Formative evaluation of the needs, opportunities, and barriers in the implementation of deprescribing in primary healthcare

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DOCTORAL DISSERTATION

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FORMATIVNA PROCJENA POTREBA, MOGUĆNOSTI I PREPREKA U PROVEDBI DEPRESKRIPCIJE TERAPIJE U PRIMARNOJ ZDRAVSTVENOJ ZAŠTITI

DOKTORSKI RAD

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SUMMARY

Deprescribing is the planned and supervised process of dose reduction or tapering, and stopping of medication, which might be causing harm, or is no longer of benefit to the patient, with the goal of managing polypharmacy and improving outcomes. This research aimed to explore the need for, and the barriers and facilitators of deprescribing in primary care in a healthcare system where it has not been researched, implemented, or provided. Four phases of research were carried out; a systematic review on the role of community-based pharmacist in deprescribing, a cross-sectional study exploring the patient-deprescribing relationship and patients' opinion on pharmacists involvement in deprescribing, tool development to explore the healthcare provider-deprescribing relationship alongside a case vignette study to examine the agreement between community pharmacists and primary care physicians on deprescribing suggestions, and lastly a cross-sectional study to assess the deprescribing potential of commonly used medications among older adults. The systematic review performed in the first phase of this research shows community-based pharmacists can successfully lead deprescribing interventions and are valuable partners in deprescribing. Second phase of research unveils the finding that the majority of adults 40 years and older (84%) would be willing to deprescribe one or more medications, with older adults (65 years and older) being more willing to have medications deprescribed than younger adults (χ^2 (1) = 4.06; p = 0.044). Furthermore, majority of participating adults (71%) would feel comfortable with pharmacist's involvement in deprescribing, and 69% believes pharmacists have competencies to suggest deprescribing to physicians. Positive opinion on pharmacists' involvement was assessed as a predictive factor for positive attitude towards deprescribing (aOR = 2.351, 95% CI = 1.176 – 4.699; p = 0.016). Comprehensive Healthcare providers' OPinions, Preferences, and attitudEs towards Deprescribing (CHOPPED) questionnaire was developed in the third phase of research, to aid in exploration of healthcare providers' determinants important for implementing and providing deprescribing regardless of their familiarization with deprescribing. The questionnaire shows satisfactory face, content, construct, and criterion validity, as well as reliability and internal consistency. Using the CHOPPED questionnaire, it was found that the majority of healthcare providers (87%) would suggest deprescribing to a patient if appropriate. For pharmacists, the most important facilitators were extrinsic factors (collaboration facilitators and healthcare facilitators factors), while for physicians intrinsic (knowledge and awareness) and patient-related factors were more prominent. Moreover, a case vignette study elucidated pharmacists

can identify potential deprescribing targets and suggest deprescribing rationales which physicians would accept. Collaborative deprescribing targets should be medicines both healthcare providers share most agreement on, such as nonsteroidal anti-inflammatories (NSAID), opioids (OPI) or diuretics. In a cross-sectional study conducted in community pharmacies across Croatia, which enrolled 388 patients older than 65 years, 55.2% of participants were identified as potential candidates for deprescribing of one or more medications; 31.1% of proton pump inhibitors (PPI) users, 74.8% of NSAID, 75.0% of OPI, and 96.1% of benzodiazepine (BZN) users met at least one deprescribing criterion. Several predictive factors were identified for increased need for deprescribing, including identifying as a woman (aOR = 2.58; 95% CI =1.59 - 4.18; $p < 0.001$), poor self-reported health (aOR = 5.14; 95% CI = 1.73-15.25; $p < 0.001$), and polypharmacy (aOR = 1.29; 95% CI = 1.17 - 1.44; $p < 0.001$). Formative evaluation, as a result of this doctoral research, can lead to an implementation strategy facilitated by CHOPPED questionnaire and interventional protocol (Collaborating for Older aduLts to Deprescribe in primarY care" (COLDY)), proposed in this doctoral thesis, which can help engage healthcare providers in collaborative patient care with the goal of promoting deprescribing to enhance patient safety and optimise pharmacotherapy.

KEY WORDS: deprescribing; primary healthcare; physician; pharmacist; patient; older adults; comprehensive geriatric assessment; tool development; formative evaluation; pre implementation research

SAŽETAK

Uvod: Politerapija je povezana s povećanim rizikom propisivanja nepotrebnih ili neprikladnih lijekova. Smatra se da je u primarnoj zdravstvenoj zaštiti jedan od pet lijekova neprikladno propisan. Korištenje potencijalno neprikladnih lijekova posebice u starijoj životnoj dobi predstavlja ozbiljan javnozdravstveni problem, a povezan je s povećanim morbiditetom i mortalitetom. Politerapija je povezana i s povećanim rizikom nepovoljnih ishoda kao što su neželjene reakcije, interakcije lijekova, pogoršanje funkcionalnog statusa, gerijatrijski sindrom, povećani troškovi zdravstvene zaštite i niska adherencija na sve oblike liječenja. Zdravstvenim radnicima je dostupno niz pristupa za rješavanje ovog rastućeg problema, jedan od njih je i depreskripcija terapije. Depreskripcija terapije je planirani proces smanjivanja doze ili potpunog ukidanja lijeka iz farmakoterapije, za koji je rizik korištenja veći od potencijalne koristi ili za kojim više nema potrebe odnosno dokazane učinkovitosti. Opisuje se i kao proces smanjenja doze ili prestanka korištenja neprikladnog lijeka, nadziranog od strane zdravstvenog radnika s ciljem upravljanja politerapijom i poboljšanja ishoda liječenja. Depreskripcija koju provodi ljekarnik, temelji na zajedničkom donošenju odluka svih sudionika, ljekarnika, liječnika i pacijenta. Uz praktične smjernice za depreskripciju, ljekarnik i/ili liječnik koji provodi depreskripciju u obzir treba uzeti kliničke, psihološke, socijalne, financijske i fizičke odrednice pacijenta, kako bi se osiguralo uspješno ukidanje lijeka iz terapije. Glavni je cilj ovog istraživanja ispitati potrebu za depreskripcijom terapije te utvrditi prepreke i mogućnosti depreskripcije terapije na razini primarne zdravstvene zaštite, u zdravstvenom sustavu u kojem do sada nije istraživana, implementirana ili sustavno provođena. Specifični ciljevi uključuju utvrđivanje potrebe za depreskripcijom terapije na uzorku kroničnih bolesnika starijih od 65 godina u primarnoj zdravstvenoj zaštiti, ispitivanje mišljenja i stavova pacijenata o depreskripciji terapije te utvrđivanje čimbenika koji mogu utjecati na potencijalnu depreskripciju terapije, razvoj i validacija alata kojim će se ispitati znanje, mišljenje i stavovi ljekarnika i liječnika u primarnoj zdravstvenoj zaštiti o depreskripciji terapije te odrediti potencijalne prepreke i mogućnosti depreskripcije terapije od strane istih, utvrđivanje slaganja ljekarnika i liječnika u primarnoj zdravstvenoj zaštiti o prijedlogu depreskripcije terapije, te sustavni pregled dostupnih dokaza o depreskripciji terapije predvođene javnim ljekarnikom, a čija je učinkovitost ispitana na kliničke i humanističke učinke.

Metode i ispitanici: Istraživanje potencijala, potreba i izazova depreskripcije terapije u primarnoj zdravstvenoj zaštiti odvijalo se u četiri faze koje su omogućile sveobuhvatni pristup temi te osigurale uključivanje u istraživanje svih sudionika (pacijenata te ljekarnika i liječnika

u primarnoj zdravstvenoj zaštiti) važnih za proces depreskripcije terapije. Prva faza istraživanja uključivala je sustavni pregled dostupnih bibliografskih baza podataka, te baze kliničkih istraživanja kako bi se prikupili dokazi o učinkovitosti depreskripcijskih intervencija predvođenih ljekarnikom u primarnoj zdravstvenoj zaštiti. Rezultati uključenih istraživanja svrstani su prema vrsti intervencije te praćenom ishodu (npr. promjene u broju propisanih lijekova, smanjivanje doze, broj prihvaćenih ljekarnikovih prijedloga, promjene u broju padova, utjecaj na kvalitetu života). U svrhu provođenja druge faze istraživanja, o mišljenjima, stavovima i preferencijama pacijenata o depreskripciji terapije, provedeno je presječno opažajno istraživanje u javnim ljekarnama u Republici Hrvatskoj koristeći validirani upitnik. Trodijelni upitnik, uz pitanja o sociodemografskim karakteristikama ispitanika, koristi i hrvatsku inačicu validiranog rPATD (engl. *Revised Patients Attitude Towards Deprescribing*) upitnika te, u posljednjem dijelu, pet pitanja o ulozi ljekarnika u depreskripciji terapije i pacijentovim željama o potencijalnoj depreskripciji određenog lijeka njihove kronične farmakoterapije. U ovu fazu istraživanja bile su uključene osobe u dobi od 40 godina ili više koje koriste barem jedan lijek dulje od mjesec dana, a isključene osobe oboljele od demencije ili koje nisu bile u stanju dati pouzdane podatke. Kako bi se ispitala mišljenja i stavovi liječnika i ljekarnika u primarnoj zdravstvenoj zaštiti, osmišljena je i provedena treća faza istraživanja. Iz temeljitog literaturnog pregleda te strukturiranih razgovora s ljekarnicima i liječnicima u primarnoj zdravstvenoj zaštiti određeni su koncepti, teme i čimbenici depreskripcije, prema kojima je razvijen i validiran sveobuhvatni upitnik (engl. *Comprehensive Healthcare providers' OPinions, Preferences, and attitudEs towards Deprescribing* (CHOPPED)). Razvijeni upitnik korišten je u presječnom opažajnom istraživanju provedenom *on-line*, kojem su pristupili liječnici i ljekarnici u primarnoj zdravstvenoj zaštiti. Posljednja faza istraživanja bila je usmjerena na određivanje potencijala depreskripcije terapije u osoba starije životne dobi. Podatci prikupljeni u multinacionalnom, presječnom istraživanju "Neprikladno propisivanje lijekova i dostupnost usluge upravljanja terapijom u starijih osoba u Europi" u sklopu projekta EuroAgeism H2020, te kriteriji za depreskripciju terapije (temeljeni na smjernicama za propisivanje i depreskripciju učestalo korištenih lijekova) korišteni su kako bi se odredio broj lijekova za koje bi pojedinom pacijentu bila korisna depreskripcija.

