavioral disorders (F 92) and psychopharmacological therapy is used only when psychotherapy is not sufficient. Therefore, it appears that child and adolescent psychiatrists in Croatia have not adopted the conceptualization of impulse control deficits and emotional instability in children and adolescents as BP and the treatment of these symptoms primarily by psychopharmacological therapy as in North America. The diagnosis of pediatric BD in Croatia is established very cautiously and treatment with medications includes Second Generation Antipsychotics (SGA) (50) and combination of SGA and antidepressants (59).

Psychotropic polypharmacy in the treatment of early-onset schizophrenia and psychotic disorders in children and adolescents

Psychotic disorders include primarily schizophrenia but also schizoaffective disorder, schizophreniform, and delusional disorder (95). Various psychotic disorders affect approximately1.6 to 1.9 per 100,000 of the child and adolescent population (96). Schizophrenia that starts before 18 years of age is known as early-onset schizophrenia (EOS) (97). The peak age for onset of schizophrenia is considered to be 15–30 years. Treatment options for the management of schizophrenia include antipsychotic medications, psychoeducation, psychosocial interventions, adjunctive medications, and electroconvulsive therapy (ECT) (97, 98).

pomoćne lijekove i elektrokonvulzivnu terapiju (EKT) (97,98).

Na temelju dostupnih dokaza antipsihotici se smatraju lijekovima prve linije za shizofreniju u adolescenata i moraju se koristiti uz psihosocijalni tretman (97,98). Većina antipsihotika prve generacije (APG) i ADG, s iznimkom klozapina, mogu se koristiti kao početna terapija u liječenju SRP (97,98). FDA je odobrila risperidon, aripiprazol, kvetiapin, paliperidon i olanzapin za liječenje shizofrenije u adolescenata starijih od 13 godina. Haloperidol i molindone odobreni su od FDA za liječenje shizofrenije kod mladih od 13 godina i starijih. Predlaže se da se odabir specifičnog lijeka temelji na profilu nuspojava i raznim drugim čimbenicima.

Podatci o sigurnosti i učinkovitosti koji se odnose na uporabu antipsihotika za psihozu i shizofreniju u djece i adolescenata ograničeni su i većinom odražavaju kratkotrajnu upotrebu. Meta-analize koje su ocjenjivale postojeće kratkoročne (6-12-tjedna ispitivanja) podatke o djelotvornosti/učinkovitosti u pogledu primjene antipsihotika u djece i adolescenata sa shizofrenijom pokazale su bolju učinkovitost antipsihotika u usporedbi s placebom (osim eventualno za ziprasidon), nedostatak značajne razlike u učinkovitosti između APG i ADG, a podnošljivost ADG je bolja od APG (99,101). Općenito, pokazalo se da antipsihotici imaju superiornu učinkovitost u smislu smanjenja pozitivnih simptoma, a nedostaje značajan povoljan učinak na negativne simptome u usporedbi s placebom. Podatci također ukazuju da nema razlike u učinkovitosti između različitih ADG, osim činjenice da je klozapin bolji od drugih antipsihotika (102) te da bi trebao biti rezerviran za bolesnike s terapijski rezistentnom shizofrenijom (97,98).

Druga generacija antipsihotika povezana je s nižim stopama prekida terapije u usporedbi s prvom generacijom (99,101). Što se tiče nuspojava, postoje različiti profili štetnih učinaka za

Based on the available evidence, antipsychotic medications are considered as the first-line treatment for schizophrenia in adolescents and they must be used along with the psychosocial management (97,98). Most first generation and second antipsychotics, with the exception of clozapine, can be used as first line treatment options for EOS (97, 98). Risperidone, aripiprazole, quetiapine, paliperidone, and olanzapine are approved by the FDA for treating schizophrenia in adolescents 13 years and older. Haloperidol and molindone are approved by the FDA for treating schizophrenia in youth 13 years and older. It is suggested that selection of a specific agent should be based on the side effect profile and various other factors.