Rezultati: Sustavni pregled (prva faza) pokazuje da depreskripcijske intervencije predvođene ljekarnikom u primarnoj zdravstvenoj zaštiti uspješno dovode do smanjenja broja korištenih lijekova i financijske koristi za zdravstveni sustav, dok je utjecaj na mortalitet, kvalitetu života, broj padova, hospitalizacije i korištenje drugih oblika zdravstvene zaštite održan ili poboljšan. Depreskripcijske intervencije koje uključuju ljekarnikovu edukaciju pokazale su se posebno uspješnima. Ljekarnikov farmakoterapijski pregled, usklađivanje terapije ili upravljanje terapijom dovode do uspješne depreskripcije antikolinergičkih i sedativnih lijekova, ali nemaju utjecaj na broj padova ili hospitalizacija. Intervencije temeljene na kolaborativnoj praksi predvođene ljekarnikom pokazale su se uspješnim ne samo u smanjenju broja neprikladno propisanih lijekova, već i u pozitivnom utjecaju na smanjenje smrtnosti i održavanje razine kvalitete života. Istraživanje druge faze pokazuje da bi velik broj pacijenata 40 godina i starijih (84%) spreman je prestati koristiti jedan ili više svojih lijekova, iako su zadovoljni propisanom farmakoterapijom. Osobe starije životne dobi (starije od 65 godina života) sklonije su prihvatiti depreskripciju terapije u usporedbi s mlađim odraslim osobama (χ^2 (1) = 4,06; p = 0,044). Većina ispitanika (71%) osjećala bi se ugodno ako bi ljekarnik bio uključen u proces depreskripcije terapije, a 69% njih dodatno smatra da ljekarnik ima dovoljno znanja, vještina i informacija predložiti depreskripciju. Analiza odgovora o preferenciji pacijenta o ukidanju lijeka iz farmakoterapije pokazuje da su pacijenti spremni prestati koristiti antihipertenzive, benzodiazepine, statine, te analgetike (nesteroidne protuupalne lijekove). Regresijskom analizom utvrđeni su prediktivni čimbenici spremnosti na depreskripciju terapije: pozitivno mišljenje o uključenosti ljekarnika u proces depreskripcije terapije (aOR = 2,351, 95% CI = 1,176 – 4,699; p = 0,016), niži broj čimbenika vezanih uz zabrinutosti o prestanku korištenja lijeka (aOR = 0,542; 95% CI = 0,35 – 0,84; p = 0,006) te niži broj čimbenika veznih uz prikladnosti terapije (aOR = 0,62; 95% CI = 0,39 – 0,98; p = 0,039). U istraživanju mješovitog pristupa (engl. *mixed-method approach*) treće faze, razvijen je i validiran CHOPPED sveobuhvatni upitnik za zdravstvene djelatnike o mišljenjima, preferencijama i stavovima o depreskripciji terapije, koji se sastoji od tri domene (Znanje i osviještenost, Prepreke i Poticatelji), deset čimbenika (znanje, osviještenost, prepreke/poticatelji povezani s pacijentom, prepreke/poticatelji osobnih kompetencija, prepreke/poticatelji suradnje i prepreke/poticatelji zdravstvenog sustava) i sveopćeg pitanja o provođenje depreskripcije terapije, a osmišljen je u dvije inačice. Upitnik pokazuje zadovoljavajuću izravnu, sadržajnu (*engl. content validity ratio (CVR)* > 0,62), konstruktnu (određenu primjenom faktorske analize uz Kaiser-Meyer-Olkinovu mjeru 0,834; Bartlett test sferičnosti p < 0,001 za ljekarničku inačicu te Kaiser-Meyer-Olkinovu mjeru 0,759; Bartlett test sferičnosti p < 0,001 za liječničku inačicu) i kriterijsku (određenu kao

povezanost između čimbenika i sveopćeg pitanja; za ljekarničku inačicu G = 0,228; p < 0,001, G = 0,292; p = 0,002 za čimbenike znanja i osviještenosti, te G = -0,182; p = 0,001 za čimbenike prepreka, odnosno za liječničku inačicu G = 0,213; p = 0,026 za čimbenike poticanja) valjanost, kao i pouzdanost i unutarnju dosljednost (Cronbachova alfa > 0,8). Dvije inačice upitnika omogućuju provođenje istraživanja u različitim skupinama zdravstvenih radnika s i bez privilegije propisivanja terapije (liječnici i ljekarnici), a jednaka pitanja i čimbenici omogućuju identifikaciju zajedničkih prepreka i poticatelja unutar istog zdravstvenog sustava. Većina ispitanika (87%) predložila bi depreskripciju terapije pacijentu, no ljekarnici pokazuju veću suzdržanost nego liječnici (12% naspram 3%; χ^2 (4) = 44,93; p < 0,001). Za oba uzorka ispitanika određeni su čimbenici povezani sa spremnošću na predlaganje depreskripcije terapije. Za ljekarnike, povezanost je utvrđena za sve čimbenike osim za čimbenik prepreka zdravstvenog sustava, a najizraženija povezanost utvrđena je za čimbenike poticatelja suradnje (G = 0,331; p < 0,001) i poticatelja zdravstvenog sustava (G = 0,309; p < 0,001). Za liječnike povezanost sa spremnošću na predlaganje depreskripcije terapije utvrđena je za čimbenike znanja (G = 0,446; p = 0,001), osviještenosti (G = 0,712; p < 0,001), poticatelja povezanih s pacijentom (G = 0,259; p = 0,043), te prepreka osobnih kompetencija (G = -0,343; p = 0,008). Rezultati studije prikaza slučaja pokazuju sljedeće: ljekarnici imaju potrebne kompetencije za prepoznavanje potencijalno neprikladnih lijekova te navođenje obrazloženja za depreskripciju terapije (1275 prijedloga za 16 lijekova), a liječnici su spremni prihvatiti ljekarnikov depreskripcijski prijedlog. Usprkos razlici u medijanu broja lijekova za koje bi liječnici i ljekarnici predložili depreskripciju terapije (deset naspram šest; U = 4124,50, z = -9,56, p < 0,0001) uočeno je slaganje u farmakoterapijskoj skupini lijeka (diuretici, nesteroidni protuupalni lijekovi, opioidni analgetici i benzodiazepini), što upućuje na mogućnost ostvarivanja uspješne suradnje liječnika i ljekarnika u depreskripciji terapije. Potencijal depreskripcije terapije određen je za 388 osoba starije životne dobi koje žive u zajednici, a koriste inhibitore protonske crpke, benzodiazepine, nesteroidne protuupalne lijekove i/ili opioidne analgetike, na temelju podatka prikupljenih ljekarnikovom procjenom zdravstvenog stanja osoba starije životne dobi te depreskripcijskih kriterija. Više od polovice ispitanika (55%) kandidati su za depreskripciju jednog ili više lijekova, od toga 31% korisnika inhibitora protonske crpke, 75% korisnika nesteroidnih protuupalnih lijekova ili opioida, te 96% korisnika benzodiazepina. Najčešće prepoznat kriteriji za depreskripciju terapije su neprikladno trajanje terapije, sigurnost (neželjeni događaji, interakcije i negativan utjecaj čimbenika rizika na pogoršanje zdravstvenog stanja), te neprikladna doza. Ženski spol (aOR = 2,58; 95% CI = 1,59 – 4,18; p < 0,001), politerapija (aOR = 1,29; 95% CI = 1,17 – 1,44; p < 0,001) i loša

samoprocjena zdravlja (aOR = 5,14; 95% CI = 1,73-15,25; p < 0,001) prediktivni su čimbenici za povećanu potrebu za depreskripcijom terapije. Uzimajući u obzir rezultate četiriju faza istraživanja predložena je implementacijska strategija te intervencijski protokol za kolaborativni pristup depreskripciji terapije osoba starije životne dobi u primarnoj zdravstvenoj zaštiti (engl. *Collaborating for Older aduLts to Deprescribe in primarY care (COLDY)*).

Zaključak: Pred-implementacijska formativna procjena potencijala, potreba i izazova depreskripcije terapije u zdravstvenom sustavu u kojem nije prepoznata, provođena i istraživana, otkriva jasnu potrebu za proaktivnom i reaktivnom depreskripcijom terapije u osoba starije životne dobi, identificira farmakoterapijske skupine kao depreskripcijske mete, razjašnjava potencijal javnog ljekarnika u predvođenju depreskripcijskih intervencija, te predstavlja alat za identifikaciju prepreka i poticatelja depreskripcije terapije unutar zdravstvenog sustava. Pacijentovo pozitivno mišljenje o ljekarnikovoj uključenosti u depreskripciju terapije podupire potencijalne ljekarnikom predvođene depreskripcijske intervencije, dok identificirani prediktivni čimbenici pomažu zdravstvenim radnicima u lakšoj identifikaciji potencijalnih depreskripcijskih kandidata. Navedeni rezultati ukazuju na potrebu za implementacijom depreskripcije na razini primarne zdravstvene zaštite, pri čemu su utvrđeni uvjeti za neophodan međustrukovni i kolaborativni pristup usmjeren na pacijenta. Rezultati također pridonose stvaranju alatom vođene implementacijske strategije koja će omogućit provođenje depreskripcijske intervencije s ciljem optimizacije farmakoterapije i poboljšanja ishoda.

KLJUČNE RIJEČI: depreskripcija terapije; primarna zdravstvena zaštita; liječnik; ljekarnik; pacijent; osobe starije živote dobi; sveobuhvatna gerijatrijska procjena; razvoj alata; formativna procjena; pre implementacijsko istraživanje

TABLE OF CONTENTS

1. INTRODUCTION

Polypharmacy has been associated with increased risk of prescribing unnecessary and inappropriate medications. It is considered that in primary care one in five medications is inappropriately prescribed (1). Use of potentially inappropriate medicines (PIMs), especially in older adults, has been associated with increased morbidity and mortality, and represents a serious public healthcare problem (2). Polypharmacy has also been linked to increased risk of negative outcomes such as adverse reactions, interactions, decrease in functional capacity, geriatric syndrome, increased healthcare expenditures, and loss of adherence to all forms of treatment (1,3,4). To combat this ever-growing problem healthcare providers have a number of approaches, one of them being *deprescribing*.

1.1. Definition of deprescribing

Deprescribing emerged in the early 2000s in Woodward's article on aspects of geriatric therapeutics in the Journal of Pharmacy Practice and Research (5). Throughout the development and evolution of deprescribing research and practice, many definitions were used, from "cessation of long-term therapy supervised by a clinician", to "medication withdrawal in older people" (6,7). In literature research one can use a variety of terms and characterizations to encompass identifying aspects of deprescribing, such as "withdrawal", "stopping", "cessation", or "discontinuation", but should have the understanding of the complexity of the deprescribing process (8). There is inconsistency in the descriptions of deprescribing, with scientists and clinicians still not having reached a consensus on what does or does not constitute deprescribing (9).

Reeve and colleagues proposed the following based on an extensive systematic review: *Deprescribing is the process of withdrawal of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes* (8). Another definition states: *Deprescribing is the planned and supervised process of dose reduction or stopping of medication that might be causing harm, or no longer be of benefit* (9–12).

Inclusion of *dose reduction* in the definition of deprescribing can be viewed as problematic, as some might consider dose reduction only as an aspect of medication optimisation (9). Other state that deprescribing can be viewed as a pharmacotherapeutic optimization concept, which includes dose reduction as well (13). Choice of definition can depend on the patient in question, type of deprescribing intervention, medication of interest, or clinical setting (14). For instance deprescribing through dose reduction can lead to less adverse effects while achieving the benefit

for the patient, which is one of the most important attributes of deprescribing. For those who research and/or provide deprescribing in the clinical setting it is important to justify the choice of definition, so that it appropriately reflects the chosen outcomes, benefits and potential harms of deprescribing, as well as ensures findings can be reported, summarised, and replicated in other settings.