Safety and effectiveness data addressing the use of antipsychotic medications for psychosis and schizophrenia in children and adolescents are limited and for the most part reflect short-term use. Meta-analyses that have evaluated the existing short-term (6–12-week trials) efficacy/effectiveness data with respect to the use of antipsychotics in children and adolescents with schizophrenia have shown superior efficacy of antipsychotic medications when compared to placebo (except possibly for ziprasidone), lack of significant difference in efficacy between the First Generation Antipsychotics (FGAs) and SGAs, and tolerability of SGAs being better than FGAs (99-101). Overall, antipsychotics have superior efficacy in terms of reduction in positive symptoms, and there is a lack of significant beneficial effect on negative symptoms when compared to placebo. Data also suggest that there is no difference in efficacy between different SGAs, except for the fact that clozapine is superior to other antipsychotics (102). Clozapine should be reserved for patients with treatment-resistant schizophrenia (97,98).

SGAs are associated with lower dropout rates compared to FGAs (99,101). In terms of adverse effects, there is differential adverse effect profile of various antipsychotics, with extrapyramidal

različite antipsihotike pri čemu su ekstrapiramidni simptomi češći u bolesnika koji primaju APG, hiperprolaktinemija je češća kod risperidona i APG, a povećanje tjelesne težine i metaboličke nuspojave su češće kod ADG, posebno olanzapina (99,101). Nuspojave antipsihotika u adolescenata slične su onima u odraslih pacijenata, osim činjenice da adolescenti imaju više nuspojava. Potreba praćenja štetnih učinaka je ključna (97,98).

Postoje ograničeni podatci u pogledu dugotrajne učinkovitosti različitih antipsihotika u bolesnika s SRP. Podatci o terapiji održavanja iz studije *Treatment of Early-Onset Schizophrenia Spectrum* (TEOSS) ukazuju da tri korištena lijeka (risperidon, olanzapin i molindone) općenito održavaju redukciju simptoma postignutu u akutnih bolesnika s SRP koji su odgovorili na terapiju (103). Međutim, sva tri lijeka imaju značajne nuspojave koje utječu na podnošljivost, što pokazuje činjenica da je vrlo malo pacijenata završilo jednogodišnje liječenje; samo 12 % mladih s SRP-om nastavilo je s prvotnom randomiziranom terapijom u 52. tjednu. Nijedan lijek nije pokazao superiornu učinkovitost, a svi su bili povezani s nuspojavama, uključujući povećanje tjelesne težine.

Antipsihotici u depo obliku nisu proučavani na pedijatrijskim pacijentima te imaju rizike za nuspojave svojstvene dugotrajnoj primjeni (97,98). Stoga ih treba razmotriti samo u adolescenata sa shizofrenijom s kroničnim psihotičnim simptomima i anamnezom loše suradljivosti s lijekovima.

Iako kao skupina lijekova antipsihotici ostaju primarni lijekovi za liječenje shizofrenije i psihoza u djece i adolescenata, liječenje može uključivati korištenje dodatnih lijekova kao što su benzodiazepini (za anksioznost, nesanicu, akatiziju, agitaciju i katatoniju), antiparkinsonici (za liječenje ekstrapiramidnih nuspojava), antidepresivi (za depresiju, negativne simptome) i stabilizatori raspoloženja (nestabilnost raspoloženja, agresija) (97,98). Me-

symptoms being more common in patients receiving FGAs, hyperprolactinemia being more common with risperidone and FGAs, and weight gain and metabolic side effects being more common with SGAs, especially olanzapine (99,101). Side effects of antipsychotics in adolescents are similar to that seen in adult patients, except for the fact that adolescents experience more side effects. The need to monitor for adverse effects is of paramount importance (97,98).