For the purposes of this research a combined definition was used. *Deprescribing is the planned and supervised process of dose reduction or tapering, and stopping of medication, which might be causing harm, or is no longer of benefit to the patient, with the goal of managing polypharmacy and improving outcomes.*

The concept of deprescribing should be distinguished from other concepts of pharmaceutical care such as medication simplification, therapeutic substitution, withholding medication, or medication non-adherence (9).

Medication simplification includes interventions to manage complex medication regimens associated with polypharmacy, and aims at reducing the complexity without changing the therapeutic intent. For example, medication simplification can include use of poly-pill to reduce the number of single drug medications, or use of extended release medications to reduce the number of doses. This is in contrast to deprescribing where the intent is to change the therapy.

Therapeutic substitution involves withdrawing or stopping one medication to introduce or begin another, with intent to change to a more appropriate medication, reduce costs or potential side effects, but does not intent to reduce medication use, as it is in deprescribing. For example, therapeutic substitution can include changing one antihypertensive for another due to adverse effects the patient is experiencing. In cases where deprescribing can lead to adverse drug withdrawal effects (ADWE), healthcare providers may try short-term therapeutic substitution to aid in deprescribing, changing the deprescribing target to a more suitable medication before commencing with medication withdrawal (15).

Withholding medication intends for a period without medication to be temporary (*i.e.*, withholding due to acute illness), and after the defined interval has passed to reinstate the medication. In deprescribing reinstatement of medication is intended if the original condition has returned.

Medication non-adherence is not an intervention, but a patient's unilateral decision to stop medication without consultation with a healthcare provider. Medication non-adherence,

especially intentional non-adherence, can be an important sign for a healthcare provider to initiate a conversation on patient's perspective of pharmacotherapy and treatment choices, and if appropriate suggest deprescribing.

Finally, deprescribing, as a collaborative process involving the patient and/or their carer, guided by a person-centred approach and shared decision-making, is an essential part of good prescribing and does not represent denying or withholding medication to patients who need them.

1.2. Principles of deprescribing

Deprescribing can be an appropriate action in a number of clinical situations. Clinical triggers for deprescribing include polypharmacy, prescribing cascades, adverse drug effects or reactions, changes in treatment strategy or goals (following hospital or residential care admissions, palliative or end-of-life care), changes in physical or mental status (disability, falls, delirium or cognitive impairment), and among other "legacy prescribing" (medications prescribed for intermediate duration, but are unintentionally continued indefinitely) (16–18).

Deprescribing should be considered as a part of standard patient care and medication review. In literature, the concepts of *reactive* and *proactive* deprescribing are being distinguished. Reactive deprescribing is discontinuing medication as a response to an adverse clinical trigger (*i.e.* patient presents with an adverse drug reaction). Continuing such therapy would be unethical and negligent. Proactive deprescribing takes into considerations future potential negative consequences of medication use, such as increased harms and/or reduced benefits (19,20).

A stepwise approach is recommended when considering deprescribing to ensure the process is patient-centred and achieves the best possible outcome (16,21,22). To provide deprescribing the following steps can be applied:

- CONSIDER THE PATIENT- patient determinants, goals and expectations, preferences and attitudes towards medications or treatment, and health in general
- MEDICATION HISTORY- complete a comprehensive medication history including prescription, over-the-counter medication, as well as supplements, complementary and alternative medications
- IDENTIFY POTENTIAL DRUG TARGETS- determine the usefulness of every medication, as well as the likelihood of any harm caused by continuous use of

medication. Assess medications based on risk: benefit ratio, indication (symptomatic *vs*. preventive medications), dose appropriateness, potential clinically significant drug-drug interactions, prescribing cascades, and safety concerns.

- DETERMINE CESSATION PRIORITY- determine medication with lowest utility: highest risk ratio for the patient in question, complexity of deprescribing process for the medication in question (requiring tapering or not, or likelihood of disease rebound) taking into account the impact on patient's wellbeing as well as patient's preferences
- PLAN AND WITHDRAW- obtain consent from patient or carer, explain the rationale and steps of deprescribing, prepare a written tapering plan if necessary
- MONITOR, SUPPORT, AND DOCUMENT- follow up on the withdrawal plan to assess potential adverse effects, symptom return, as well as efficacy and health related improvements. Patient's feedback should be documented alongside with monitored outcomes.

Principles of deprescribing and their application is not one-off proposal, but rather should be routinely recommended to patients as a part of standard care on all levels of healthcare.

1.3. Determinants of deprescribing

Besides following the principles of deprescribing it is important to take into consideration determinants (patient, healthcare provider, healthcare system) which can affect the provision of deprescribing.

Deprescribing represents a new domain of pharmaceutical care, based on shared-decision making. *Shared-decision making* is the process of clinicians and patients participating jointly in making a health care decision, having discussed evidence based treatment options (including no treatment), the possible benefits and harms of each option, taking into consideration the patients' individual preferences and values (23). Shared-decision making, therefore, encompasses both patient centred care and informed consent. Healthcare system stakeholders should recognise and introduce deprescribing as a positive intervention aimed to improve, not only clinical outcomes, but outcomes important to the patient in question.

Different models are available which explore determinants of deprescribing, majority of them using the theoretical domains framework and/or the behaviour change wheel framework (24–29). Patient determinants can be presented as patient typology regarding treatment and medication- related decisions, or viewed as clinical, psychological, social, financial, and physical factors influencing the decision-making process (30,31). Healthcare provider

determinants are influenced by intrinsic and extrinsic factors such as skills and cognition, social interactions, influences and consequences, as well as resources and environmental context (25). For both patients and healthcare providers, influences on drivers of behaviour change, such as capability, opportunity and motivation, can be used to impact determinants important for acceptance of deprescribing. Healthcare culture, priorities and goals, incentives, resources, legislation, and costs are main determinants of healthcare systems when it comes to deprescribing. Healthcare system determinants can be modified and influenced by outcomes resulting from changes in patients' and healthcare providers' determinants.

1.4. Overview of deprescribing tools

To aid in deprescribing, healthcare providers are presented with a number of tools (33,34). Tools can be classified as those that aid in the overall process of deprescribing and those that guide or help with a specific part of the process (34). Overview of subclasses of tools can be seen in Figure 1.

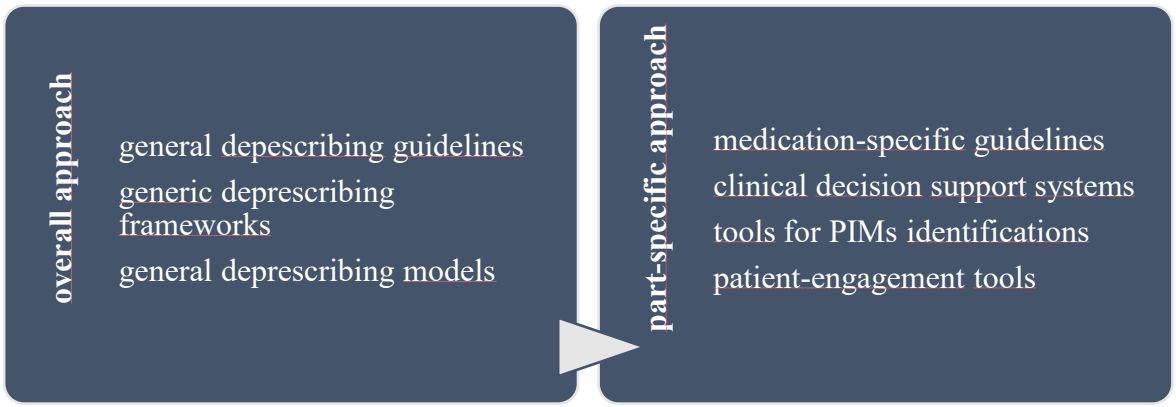

Figure 1 Overview of deprescribing tools

General deprescribing guidelines, such as national or international position papers and reports, provide guidance on most steps in the deprescribing process, are useful as educational resources, and can be used as a valuable introduction to the concept of deprescribing (10,33,35–38). *Generic deprescribing frameworks and/or models,* in a stepwise approach, consider the whole patient and medication list. Differences in frameworks lie in the emphasis to detail on certain steps. For instance, some frameworks provide detail on medication identification, while others focus on other aspects of deprescribing such as the patient-centred context. Use of these implicit judgement-based tools will depend on clinician's skills and knowledge. Examples include, 5-step frameworks (*i.e.* CEASE or ERASE) (10,15,21), The Deprescribing Rainbow framework (32), or The Novel Comprehensive Conceptual framework (12). Additional implicit tools which can provide guidance in clinical decision making are the MAI-medication

appropriateness index (39) and Good-Palliative-Geriatric Practice algorithm (40), which have been shown to be straightforward in the identification of potentially inappropriate medications, but painstaking and time-consuming for the clinician. Limitations of implicit tools include use in the research setting and lack of evidence for use in everyday practice (13,34,41).

Numerous *medication-specific guidelines* are available to healthcare providers with evidence-based advice on when and to whom to suggest deprescribing (42–44). Guidelines are available for most common deprescribing targets such as benzodiazepines (BZN), anticholinergics, proton pump inhibitors (PPI), non-steroidal anti-inflammatory drugs (NSAID), antipsychotics, antihyperglycemics, cholinesterase inhibitors, opioid analgesics (OPI), bisphosphonates, antiplatelets, anticoagulants, or antihypertensives (AHTN). With increasing evidence on deprescribing other medication classes, it is expected additional guidelines will become available to clinicians. Deprescribing tools should ideally be integrated into clinician's everyday workflow, and readily available to be used at points of care. With widespread use of electronic medical records and electronic prescribing, electronic *clinical decision support systems* for deprescribing are being developed to aid, or guide deprescribing activities. These include MedSafer (45), TaperMD (46), MedStopper (47), MediQuit (48), De-TOPPLE (49), or G-MEDSS (50) to name a few. Clinical decision support systems can speed-up and address multiple aspects of the deprescribing process, but limitations include "alert fatigue", inability to extract and interpret entered clinical information, and limited geographic availability.

Explicit criteria and tools, give criterion-based and drug-specific advice, and are available to aid in *identification of potentially inappropriate medications* (*i.e.* START/STOPP criteria, STOPPFrail, STOPPFall, Beers criteria, PRISCUS list, EU-PIM-7 list, LESS-CHRON, EURO FORTA) (51–58). Limitations of such tools include potential lack in utility in deprescribing, as they lack considerations of important patient characteristics, are often missing evidence of association with clinical outcomes, and lack details on how to deprescribe (34). Regardless, tools for PIMs identifications are often used in deprescribing decision-making.

Patient-engagement tools mostly represent patient education materials such as fact sheets and brochures (42), and are mostly used in research settings (59). Majority of tools provide general support for deprescribing, while medication-specific tools are aimed at benzodiazepines, anticholinergics, and proton-pump inhibitors (60). Patient-engagement tools need to be adapted to average patient's health literacy levels to have value in everyday practice. Additionally,

validation of such tools is needed to ensure appropriate comparison between different populations is possible.