There are limited data in terms of long-term efficacy of various antipsychotics in patients with EOS. The maintenance treatment data of the Treatment of Early-Onset Schizophrenia Spectrum (TEOSS) study suggest that the three agents used (risperidone, olanzapine and molindone) generally maintain symptom reductions achieved in acute responders with EOSS (103). However, all three drugs have significant side effects that affect tolerability, as shown by the fact that very few patients completed one year of treatment; only 12% of youth with EOSS continued on their originally randomized treatment at 52 weeks. No agent demonstrated superior efficacy, and all were associated with side effects, including weight gain.

Depot antipsychotics have not been studied in pediatric age groups and have inherent risks with long-term use to side effects (97,98). Therefore, they should be considered only in schizophrenic adolescents with chronic psychotic symptoms and a history of poor medication adherence.

Although as a class of medications, antipsychotic agents remain the primary drugs for management of schizophrenia and psychoses in children and adolescents, management may involve the use of adjunctive treatments such as benzodiazepines (for anxiety, insomnia, akathisia, agitation, and catatonia), antiparkinsonian medications (for the management of extrapyramidal side effects), antidepressants (for depression, negative symptoms), and mood stabilizers (mood instability, aggression) (97, 98). Howev-

đutim, ne postoje studije koje bi se sustavno bavile upotrebom pomoćnih lijekova kod mladih sa shizofrenijom. Stoga, ako se ovi lijekovi moraju koristiti, treba ih davati s odgovarajućim obrazloženjem i u najkraćem mogućem trajanju, nakon što se pacijentu i/ili članovima obitelji objasni profil nuspojava i nedostatak podupirućih dokaza (97,98). Ne preporučuje se profilaktička primjena antikolinergika, ali oni se mogu dati u najnižim mogućim dozama i u najkraćem mogućem vremenu, ako pacijent razvije ekstrapiramidne simptome (97,98). Profilaktička primjena antikolinergika može se razmotriti u bolesnika s anamnezom akutne distonije i onih kod kojih postoji rizik od razvoja akutne distonije.

Iako se često pretpostavlja da mladi sa shizoafektivnim poremećajem zahtijevaju istodobnu primjenu antidepresiva ili stabilizatora raspoloženja, ove kombinacije nisu sustavno proučavane (97,98). U studiji TEOSS nije bilo značajnih razlika u odgovoru na liječenje među bolesnicima sa shizofrenijom i onih sa shizoafektivnim poremećajem (103).

ADG su najčešće propisivani antipsihotici psihijatrijskim pedijatrijskim bolesnicima u Hrvatskoj u svim dijagnostičkim kategorijama (50). No, ADG se najčešće propisuju za liječenje agresije kod poremećaja ponašanja i pacijenata s intelektualnim teškoćama, a tek zatim slijede psihotični poremećaji. PP antipsihotika s drugim lijekovima uključuje teške slučajeve otporne na monoterapiju i to uglavnom sa stabilizatorima raspoloženja, antidepresivima i rijetko s APG.

Psihotropna polifarmacija u liječenju poremećaja ometajućeg ponašanja u djece i adolescenata

Smjernice za liječenje poremećaja ometajućeg ponašanja (POP), uključujući poremećaj s prkošenjem i suprostavljanjem (PPS), poremećaj ponašanja (PP), hiperkinetski poreme-

er, there are no studies systematically addressing the use of adjunctive agents in youth with schizophrenia. Hence, if these medications have to be used, they may be used with proper rationale and for shortest possible duration after explaining the patient and/or the family members about the side effect profile and lack of supportive evidence (97,98). Prophylactic use of anticholinergics is not recommended; however, these can be given if a patient develops extrapyramidal symptoms in the lowest possible doses and for the shortest possible time (97,98). Prophylactic use of anticholinergic agents may be considered in patients with a past history of acute dystonias and those who are at risk of developing acute dystonia.

Although youths with schizoaffective disorder are often assumed to need concurrent antidepressants or mood stabilizers, these combinations have not been systematically studied (97, 98). In the TEOSS, there were no significant differences in treatment response between patients with schizophrenia and those with schizoaffective disorder (103).

SGAs are the most widely prescribed antipsychotic medications to pediatric patients in Croatia in all diagnostic categories (50). However, SGAs are mostly prescribed for the treatment of aggression in behavioral disorders and intellectual disability patients, followed by psychotic disorders. PP of antipsychotic medications with other agents includes severe cases resistant to monotherapy mostly with mood stabilizers, antidepressants and rarely the FGA.

Psychotropic polypharmacy in the treatment of disruptive behavior disorders in children and adolescents

The guidelines for the treatment of disruptive behavior disorders (DBD), including oppositional defiant disorder (ODD), conduct disorder (CD), hipekynetic conduct disorder, rec-

ćaj ponašanja, preporučuju psihoedukaciju i trening vještina za roditelje i dijete prikladno dobi tijekom svih faza temeljenih na dokazima (104-106). Sustavni pregledi su pokazali da je učinkovitost psihosocijalnih intervencija u istom rasponu kao i učinkovitost većine lijekova u liječenju POP-pa bi se stoga psihosocijalne intervencije trebale koristiti kao početno liječenje ometajućeg i agresivnog ponašanja u djece s ADHD-om, PPS ili PP-om. Provedba psihosocijalnih intervencija ograničena je u mnogim sredinama zbog financijskih, sustavnih i kulturoloških prepreka koje su vjerojatno značajno pridonijele sve većoj upotrebi lijekova za POP (107).

Postoje dokazi umjerene kvalitete da risperidon ima umjeren do velik učinak na probleme ponašanja i agresiju kod mladih s prosječnim i ispodprosječnim intelektualnim funkcioniranjem i PPS-om, PP-om ili POP, neodređen, s ADHD-om i bez ADHD-a (108). Ovi se dokazi moraju odvagati u odnosu na potencijalne štetne učinke risperidona i razmotriti u svjetlu dokaza koji podupiru upotrebu psihosocijalnih metoda liječenja. Dokazi koji podržavaju upotrebu drugih antipsihotika i stabilizatora raspoloženja niske su kvalitete (109,110).

Postoje uvjerljivi dokazi da se, kada se ADHD javlja u komorbiditetu s poremećajima ponašanja i liječi stimulansima, mogu uočiti poboljšanja kod poremećaja ometajućeg ponašanja i agresije (111).

S obzirom na ozbiljnost ishoda povezanih s POP-om i fizičkom agresijom upotreba višestrukih psihotropnih lijekova za rješavanje simptoma koji ne reagiraju na monoterapiju stimulansima sve je učestalija praksa (10,12,14). Trenutno postoji trend kombiniranog liječenja ADG i stimulansima (112,113).

Studija *Treatment of Severe Childhood Aggression* (TOSCA) bila je jedno od prvih velikih istraživanja koja su ispitala pojačavajući učinak

ommend psychoeducation and the provision of age-appropriate, evidence-based parent and child skills training during all phases (104-106). Systematic reviews have shown that the effect sizes for psychosocial interventions are in the same range as the effect sizes of most medications in the treatment of DBD; therefore, psychosocial interventions should be used as initial management of disruptive and aggressive behaviour in children with ADHD, ODD, or CD. The implementation of psychosocial interventions is limited in many communities due to financial, systemic, and cultural barriers, which has likely contributed significantly to the increasing use of medication for DBD (107).

There is moderate-quality evidence that risperidone has a moderate–to-large effect on conduct problems and aggression in youths with an average and subaverage intellectual functioning and ODD, CD, or DBD-NOS, with and without ADHD (108). This evidence must be weighed against potential adverse effects of risperidone and considered in light of evidence supporting the use of psychosocial therapies. The evidence to support the use of other antipsychotics and mood stabilizers is of low quality (109,110). There is convincing evidence that when ADHD co-occurs with disruptive behaviour disorders and is treated with stimulant medications, improvements can be observed in disruptive behaviour disorder and aggression (111).