With the development and increasingly widespread use of artificial intelligence models (AI) in healthcare, different hybrid and augmented decision-support systems, models, and approaches using AI are being developed and used in the pharmacy practice as well. Promising applications of AI in the pharmacy practice include identification and reduction of medication errors and drug therapy problems, aid in medication review and prescribing optimisation, and/or analysis of large data and use of machine learning techniques for identification of patterns and trends important for decision-making (61,62). It can be predicted that AI will play an important role in further development and advancement of pharmacy practice, including the deprescribing approach as well, but it is pivotal to consider the potential ethical, legal, and regulatory aspects during its integration into everyday practice.

1.5. Effectiveness of deprescribing

Evidence on effectiveness of deprescribing has been gathered through heterogeneous types of studies and settings, including occasional interventional randomized controlled trial, quasi-experimental, and observational studies performed in hospital, long-term care, and community settings.

In meta-analysis and systematic reviews it has been proven that deprescribing interventions in hospitals and long-term care facilities (*i.e.*, nursing homes, residential care facilities) positively affects several outcomes. Noticeable effects include reduction in number of potentially inappropriate medications, reduction in number of falls (injurious falls), reduction in anticholinergic drug burden, increase in functional status of the elderly, and reduction in healthcare costs (63–67). Mixed results were found for the effect on number of rehospitalizations and emergency department visits, mortality (with reduction trend), quality of life (with trend towards increase).

In hospital setting a comprehensive multidisciplinary deprescribing approach (including pharmacist as intervention leader, nurses, general physicians, specialist physicians, and geriatricians) leads to reduction in number of prescriptions, and in number of doses of potentially inappropriate medications (68). Similarly, deprescribing through physician-led medication review led to decrease in use of potentially inappropriate medication in frail older adults living in a nursing home (69). Furthermore, the “DEFEAT-polypharmacy” feasibility trail describes a successful pharmacist-led deprescribing intervention in long-term care

facilities. An exceptionally high percentage of residents (96%) agreed with deprescribing recommendations, and more than 70% of pharmacists' recommendations were accepted and implemented. Intervention resulted in decrease in anticholinergic drug burden index, reduction in number of falls, and reduction in adverse drug reactions. Residents reported lower depression scores post-deprescribing interventions, as well as scored lower on frailty score. There was no improvement in quality of life or cognition (70). Quality of life was reported as secondary outcome in most studies and results vary (63). In nursing homes pharmacist-led medication review with deprescribing can have a positive effect on quality of life of patients living with dementia (67).

Deprescribing medications resulted in reduction in number of falls and injurious falls in hospitalised patients, but same was not found for patients in nursing homes. Pharmacists medication review-oriented deprescribing intervention can help lower the number of nursing home patients who experience a fall, by 24% (66).

Limited evidence is available in regard to economic evaluations of describing in secondary or tertiary settings. Interventions oriented on deprescribing medications are cost-effective, through lowering both direct (reduction in cost of medications) and indirect costs (reduction in costs of healthcare utilization) (70). Further healthcare economic evaluations are needed to assess the effect for deprescribing on healthcare costs in both long-term and hospital settings.

In primary healthcare setting deprescribing can be led by pharmacists and/or physicians (58,71,72). In primary healthcare, pharmacists can greatly contribute to pharmacotherapy rationalisation, and lead reactive and proactive deprescribing interventions. Pharmacists can recognise potential candidates, suggest deprescribing protocols to patients and prescribers, monitor and follow-up patients, and document outcomes. Actively involving pharmacists in deprescribing would ensure the needed multidisciplinary approach. Interventions such as pharmacists' patient education or pharmacists' medication review were particularly successful (73–75).

Outcomes reported in studies involving deprescribing in primary healthcare included changes in number of prescriptions, changes in number of potentially inappropriate medications, adherence, quality of life, anticholinergic drug burden, falls and injurious falls, adverse drug withdrawal events, hospitalisations and emergency department visits, and effect on healthcare costs.

Most noticeable positive effect of deprescribing in primary care is in regard to reduction in use of PIMs. All types of interventions, and all types of studies show that deprescribing leads to reduction in use of medications and especially PIMs, reduction in prescribing of PIMs, and reduction in tablet load (total number of tablets a patient takes daily) (76). Deprescribing positively effects patient's adherence, specifically pharmacist-led deprescribing interventions led to increase in adherence in older adults exposed to polypharmacy (75). When it comes to incidence, number, or injuries related to falls (including hospitalisations and emergency department visits), deprescribing interventions did not lead to statistically significant changes (77,78). On the other hand, pharmacist's comprehensive medication review and deprescribing lead to reduction in use of anticholinergic medication and anticholinergic side effects. Pharmacist-led deprescribing of anticholinergics is safe and effective in vulnerable patient groups, such as those with severe mental illnesses or dementia, and leads to increase in quality of life and positively affects cognitive functions (79–81).

Limited evidence on economic evaluations of deprescribing in primary healthcare indicate that deprescribing interventions are cost effective, but further research is needed (82).

1.6. Need for deprescribing research

Healthcare systems of developed countries confirm the benefits and advantages of deprescribing by establishing professional societies, organizations, and networks dedicated to deprescribing, its research and implementation into healthcare systems. The most prominent ones are CaDeN (Canadian Medication Appropriateness and Deprescribing Network), ADeN (Australian Deprescribing Network), EDeN (English Deprescribing Network), NERD (Network of European Researchers in Deprescribing), and USDeN (US Deprescribing Research Network).

In Europe, deprescribing in primary care is coming into research focus in the last couple of years, with a small number of published research by Scandinavian researchers (74). As deprescribing as a topic is gaining visibility and importance, it is expected researchers across Europe will contribute to the scientific dialogue on all aspects of deprescribing.

At the moment there is no data regarding deprescribing for Croatia, central, and eastern Europe. In Croatia deprescribing is not defined neither as a part nor a complete diagnostic-therapeutic service by the Croatian health insurance fund (83). There are no available national or pan-European guidelines, initiatives, or recommendations which would encourage systematic

implementation, conducting, documenting, or sustaining deprescribing as a valuable approach to combat inappropriate polypharmacy.

In 2020 European Commission and Council of Europe adopted a resolution on the implementation of pharmaceutical care for the benefit of patients and health services (84). In healthcare systems with developing pharmaceutical care before implementation of a new service or intervention, it is crucial to identify all factors influencing the provision of such service. Besides the development of policy and legislative framework, it is vital to examine the opinions, preferences, and attitudes of all stakeholders involved, as well as explore all barriers and facilitators influencing implementation. This is especially important for deprescribing as a patient-centred service (12).

A position paper by Thompson et al. states a number of deprescribing research priorities (85). While there is evidence on effectiveness of deprescribing gathered from clinical trials, informative, high-quality clinical trial of broad patient-centred deprescribing interventions, as well as targeted medication-specific withdrawal trials are still needed (85). There is a need for development, consensus and application of a core outcome set for deprescribing research, including measurements for downstream effects of deprescribing, such as re-prescribing or need of therapeutic substitution (86). When randomized controlled trials are not feasible, researchers suggest utilizing pharmacoepidemiological methods and pragmatic trails, which can be useful in brining real-world data to focus (85,86).

Researchers from countries with well-developed pharmaceutical care (United Kingdom, Australia, Canada, United States of America) find that special focus and interest should be given to research on implementation of deprescribing in primary care (87,88). There is lack of research on barriers and facilitators of deprescribing in healthcare systems with developing pharmaceutical care, as well as need for research on deprescribing in central and eastern European countries.

Research needs to focus on identifying patient groups that are most likely to benefit from deprescribing. Patients' perspective is another focal point requiring additional research. Evidence, knowledge, and data are needed on how to engage patients in shared-decision making regarding deprescribing, how deprescribing aligns with patient preferences, treatment goals, and values (85). Currently, there is lack of research and evidence on the need for deprescribing of medications in older adults, as well as lack of research on patients' opinions and attitudes towards pharmacists' involvement in deprescribing. Research is needed into deprescribing

roles, respectively to contribution of each individual healthcare provider (85). There is lack of research on community pharmacists' and primary care physicans' opinions, attitudes, and preferences of pharmacists' involvement in deprescribing, as well as lack of research and evidence on the readiness to accept community pharmacists deprescribing suggestions (89), even though there is evidence that pharmacist-led deprescribing interventions are successful (9,66,75,90).

Finally, there is lack of evidence on pharmacoeconomic aspects of deprescribing, especially when it comes to cost-effectiveness of implementing deprescribing into different levels of different healthcare systems.

2. HYPOTHESIS AND AIM

2.1. Hypothesis

In primary care a substantial proportion of patients, especially older adults, are using potentially inappropriate medications. Patients, community pharmacists and primary care physicians are willing to accept deprescribing as a new aspect of patient care in order to decrease the use of potentially inappropriate medications.

2.2. Main aim

The main aim of this research is to examine the need for, and the barriers and facilitators of deprescribing in primary care in a healthcare system where it has not been researched, implemented, or provided.

2.3. Specific aims

The following specific aims intend to provide a comprehensive approach to the research questions, and include:

- systematically review available evidence on community-based pharmacists' role in deprescribing, evaluating clinical and humanistic outcomes
- to examine patients' opinions and attitudes towards deprescribing and identify factors which can influence their willingness to have medications deprescribed
- to develop and validate a tool which can assess knowledge, opinions, and attitudes of physicians and pharmacists in primary healthcare towards deprescribing, and identify barriers and facilitators of deprescribing
- to evaluate the level of agreement on deprescribing suggestions between pharmacists and physicians in primary healthcare
- to evaluate the need for deprescribing on a sample of community-dwelling patients 65 years and older in primary healthcare

3. MATERIALS AND METHODS

Research on potential for deprescribing in primary care, which assesses the needs and challenges, has been carried out in four phases which enabled a comprehensive approach to the topic, and ensured all the important stakeholders (patients, pharmacists and physicians in primary healthcare) were involved.

Figure 2 depicts the four research phases, while a detailed description of methodology, inclusion and exclusion criteria, participants, and outcome measures can be found in paragraphs bellow.

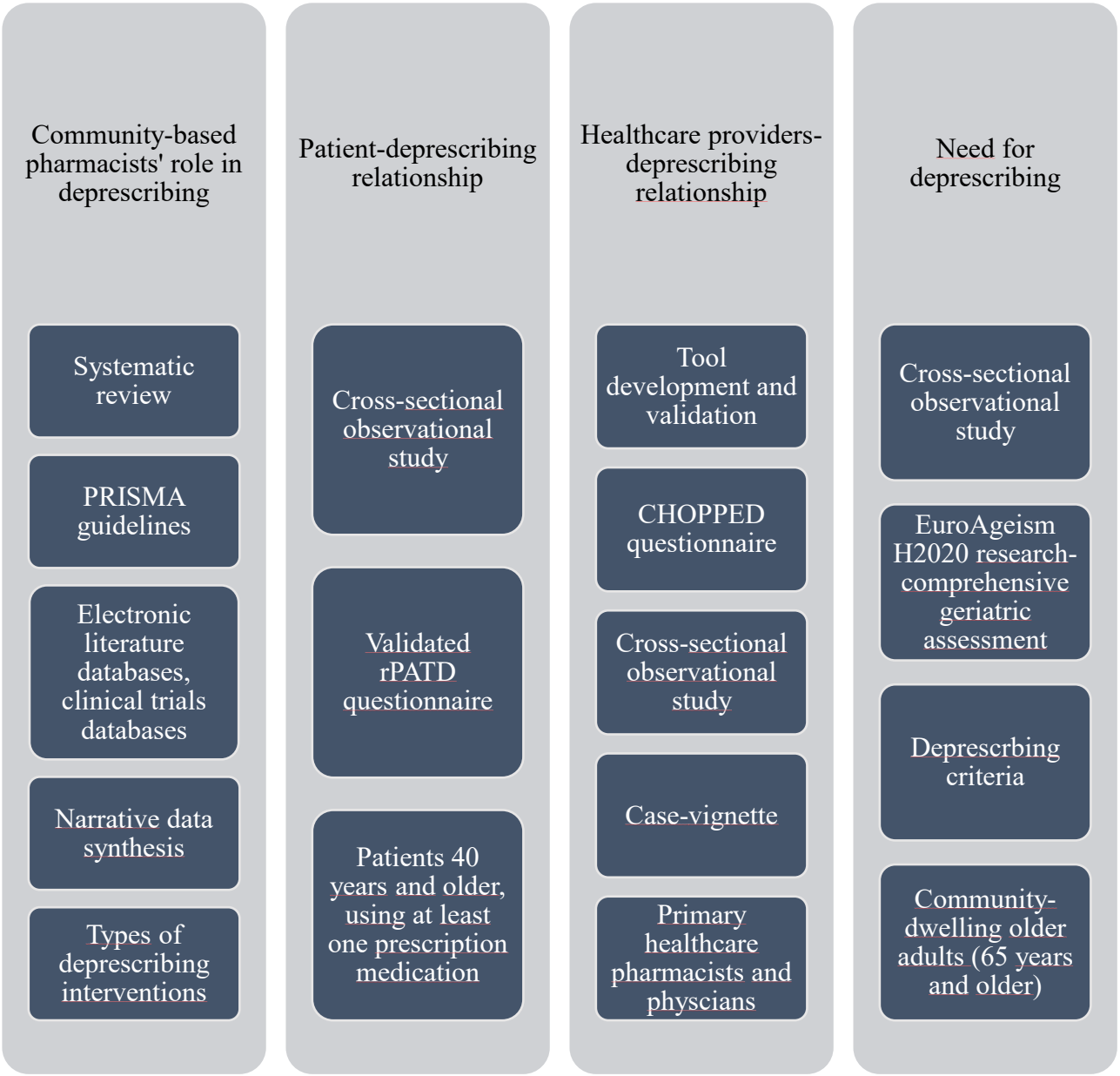

Figure 2 Four phases of research

3.1. Systematic review of evidence on the effectiveness of deprescribing

Methodology: Preferred Reporting Items for Systematic Reviews and Meta Analysis guidelines (PRISMA guidelines) was applied for conducting the systematic review (91). Available electronic literature databases (Embase, PubMed, Scopus, Web of Science) as well as clinical trial databases (Cochrane Central Library, International Clinical Trials Registry Platform, the European Union Clinical Trials Register and ClinicalTrials.gov) were searched for research on deprescribing interventions led by or involving a pharmacist in primary healthcare.

Inclusion and exclusion criteria: Original research articles, published in English, and studies involving community-based pharmacists, reporting clinical and humanistic outcomes were included. Abstracts, opinions, study protocols and/or poster presentations were excluded, as well as studies performed in residential care facilities, nursing homes, hospitals or other long-term care facilities. Earlier systematic reviews, meta-analysis and selected articles were also cross-checked to identify potential studies or articles. Four researchers (three junior researchers and one senior researcher) participated in the reviewing inclusion and exclusion criteria, with junior researchers independently performing title and abstracts screening. Differences which arose during study screening and selection were resolved through consensus and consultation with the senior researcher.

Data extraction: One pair of researchers (two junior researchers), using a pre-arranged template, independently extracted data which included information on author, methodology and study duration, study setting and participant characteristics, type of intervention, measured outcome, and results. Additionally, an overall assessment of results was performed, and studies were evaluated as reporting a positive or negative impact on the outcomes.

Risk of bias assessment: Second pair of researchers (two junior researchers) independently critically assessed the risk of bias, using the "The Joanna Briggs Institute Critical Appraisal Tools" which enables assessment of methodologically different studies, including experimental and observational studies, as well as economic evaluations and quasi-experimental studies (92). Differences which arose during risk of bias assessment were resolved through consensus and consultation with the senior researcher.

Outcome measures: Results were grouped based on intervention type and clinical outcomes, such as reduction in number of prescriptions, reduction in dose, number of accepted

pharmacist's suggestions and interventions, change in number of falls, and changes in quality of life.

The review was registered with PROSPERO (International prospective register of systematic reviews, Centre for Reviews and Dissemination, University of York) under identifier CRD42020177525 where one can find the detailed description of all the determinants of the systematic review (searches, databases, key words, MeSH terms, types of included studies, participants, interventions, control group, outcomes of selected studies, data extraction methods (selection and coding), assessment of data quality (risk of bias), strategy for data synthesis)(93).

3.2. Exploring patients' attitudes and opinions towards deprescribing

Methodology: A cross-sectional observational study using a validated questionnaire. The questionnaire is composed of three parts. First part consists of sociodemographic questions. Second part is the cross-culturally adapted Croatian version of the validated rPATD questionnaire with 22 questions (two global questions and four deprescribing factors) (94). Each question within rPATD uses a 5-point Likert scale, from "strongly disagree" to "strongly agree" as possible answers. The permission to use and translate the rPATD questionnaire was given in writing by the author. This information was stated in a footnote on the questionnaire given to participants. Following the Brislin translation model, the questionnaire was translated into Croatian and then back-translated to English to ensure no loss of meaning. The third part of the questionnaire contains of five questions regarding patients' perspective of pharmacists' involvement in deprescribing, and preferences on potential deprescribing of specific medications.

Setting: Community pharmacies across Croatia. Community pharmacists recruited potential participants while dispensing prescriptions or counselling on the use of prescription medications. Informed consent and questionnaires were given to interested participants, who were able complete the questionnaire at home or at the pharmacy. Participants were selected randomly.

Participants: Inclusion criteria was age 40 years and older and the use of at least one prescription medication long term, and exclusion criteria was patients living with dementia or other conditions affecting the ability to provide reliably information.

Outcome measures: Attitude towards deprescribing expressed as deprescribing factors (appropriateness of medications, burden of medications, concerns about stopping, and

involvement factors), preferences towards pharmacist's involvement in deprescribing, preferences on potential deprescribing of specific medications.

3.3. Exploring community pharmacists' and primary care physicians' opinions, preferences and attitudes towards deprescribing

Based on extensive literature review it has been determined that there was a lack of developed tools which adequately explore healthcare providers' opinions and attitudes towards deprescribing (95,96), therefore this phase of research was divided into two sub-phases. The first sub-phase aimed to develop and validate a tool, and the second sub-phase aimed to explore healthcare providers' opinions, preferences, and attitudes towards deprescribing using the aforementioned tool.

3.3.1. Tool development and validation

Methodology: A thorough literature review was conducted to identify key concepts, themes and factors of deprescribing which were used as prompts for structured interviews (focus groups and expert opinions) with community pharmacists and primary care physicians. Data collected from the interviews and literature review was used to form a preliminary comprehensive questionnaire.

Validation analysis: For validation purposes face, content, construct, and criterion validity was determined. The reliability of the final versions of questionnaire was assessed by determining internal consistency (Cronbach's alpha) of the questionnaire and performing a test–retest.

3.3.2. Cross-sectional observational study

Methodology: A cross-sectional observational study conducted via an online survey. Survey was comprised of three parts. First part of the survey consisted of sociodemographic questions (age, sex, professional experience, practice characteristics, number of older patients provided healthcare). Second part explored knowledge and awareness, willingness, and barriers and facilitators of deprescribing using the aforementioned validated questionnaire. Each question within the second part of the questionnaire uses a 5-point Likert scale, from "strongly disagree" to "strongly agree" as possible answers. Third part of the questionnaire utilised a *case-vignette* based on a real-life patient. Link to the online questionnaire was sent via email to community pharmacists and primary care physicians via professional affiliations (Croatian chamber of pharmacists and Croatian medical chamber). Participants were asked to forward the link to the questionnaire to colleagues who might be interested in participating. Informed consent form

was included in the survey and set as a required response to ensure all participants are informed on all aspects of the study. Potential participants who did not digitally authorise the informed consent were not able to access the survey**.**

Participants: Primary care physicians and community pharmacists with a valid licence to practice in the primary care setting. Exclusion criteria were participants who did not digitally authorise the inform consent or who did not complete the survey.

Outcome measures: Opinions, attitudes, knowledge and awareness of deprescribing, perceptions of barriers and facilitators of deprescribing, agreement between pharmacists and physicians on deprescribing suggestions (*case-vignette*), qualitative analysis of pharmacists' deprescribing rationales.

3.4. The potential and need for deprescribing in older patients

Methodology: A sample of older patients whose data were collected from a multinational, non-interventional, cross-sectional study "*Inappropriate prescribing and availability of medication safety and medication management services in older patients in Europe*" within the EuroAgeism H2020 project. Questionnaire used in the EuroAgeism H2020 project collected sociodemographic data, and enabled a comprehensive geriatric assessment using data on lifestyle, nutritional status, mobility and strength, activities of daily living, frailty, cognitive status, information on healthcare utilization, symptoms, diagnoses, and pharmacotherapy. Deprescribing criteria were formed based on available prescribing and medication-specific deprescribing guidelines. Data from the comprehensive geriatric assessment and deprescribing criteria were used to assess the appropriateness of medications, and the need for deprescribing.

Setting: Community pharmacies in three Croatian regions (City of Zagreb, Istria and Kvarner, and Slavonia).

Participants: Community-dwelling older adults (65 years and older) using at least one medication. Participants with sever communication disabilities (unable to hear or talk), dementia, acute worsening of health (hospitalisation within the last three days), or unwilling to sign the informed consent were excluded from the study.

Outcome measures: Number and type of medications potentially needing to be deprescribed, patient characteristic associated with the need for deprescribing.

3.5. Statistical analysis

All statistical tests were performed at a significance level of 95% (α=0.05). Shapiro-Wilk test was used to examine the normality of data distribution. Sociodemographic data were analysed using descriptive statistics such as frequencies or percentages, and depending on data distribution, either mean and standard deviation, or median and interquartile range were used. Statistical test included $\chi 2$ (differences between groups based on gender, age, number of medications, profession, location,…), Mann-Whitney U test (differences in CHOPPED factor scores between healthcare professions), Spearman's ρ (relationship between patients' deprescribing factor scores and global questions from the rPATD questionnaire) or Gamma rank (association between CHOPPED factors scores and willingness to deprescribe) correlation, and regression analysis (binary logistic regression to determine potential predictive factors or characteristics). Exploratory factor analysis, CVR, Cronbach's alpha, and linear-weighted Cohen's kappa, were used for assessment of validity and reliability of the CHOPPED questionnaire while Cronbach's alpha and intraclass corelation coefficient were used to assess the reliability of the Croatian version of the rPATD questionnaire. Qualitative conceptual content analysis was used to explore pharmacists' deprescribing suggestions in the case vignette study.