Given the severity of the outcomes associated with DBDs and physical aggression, the use of multiple psychotropic medications to address symptoms unresponsive to stimulant monotherapy is an increasing practice (10,12,14). Currently there is a trend towards combination treatment with SGA and stimulant medication (112,113).

The Treatment of Severe Childhood Aggression (TOSCA) study was one of the first large-scale investigations to examine antipsychotic augmentation (risperidone) of established

antipsihotika (risperidona) kod utvrđenih metoda liječenja za dječju agresiju temeljenih na dokazima koji uključuju trening roditelja (engl. *parental training* - PT) + stimulans (108). Rezultati studije TOSCA ukazuju da bi liječnici trebali odgoditi primjenu antipsihotika najmanje 1 mjesec nakon što se postigne optimalna doza stimulansa i započne PT, kako bi se smanjilo nepotrebno liječenje višestrukim lijekovima. Kombinirano liječenje PT + stimulans bilo je vrlo učinkovito u liječenju fizičke agresije povezane s ADHD-om, PPS-om ili PP-om i postaje sve učinkovitije tijekom najmanje 6 tjedana (114). Kada je opravdano, pojačavajući učinak risperidona dovodi do dodatnih umjerenih poboljšanja u funkcioniranju s podnošljivim nuspojavama.

ADG imaju rizik od nuspojava, uključujući porast tjelesne težine i metabolički sindrom, ekstrapiramidne simptome i povišenje prolaktina što je sve problematičnije kod djece i adolescenata (10,20,25). Nadalje, sedativni učinak ovih lijekova može narušiti kogniciju i školski uspjeh (27,115).

POP je bila primarna dijagnoza za liječenje antipsihoticima u djece i adolescenata u Hrvatskoj (50), često u kombinaciji s antidepresivima i stabilizatorima raspoloženja u težim i refrakternim slučajevima. Nedostatak kombinacije antipsihotika i stimulansa u liječenju djece i adolescenata u Hrvatskoj odražava rijetku primjenu psihostimulansa u Hrvatskoj jer nisu plaćeni od nacionalnog zdravstvenog osiguranja.

ZAKLJUČAK

PP je postala široko rasprostranjena praksa na svim razinama skrbi u liječenju mentalnih poremećaja djece i adolescenata, iako nedostaju čvrsti dokazi o njezinim prednostima uz nekoliko iznimaka te uz popratne nuspojave. S obzirom na trenutnu prevalenciju PP-a potrebne

evidence-based treatments for childhood aggression that include parent training (PT) and stimulant medication (108). The results of the TOSCA study suggest that practitioners should delay an antipsychotic drug for at least 1 month after the optimal stimulant dose is achieved and PT has commenced in order to reduce unnecessary treatment with multiple medications.

Combined PT + stimulant treatment was highly effective in treating physical aggression associated with ADHD and ODD or CD and becomes more effective with time at least through 6 weeks (114). When warranted, augmentation of treatment with risperidone leads to additional moderate improvements in functioning with tolerable side effects.

SGAs have the risk of adverse effects including weight gain and metabolic syndrome, extrapyramidal symptoms and prolactin elevation, all of which appear more problematic in children and adolescents (10,20, 25). Furthermore, the sedative effect of these drugs may impair cognition and academic performance (115). The lasting impact of these adverse effects on health and development must also be considered (27, 115).

DBD was the primary diagnosis for the treatment with antipsychotics in children and adolescents in Croatia (50), often combined with antidepressants and mood stabilizators in more severe and refractory cases. The lack of antipsychotic-stimulant combination in the treatment of children and adolescents in Croatia reflects seldom use of psychostimulants because they are not reimbursed by the national health insurance.