4. COMMUNITY-BASED PHARMACISTS' ROLE IN DEPRESCRIBING: A SYSTEMATIC REVIEW

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REVIEW ARTICLE

Community-based pharmacists' role in deprescribing: A systematic review

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Aims: Community-based pharmacists are an important stakeholder in providing continuing care for chronic multi-morbid patients, and their role is steadily expanding. The aim of this study is to examine the literature exploring community-based pharmacist-initiated and/or -led deprescribing and to evaluate the impact on the success of deprescribing and clinical outcomes.

Methods: Library and clinical trials databases were searched from inception to March 2020. Studies were included if they explored deprescribing in adults, by community-based pharmacists and were available in English. Two reviewers extracted data independently using a pre-agreed data extraction template. Meta-analysis was not performed due to heterogeneity of study designs, types of intervention and outcomes.

Results: A total of 24 studies were included in the review. Results were grouped based on intervention method into four categories: educational interventions; interventions involving medication review, consultation or therapy management; predefined pharmacist-led deprescribing interventions; and pharmacist-led collaborative interventions. All types of interventions resulted in greater discontinuation of medications in comparison to usual care. Educational interventions reported financial benefits as well. Medication review by community-based pharmacist can lead to successful deprescribing of high-risk medication, but do not affect the risk or rate of falls, rate of hospitalisations, mortality or quality of life. Pharmacist-led medication review, in patients with mental illness, resulting in deprescribing improves anticholinergic side effects, memory and quality of life. Pre-defined pharmacist-led deprescribing did not reduce healthcare resource consumptions but can contribute to financial savings. Short follow-up periods prevent evaluation of long-term sustainability of deprescribing interventions.

Conclusion: This systematic review suggests community-based pharmacists can lead deprescribing interventions and that they are valuable partners in deprescribing collaborations, providing necessary monitoring throughout tapering and post-follow-up to ensure the success of an intervention.

KEYWORDS
community pharmacist, community-based pharmacist, cost evaluation, deprescribing, medication, outcomes, systematic review

1 | INTRODUCTION

Community-based pharmacists are an important stakeholder in providing continuing care for chronic multi-morbid patients, and their role is steadily expanding. The usefulness of pharmacy services has been established for older patients, patients with polypharmacy, and patients taking potentially inappropriate medications (PIMs). Interventions by pharmacists have been proven to reduce cost of care, contribute to safe and effective use of medications, increase adherence and positively affect disease control.[1,2] Nonetheless, polypharmacy, adverse medication events, and unplanned hospitalisations due to medication use are on the rise.

Deprescribing is defined as the process of withdrawal of an inappropriate medication, supervised by a healthcare professional, with the goal of managing polypharmacy and improving outcomes.[3] The benefits of deprescribing interventions involving pharmacists have been proven for patients in both hospital and long-term facilities such as nursing homes. Reduced costs, better adherence, lower incidence of polypharmacy and reduced pill burden have been reported.[4] As deprescribing continues to rise as a focal point of pharmacy research and practice, it is important to review existing data emerging from community-based pharmacists. The aim of this review is to systematically examine the literature exploring the practice of deprescribing initiated and/or led by community-based pharmacists and to evaluate its efficacy and impact on clinical outcomes. The specific research questions are as follows: Can a community-based pharmacist successfully lead and/or initiate deprescribing in the community setting? How does pharmacist-initiated deprescribing affect clinical outcomes?

This study seeks to highlight that evidence from primary care is essential as community-based pharmacists are the most accessible healthcare providers, and their contribution to medicine optimization in terms of deprescribing could prevent the negative outcomes of potentially inappropriate drug usage in a wide population.

2 | METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist and guidelines were followed in conducting and reporting this systematic review.[5] The review is registered with PROSPERO under CRD42020177525.

A comprehensive, systematic literature search was performed by one investigator (I.B.). Electronic literature databases including Web of Science, EMBASE, PubMed/Medline, and Scopus were searched from inception until March 2020. The searched terms included the following: "deprescribing medication", "medication withdrawal", "discontinuing medication", "stopping medication", "reducing medication", "pharmacist", "community pharmacist", "community-based pharmacist" (see Appendix S1 in the Supporting Information). Only original research articles were included. Conference abstracts, opinions, study protocols and poster presentations were excluded. Bibliography and reference lists of systematic reviews, meta-analysis and selected articles were cross-checked to identify additional studies or articles. Clinical trials databases (Cochrane Central Library, International Clinical Trials Registry Platform, the European Union Clinical Trials Register and ClinicalTrials.gov) were also explored in order to include completed and published trials for evaluation. The search was limited to articles available in English and studies conducted in adults 18 years and older. Studies performed in residential care facilities, nursing homes, hospitals or other long-term care facilities were excluded.

2.1 | Selection of studies and outcomes

Three investigators (I.B., M.D. and I.K.) independently screened titles and abstracts for relevant studies. Studies that explored deprescribing in a community setting by a community-based pharmacist were eligible for inclusion, irrespective of methodology. We define a community-based pharmacist as a healthcare professional working in the primary care setting, regardless of their designation (community pharmacist, clinical pharmacist, consultant pharmacist), with a special focus on pharmacists working in community pharmacies. To gain comprehensive insight into community-based pharmacists' role in deprescribing, all health-related outcomes resulting from deprescribing interventions were extracted (i.e., change in medication number, dose reduction, change in cognitive status, number of accepted pharmacist recommendations, rate of falls, reduction in cost, impact on quality of life [QoL]). Two reviewers (I.B. and M.D.) extracted data independently and used a pre-agreed data extraction template (see Appendix S2 in the Supporting Information). The template consisted of author (year), methodology and study duration (length of follow-up), study setting and participant characteristics (number and age of participants), type of intervention (method of intervention), measured outcome (primary and/or secondary), results and overall assessment of results (positive or negative).

2.2 | Assessment of risk of bias

Two reviewers (I.B. and I.K.) independently assessed the risk of bias. The Joanna Briggs Institute Critical Appraisal Tools were used to evaluate risk of bias in individual studies for all selected studies (see Appendix S3 in the Supporting Information). This tool was used as it provides critical appraisal checklists for all types of studies including economic evaluations, quasi-experimental studies (QES), randomised controlled trials (RCTs) and cohort studies.[6–8] To appraise the risk of bias across studies, RCTs and QES were evaluated across five domains, including selection bias (two questions in RCT, one question in QES), performance bias (five questions in RCT, four questions in QES), attrition bias (one question in both RCT and QES), detection bias (four questions in RCT, two questions in QES) and reporting bias (one question in both RCT and QES). Cohort studies were appraised in three domains: selection bias (one question), information bias

(eight questions), and confounding (two questions). For each domain, the following criteria were determined. If one or more questions within a domain were assessed as unclear, the overall domain risk was moderate. If one or more questions were assessed as high-risk, the overall domain risk was high. If a combination of unclear and high-risk assessments was presented, then the overall domain risk was assessed as high. If one or more questions were assessed as not applicable, the overall domain risk was assessed based on other questions within the domain. For overall study risk appraisal, the following principles were established. If one or more domains were assessed as unclear or if one domain was assessed as high-risk and all others were low-risk, the overall risk for that study was moderate. If there were two or more domains with high risk of bias, the overall risk for that study was high. If more than one domain was assessed as not applicable, the choice of appraisal tool was reviewed; subsequently, if we were unable to find the suitable tool, the overall study risk was assessed as high.

Any differences in study selection, data extraction or risk of bias evaluation were resolved through additional examination of included articles, dialogue and consultation with the fourth author (M.O.-H.).

2.3 | Strategy for data synthesis

A narrative synthesis was chosen as a preferred method of reporting results because of heterogeneity in study designs, types of intervention and outcomes. Consequently, a meta-analysis could not be performed.

3 | RESULTS

3.1 | Description of included studies

The preliminary database searches identified 5848 records. During eligibility assessment, 77 articles were found to be qualitative studies exploring patients' or pharmacist opinions on deprescribing and did not involve any deprescribing interventions, and 54 articles were poster presentations, opinions or descriptive articles; these were therefore excluded. One article, although reporting an intervention, included participants younger than 18 years and thus was excluded. The final narrative synthesis included 24 studies (Figure 1).

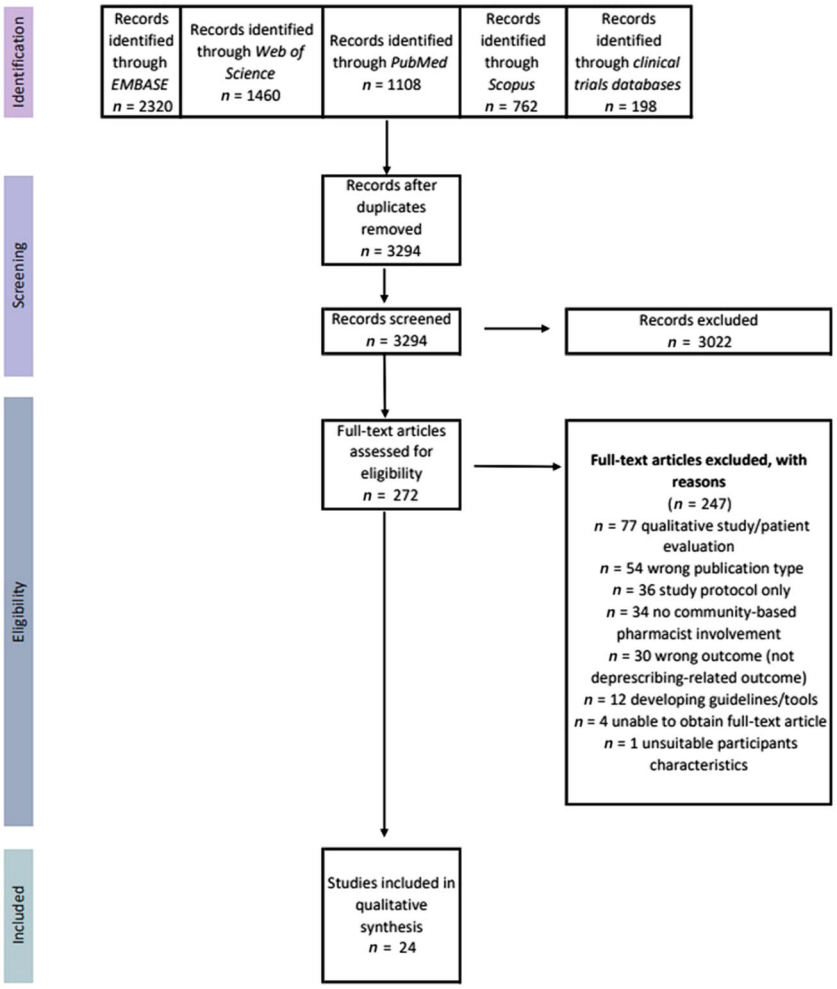

FIGURE 1 Prisma flow diagram of study selection

3.2 | Study characteristics

The selected studies comprised nine RCTs with 2304 participant,[9–17] nine QES with 461 participants,[18–26] five cohort studies with 1466 participants[27–31] and one economic evaluation.[32] The economic evaluation reported the cost effectiveness of deprescribing interventions on a subpopulation from another RCT, which was also included in the review. It did not mention the number or characteristics of participants, as it was not within its scope of interest.