CONCLUSION

PP has become a widespread practice across various levels of care in the treatment of mental disorders in children and adolescents, although

su dodatne visokokvalitetne studije za procjenu koristi i rizika uobičajenih kombinacija. Do tada, odnos prema kombiniranoj farmakoterapiji trebao bi biti konzervativan, a kombiniranje psihotropnih lijekova pažljivo praćeno. Zbog složenosti etiologije i težine psihičkih poremećaja u djece primjena psihotropne polifarmacije ponekad je neizbježna. U takvim slučajevima svaka kombinacija korištenih lijekova mora imati svoje etiološko i kliničko opravdanje, jer će samo tada PP biti korisna i opravdana, a ne pretjerana i opterećena nuspojavama. U tablici 1. prikazane su kombinacije psihotropnih lijekova za liječenje psihičkih poremećaja u djece i adolescenata za koje trenutno postoji najviše dokaza.

it is lacking strong evidence of its benefits with few exceptions and has associated risks. Given the current prevalence of PP, additional high-quality studies are needed to evaluate the benefits and risks of common combinations. Until such a time, the attitude to combination pharmacotherapy should be conservative, and combining psychotropic medications should be closely monitored. Due to the complexity of the etiology and severity of mental disorders in children, the use of PP is sometimes unavoidable. In such cases, each combination of drugs used must have its etiological and clinical justification because only then PP will be useful and justified, not excessive and burdened with side effects. Table 1 presents combinations of

TABLICA 1. Kombinacije psihotropnih lijekova za liječenje psihičkih poremećaja u djece i adolescenata za koje trenutno postoji najviše dokaza
TABLE 1. The most justified pediatric psychotropic polypharmacy

Poremećaj / Disorder	Kombinacije psihotropnih lijekova / Psychotropic drugs combinations
ADHD	• Psihostimulansi + središnji alfa agonisti (ER klonidin i gvanfacin) (29-31) ili atomoksetin (32) / Psychostimulants + central alpha agonists (ER clonidine and guanfacine) (29-31) or Atomoxetine (32) • Psihostimulans + valproat ili risperidon za komorbidnu agresiju i ometajuće ponašanje (22,33,34) / Psychostimulant + divalproex or risperidone for comorbid aggression and disruptive behavior (22, 33, 34) • atomoksetin i niske doze antipsihotika za komorbidni Tourettov sindrom (10) / Atomoxetine and low doses of antipsychotics for comorbid Tourette's syndrome (10)
Autizam / Autism	• Antipsihotici i lijekovi za ADHD za komorbidni ADHD / Antipsychotics and ADHD medications for comorbid ADHD • Antipsihotici i antidepresivi za komorbidni anksiozni i depresivni poremećaj (44,46) / Antipsychotics and antidepressants for comorbid anxiety and depressive disorders (44, 46)
Anksiozni poremećaji / Anxiety Disorders	• SIPPS + antipsihotici druge generacije (ADG) kod terapijski rezistentnog pedijatrijskog OKP-a (58) / SSRIs + second generation antipsychotics (SGA) in treatment-resistant paediatric OCD (58) • SIPPS + klomipramin (58) / SSRIs + clomipramine (58)
Depresija / Depression	• Antidepresivi (SIPPS ili venlafaksin) + stabilizator raspoloženja (valproat, topiramat, litij, ADG) za terapijski rezistentnu depresiju u adolescenata (73) / Antidepressants (SSRI or venlafaxine) + mood stabilizer (divalproate, topiramate, lithium, antipsychotic) in adolescent treatment-resistant depression (73)
Bipolarni poremećaj / Bipolar Disorder	• Kombinacija stabilizatora raspoloženja (82,83) ili kombinacija stabilizatora raspoloženja i antipsihotika druge generacije (ADG) (84-86) za terapijski rezistentni pedijatrijski BP / Combination of mood stabilizers (82, 83) or a combination of mood stabilizers and second generation antipsychotics (SGA) (84,85, 86) for treatment-resistant pediatric BD • Antidepresivi + stabilizatori raspoloženja za bipolarnu depresiju u adolescenata (88) / Antidepressants + mood-stabilizing medication in adolescent bipolar depression (88)
Shizofrenija i psihotični poremećaji (97, 98) / Schizophrenia and Psychotic Disorders (97, 98)	• Antipsihotik + benzodijazepini za anksioznost, nesanicu, akatiziju, agitaciju i katatoniju / Antipsychotic + benzodiazepines for anxiety, insomnia, akathisia, agitation, and catatonia • Antipsihotik + antiparkinsonik za liječenje akutnih ekstrapiramidnih nuspojava / Antipsychotic + antiparkinsonian medications for management of acute extrapyramidal side effects • Antipsihotik + antidepresiv za depresiju, negativne simptome) / Antipsychotic + antidepressants for depression, negative symptoms) • Antipsihotik + stabilizator raspoloženja za nestabilno ponašanje i agresiju / Antipsychotic + mood stabilizers for mood instability and aggression • Kombinacija prve i druge generacije antipsihotika u terapijski rezistentnim psihotičnim poremećajima / Combination of the first- and second-generation antipsychotics in treatment-resistant psychotic disorders
Poremećaj ometajućeg ponašanja / Disruptive Behavior Disorders	• Druga generacija antipsihotika i stimulansi (112,113) / Second generation antipsychotics and stimulant medication (112, 113)