The number of participants varied from 17 in the smallest study[21] to 685 in the largest study.[28] Eleven studies originated from the United States, four each from Canada and Europe (Sweden, Netherlands, Spain and Slovenia), three from Australia, and one each from Thailand and Japan. Considering participants' age, three studies included participants aged 18 and older, while the remaining 20 included participants aged 65 or older. The mean ages ranged from 28 to 98 years, and 19 studies had more than 50% female participants (ranging from 57% to 84%). Twelve studies were conducted in primary healthcare centres,[10,11,18–22,24,26,27,29,31] seven in one or more community pharmacies,[9,13,15–17,30,32] two in integrated healthcare systems,[14,28] and three in outpatient clinics (dealing with mental illnesses and/or dementia).[12,23,25]

3.3 | Risk of bias

Three out of nine RCTs had low overall risk of bias on all domains. The remaining six RCTs had moderate risk of bias due to one or more domains having unclear or high risk of bias.[9–12,14,16] Among the RCTs, selection bias and performance bias were two domains with most unclear or high risk. One out of ten QES had low overall risk of bias on all domains.[22] Seven QES had moderate overall risk of bias with one or two domains assessed as unclear or high risk of bias.[19,21,23–26,31] The remaining two had more than two domains assessed as unclear or high risk of bias and were therefore assessed with high overall risk of bias.[18,20] All but one QES study had high risk in performance bias due to the lack of a control group. Four QES had unclear risk of bias in the reporting domain because of unsatisfactory data on statistical analysis. One cohort study had low,[28] two had moderate,[27,30] and one had high overall risk of bias.[29] Economic evaluation of a cost effectiveness analysis was appraised to have low overall risk of bias as it had low risk in all questions.[32]

3.4 | Outcomes of interventions

Based on the types of interventions involved in the process of deprescribing, four studies were categorised as educational interventions,[13–15,32] eight as interventions including medication review, medication consultation or therapy management,[9,10,16,17,19,25,29,30] eight as pre-defined pharmacist-led deprescribing intervention/protocol,[11,12,20,22–24,26,31] and four as pharmacist-led collaborative interventions.[18,21,27,28] Appendix S2 in the Supporting Information presents a detailed summary of the findings categorised by intervention type.

The reported outcomes, both primary and secondary, differed widely across studies. The follow-up time varied from 3 to 12 months. The most reported primary outcome was reduction in the number of medications or prescriptions, followed by success of interventions and the number of patients with changes in medications. Only one study explored the impact of deprescribing on QoL as a primary outcome.[22] The acceptance rate of pharmacists' recommendations, success of deprescribing, mortality, financial savings and utilisation of medical services were the most reported secondary outcomes. The utilisation of medical services was defined as and included hospitalisation rate and emergency department or general physicians' visits. Three studies reported on QoL as a secondary outcome.[9,11,25] The rate of falls was reported as a primary outcome in two studies[16,17] and as a secondary outcome in one study.[9] All but three studies reported both primary and secondary outcomes.[18,21,31] The overall result of interventions conducted in the studies was positive for 17 studies,[10,12,13,15,18,20–22,24–32] while four studies[11,16,17,23] indicated both positive and negative results of intervention. Three studies had negative overall results.[9,14,19]

PIMs or high-risk medications, including fall risk-increasing drugs (FRIDs), were the most targeted medication group for deprescribing in three RCTs, four QES and two cohort studies.[15–19,21,23,27,29] Two RCTs and one QES targeted deprescribing of benzodiazepines.[13,14,22] Two RCTs, one QES and one cohort study targeted anticholinergics.[9,12,25,30] All medications were a deprescribing target in two RCTs and one QES.[10,11,24] Proton pump inhibitors (PPIs) were targeted in two QES,[20,31] one QES targeted non-statin lipid-lowering medication[26] and one cohort study targeted antidiabetics.[28] Regarding the success of deprescribing of a certain medication class, PIMs, benzodiazepines and anticholinergics were considered in only one study each, with a negative overall result.[9,14,19]

Access to electronic health records was reported as the tool used in ten studies.[14,17–20,24,26–28,31] Four studies used the Screening Tool of Older Persons' Prescriptions/Screening Tool to Alert to Right Treatment (STOPP/START) tool,[11,18,21,23] three used Beers criteria,[18,23,24] two studies employed drug burden index (DBI) calculator,[9,30] one study each made use of PRISCUS list[29] and good palliative geriatric practice tool.[13,15,17]

3.5 | Educational interventions

Three RCTs and one cost-effectiveness analysis of an RCT explored deprescribing through educational interventions. The results revealed greater discontinuation of inappropriate medications and lower system costs.[13,15,32] One RCT showed no difference in discontinuation of alprazolam between groups, but revealed positive sub-group analyses of the intervention group.[14] Participants who contacted the pharmacist had a higher rate of medication discontinuation than participants who did not (Table 1).

TABLE 1 Educational interventions

Author (year)	Methodology, setting, country	Overall result (positive/negative)	Risk of bias appraisal
Martin et al. (2018)[15]	RCT 69 community pharmacies, Canada	**Positive:** Pharmacist-led educational intervention results in greater discontinuation of inappropriate prescriptions (sedative-hypnotic drugs, glyburide, NSAID, first generation antihistamines)	LOW RISK
Navy et al. (2018)[14]	RCT Integrated health care system, USA	**Negative:** No difference between groups in alprazolam discontinuation or individual outcomes ***Positive sub analyses*** *of IG in reduction of alprazolam use in those who called the pharmacist* vs. *those who did not*	MODERATE RISK
Tannenbaum et al. (2014)[13]	RCT 30 community pharmacies, Canada	**Positive:** Higher likelihood of achieving discontinuation of benzodiazepines in IG, 11% of IG participants achieved 25% or greater dose reduction	LOW RISK
Sanyal et al. (2020)[32]	Economic evaluation Cost effectiveness analysis Community pharmacies, Canada	**Positive:** Greater benefits at lower system costs	LOW RISK

Abbreviations: IG, intervention group; NSAID, non-steroidal anti-inflammatory drugs; RCT, randomised controlled trial.

3.6 | Interventions involving medication review, medication consultation, medication reconciliation or medication therapy management

Medication consultation, review, therapy management or reconciliation by community-based pharmacists can lead to successful deprescribing of HRMs such as anticholinergic or sedative medications (Table 2). Success was measured as the reduced number of medications, higher rate of stopping the use of medication, decrease in DBI, and high acceptance of pharmacists' recommendations. These types of deprescribing interventions, however, did not affect the risk or rate of falls, rate of hospitalisations, mortality or QoL.[9,10,16,17,29,30] One QES reported barriers implementing a pharmacists' service in primary care, which resulted in providers' unwillingness to attempt deprescribing activities.[19] A small-sample QES on patients with severe mental illness indicated that a pharmacist-led comprehensive medication review, resulting in deprescribing of medications, reduces anticholinergic side effects and improves memory and QoL.[25]

3.7 | Pre-defined pharmacist-led deprescribing interventions

Eight studies exploring pharmacist-led deprescribing interventions reported positive results in terms of reduction in number of medications or prescriptions, and high acceptance of pharmacists' discontinuation recommendations.[11,20,22–24,26,31] Most successful interventions were those deprescribing PPIs,[20,31] non-statin lipid-lowering medication[26] and benzodiazepines.[22] One RCT noted improvement of cognitive functions and psychopathological symptoms in patients with schizophrenia.[12] A small-sample QES from Japan reported that deprescribing interventions increased the activities of daily living (ADL) score and maintained the QoL score.[22] Pre-defined pharmacist-led deprescribing interventions do not reduce healthcare resource consumptions but can contribute to financial savings[23,26] (Table 3). In all studies, the acceptance rate of pharmacists' recommendations was high.

3.8 | Pharmacist-led collaborative interventions

Two quasi-experimental and two cohort studies explored collaborative pharmacist-led interventions (Table 4). Three studies reported positive outcomes in terms of reduction in use of PIMs[18,21,27] and one recorded lower hypoglycaemia incidence and lower mortality.[28] One cohort study on collaborative drug therapy management on deprescribing antidiabetic medication showed no economic difference in medication costs between groups.[28]

4 | DISCUSSION

This is believed to be the first systematic review assessing information on deprescribing interventions initiated and/or led by community-based pharmacists and their efficacy and impact on clinical outcomes. This review identified 24 studies reporting community-based pharmacist-led deprescribing interventions in patients aged 18 years and older.

A broad range of studies was deliberately included to improve understanding of different deprescribing approaches. Due to the heterogeneity of the included studies, a qualitative analysis was performed. Based on this review, it is easy to conclude that no consistent method of deprescribing is incorporated into community-pharmacy practice.

The pharmacist's role as patient educators is known to improve health outcomes and increase patient satisfaction.[33] Deprescribing can be added as a positive outcome of educational interventions. One of the key steps for successful deprescribing is patient education

TABLE 2 Deprescribing intervention involving medication review, medication consultation, medication reconciliation, or medication therapy management

Author (year)	Methodology, setting, country	Overall result (positive/negative)	Risk of bias appraisal
Blalock et al. (2010)[17]	RCT Community pharmacies, USA	**Negative**: No statistically significant differences in the rate of falls, injurious falls, or the rate of filling prescriptions for high-risk medications. **Positive:** Statistically significant difference in discontinuation of high risk medication or dosage reduction between IG and CG	LOW RISK
Lenander et al. (2014.)[10]	RCT Primary health care Centre, Sweden	**Positive**: Statistically significant reduction in number of medications, prevented a decrease in self-rated health	MODERATE RISK
Mott et al. (2003)[16]	RCT 1 community pharmacy, USA	**Positive**: Significantly higher rate of IG participants stopped using FRIDs, high acceptance of pharmacist recommendations **Negative:** No influence on falls rate	MODERATE RISK
Van der Meer et al. (2018)[9]	RCT 15 community pharmacies, Netherlands	**Negative:** No difference between groups in intended DBI decrease; no effect on QoL, side effects, ADL, risk of falls, hospitalisation, and mortality	MODERATE RISK
Clark et al. (2019)[19]	Quasi-experimental study Family medicine patient-centred medical home clinic, USA	**Negative:** Overall acceptance rate for pharmacist recommendations was low and several barriers to integrating the pharmacist into the workflow were encountered	MODERATE RISK
Lupu et al. (2017)[25]	Quasi-experimental study Severe mental illness outpatient clinic, USA	**Positive:** Reduction in number of anticholinergic drug prescriptions, improvement in side effects, memory and QoL	MODERATE RISK
Kouladjian O'Donell et al. (2019)[30]	Cohort study Community (pharmacist home visit), Australia	**Positive:** Intervention significantly decreased median DBI; pharmacist and GP find implementation feasible	MODERATE RISK
Stuhec et al. (2019)[29]	Cohort study Primary community health Centre, Slovenia	**Positive:** Reduction in number of medications, PIMs, and drug–drug interactions; satisfactory acceptance rate of pharmacist recommendations	HIGH RISK

Abbreviations: ADL, activities of daily living; CG, control group; DBI, drug burden index; FRID, fall risk increasing drugs; GP, general practitioner/general physician; IG, intervention group; PIMs, potentially inappropriate medicines; QES, quasi-experimental study; QoL, quality of life; RCT, randomised controlled trial.

regarding the necessity and benefits of potential medication cessation. Accessibility of both patient education materials and community-based pharmacists can empower patients to engage in conversations about deprescribing with their healthcare providers.[34,35] Educational interventions rely on pharmacist incentive and patient initiative with regard to initiating deprescribing. In the selected studies, the prescribers played a supporting role, receiving the pharmacist's opinion or notification about the intervention, and were contacted by patients to discuss deprescribing. This enables shared decision-making, which ensures that the patients obtain all the necessary information and help from their pharmacists but ultimately make the decision to initiate deprescribing themselves. The pharmacists ensured safe and successful tapering. A potential problem in educational interventions is low health literacy and linguistic barriers in implementing foreign materials in non-English-speaking countries. Nevertheless, community-based pharmacists should embrace deprescribing through educational interventions as it leads to a decrease in the number of inappropriate medications and is cost effective. A limiting factor in studies incorporating deprescribing through educational interventions is the lack of evidence on tangible clinical outcomes such as impact on mortality or hospitalisations.