Sljedeće strategije su predložene pri započinjanju polifarmacije: procijeniti suradljivost, pratiti ciljane simptome kako bi se osigurala korist liječenja, pričekati nakon promjene jednog lijeka, zamjena lijeka umjesto pojačavanja kod djelomičnog odgovora na liječenje, pokušati s polifarmacijom nakon dva neuspješna pokušaja monoterapijom, izbjegavati istovremeno mijenjanje više od jednog lijeka (116).

Složene načine uzimanja lijekova treba redovito evaluirati, uzimajući u obzir mogućnost postupnog ukidanja lijekova koji su neučinkoviti ili nisu više potrebni. Praksa postupnog ukidanja lijekova od psihijatara i drugih kliničara koji propisuju lijekove također može biti jedna od mogućnosti izbjegavanja i smanjenja psihotropne polifarmacije (117). Postupno ukidanje dio je dobre prakse propisivanja lijekova koja pruža sustavni pristup prestanku uzimanja lijekova kada su štete veće od koristi. Također, psihosocijalne intervencije temeljene na dokazima moraju se provoditi istovremeno s liječenjem psihofarmacima kako bi olakšale stabilizaciju i prekid uzimanja lijekova koji imaju više rizika. Zajedno, ovi koraci mogu spriječiti da PP bude neograničena, bez jasnog praćenja koristi liječenja ili bez definiranog trajanja.

psychotropic drugs for treatment of mental disorders in children and adolescents with the most current evidence.

The following strategies have been sugessted when initiating polypharmacy: evaluate adherence, track target symptoms to ensure benefits, wait after making changes to one medicine, switch the drug rather than augment for a partial response, try polypharmacy after two failed trials of monotherapy, avoid changing more than one medication at a time (116).

Complex medication regimes should be reviewed regularly, considering the possibility of withdrawing medications that are ineffective or no longer necessary. Deprescribing practices by psychiatrists and other prescribing clinicians may also be one of the possibilities to avoid and reduce PP (117). Deprescribing is part of good prescribing practice, providing a systematic approach to discontinue medications when the harms outweigh the benefits. Also, evidence-based psychosocial interventions need to be simultaneously implemented with medication that would facilitate stabilization and discontinuation of higher risk medications. Together, these steps may prevent PP being indefinite without a clear observation of benefit or defined endpoint.

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