Deprescribing through interventions involving medication review, medication consultation or therapy management showed mixed overall results. It can successfully reduce both the number of medications and side effects, as well as prevent a decrease in self-rated health. However, it has no effect on patients' QoL, rate of falls, hospitalisation or mortality. While acceptance of pharmacists' recommendations is not without evidence, the integration of community-based

TABLE 3 Deprescribing through predefined pharmacist-led protocols

Author (year)	Methodology, setting, country	Overall result (positive/negative)	Risk of bias appraisal
Campins et al. (2016)[11]	RCT Primary health care centres, Spain	**Positive**: Statistically significant reduction in number of drugs in IG, improved treatment adherence in IG **Negative:** No reduction in health care resource consumption; no difference in self-reported QoL	MODERATE RISK
Sathienluckana et al. (2018)[12]	RCT Psychiatry outpatient department, Thailand	**Positive:** Pharmacist could help improve cognitive functions and psychopathological symptoms	MODERATE RISK
Coffey et al. (2019)[20]	Quasi-experimental study NCQA tier-3 patient-centred medical home, USA	**Positive:** Pharmacist can successfully initiate and conduct deprescribing of PPIs	HIGH RISK
Cross et al. (2020)[23]	Quasi-experimental study Outpatient memory clinic, Australia $n = 50$, intervention made for 46 Adults 65 years and older	**Positive:** Pharmacist-led deprescribing intervention is feasible (1/3 of patients were eligible and more than 60% of those consented), 43% of medications that pharmacist recommended for deprescribing were reduced or ceased at 6 months **Negative:** No changes in health outcomes, QoL	MODERATE RISK
Odenthal et al. (2019)[31]	Quasi-experimental study Primary care clinic, USA	**Positive:** Pharmacist can successfully initiate and conduct deprescribing of PPIs	MODERATE RISK
Sakakibara et al. (2015)[22]	Quasi-experimental study Primary care clinic, Japan	**Positive:** Decrease in number of medications, stable QoL score, increase in ADL score	LOW RISK
Vande Griend (2014)[26]	Quasi-experimental study, seniors' clinic (primary care), USA	**Positive:** Reduction in medicines, financial savings; no increase in health care utilization	MODERATE RISK
Deyo et al. (2020)[24]	Quasi-experimental study, federally qualified health Centre, USA	**Positive:** Statistically significant rate of high-risk medication discontinuation, high acceptance rate of pharmacist recommendations	MODERATE RISK

Abbreviations: ADL, activities of daily living; CG, control group; IG, intervention group; PPI, proton pump inhibitor; QES, quasi-experimental study; QoL, quality of life; RCT, randomised controlled trial.

TABLE 4 Deprescribing through pharmacist-led collaborative interventions

Author (year)	Methodology, setting, country	Overall result (positive/negative)	Risk of bias appraisal
Cossette et al. (2019)[18]	QES Family health team clinic (primary care), Canada	**Positive:** Overall reduction in the use of PIMs	HIGH RISK
Mudge et al. (2015)[21]	QES General medicine service, Australia	**Positive:** Statistically significant reduction in mean medication count, mean tablet load and reduction in PIMs	MODERATE RISK
Ammerman et al. (2018)[27]	Cohort study Veterans affair medical centre (Geri PACT clinic), USA	**Positive:** Statistically and clinically significantly greater reduction in PIMs use in IG then UC (marked increase in deprescribed PIMs in IG), greater dose reductions for PIMs not deprescribed, more discussions on continuing PIMs	MODERATE RISK
Hui et al. (2019)[28]	Cohort study Integrated health care system, USA	**Positive:** Lower hypoglycaemia incidence, lower mortality, no effect on hyperglycaemia, A1c levels and change in monthly antidiabetic drug cost	LOW RISK

Abbreviations: Geri PACT, Geriatric Patient Aligned Care Team; IG, intervention group; PIMs, potentially inappropriate medicines; QES, quasi-experimental study; UC, usual care.

pharmacists in everyday workflow of primary care teams might require additional effort.[36–38] As community-based pharmacists are accepting more non-dispensing roles, deprescribing through medication review should also be regarded as an important tool to combat polypharmacy and improve patients' health status.

Pharmacist-guided interventions at the primary care level, such as that described by Freudenberg et al.,[39] showed an increase in the rate of guideline-concordant prescribing and could indicate that positive results are possible for other types of pharmacist-led interventions as well. Pre-defined pharmacist-led deprescribing interventions included step-by-step protocols implemented and managed by pharmacists. This type of intervention successfully reduces the number of prescribed medicines, but has no effect on healthcare utilisation, emergency department visits, hospitalisation rate or mortality. A moderate risk RCT explored such an intervention on deprescribing all types of medications and showed no added risk to health and an improvement in treatment adherence.[11] In this review, pre-defined protocols have been demonstrated to be most useful while deprescribing a specific medication type such as PPIs, non-statin lipid-lowering medication or anticholinergic medication. Currently evidence-based deprescribing guidelines are available for a limited number of medication classes.[40] Other tools that pharmacists can use to aid in deprescribing decisions include tools for identifying inappropriate medicines (STOPP/START tool, Beers criteria), risk scales for anticholinergic and sedative burden (DBI, anticholinergic risk scale), and algorithms (geriatric medication evaluation algorithm, Good Palliative-Geriatric Algorithm, Geriatric Risk Assessment MedGuide, CEASE [confirm, estimate, assess, sort, eliminate] protocol).[41] Most tools were developed for elderly patients with polypharmacy and polymorbidity and for inpatient settings. The use of tools proved to be valuable in a long-term care hospital resulting in a 31% improvement in prescribing appropriateness and led to deprescribing.[42] Although the study was conducted in a different care setting, it is reasonable to expect positive results to be translated amongst patients residing in community healthcare. Available tools and aids warrant a critical approach when applying to different settings and patients and should not replace a personalised approach to every deprescribing case. For pharmacists, access to patient information could be crucial for initiating deprescribing. Future development of health information technology should include community-based pharmacists' input. More high-quality RCTs are needed to explore potential benefits for other outcomes.

Pharmacist-led collaborative interventions demonstrated positive overall results. Collaborative interventions successfully reduced PIMs use,[21,27,28] and one low-risk cohort study showed how such collaboration can lead to lower hypoglycaemia incidence and mortality[28] as well. At the same time, the aforementioned study showed no economic difference in medication costs between groups.[28] Ros et al. indicated that a team consisting of a clinical pharmacist and a clinical geriatrician achieved statistically significant improvement in patients' pharmacotherapy.[43] Community-based pharmacists can find themselves in an unfavourable position in comparison to a pharmacist working in inpatient facilities, as communication and collaboration with other healthcare providers is often complicated due to logistics-related obstacles. Research shows there are several barriers to initiating pharmacist–physician collaboration—differences in perceptions of the pharmacists' role, lack of time and access to information, lack of knowledge about pharmacists' occupation, and the need to collaborate with multiple personnel.[44,45] Another barrier to pharmacist–physician collaboration could be reported patients' confusion over healthcare professionals' roles.[46] Physicians are still reluctant to accept pharmacists' autonomous decision-making role, but they welcome and support a consultative role.[47,48] Lack of knowledge and experience about collaborative agreements or practices is also one of the perceived barriers for healthcare workers.[49] Physicians are for most patients a logical choice as the one who leads or initiates deprescribing. Moreover, physicians report that deprescribing is challenging for several reasons—lack of time, lack of confidence in knowing when and how to stop medications, lack of direct reimbursement, and patients' resistance to deprescribing interventions.[50–54] Meanwhile, the patients who feel insufficiently informed or monitored by their physician during the deprescribing process are especially hesitant about accepting it. Community pharmacists, whose professional scope focuses on managing medication therapy, can undoubtedly contribute to the deprescribing process. Through collaboration with both patients and prescribers, they are well positioned to identify and assess deprescribing opportunities, facilitate patient intervention agreements and monitor the tapering process and outcomes. Unlike patients in hospitals or long-term facilities, community dwelling patients do not have personnel for constant supervision over use of their medication. The foundation of deprescribing lies in shared decision-making, and in the case of community-dwelling patients, a pharmacist could be a valuable collaborator. Patients with chronic conditions often visit their community pharmacist more regularly than their prescriber. Pharmacists' unique relationship with patients should enable them to identify and assess deprescribing opportunities.

4.1 | Impact on outcomes

This review suggests that community-based pharmacist-led deprescribing interventions can reduce side effects as well as improve cognitive functions and psychopathological symptoms in patients with mental illnesses.

Regarding QoL, there is mixed evidence of usefulness of deprescribing interventions led by community pharmacists. One RCT and one QES on deprescribing anticholinergics and PIMs reported no positive change in patients' QoL.[9,23] However, two small-sample QES (conducted in patients with dementia and severe mental illnesses) on deprescribing benzodiazepines and anticholinergics showed slight improvement or maintenance of QoL score.[22,25] Future studies should explore how deprescribing interventions affect QoL when other medication classes are deprescribed.

Falls are often reported as a negative health outcome of polypharmacy, especially in the elderly.[55] Research shows that in acute settings, pharmacist involvement is necessary for timely recognition of FRIDs.[56] Deprescribing interventions led by community-based

pharmacists have yet to show a positive impact on the rate of falls but have been successful in decreasing the number of FRIDs. Fall prevention and fall risk assessment are complex tasks and require a multidisciplinary approach.[57]

Impact of deprescribing interventions on healthcare utilisation was reported in five studies, among which three studies involved medication review and two studies involved pre-defined protocols. They reported no increase in healthcare consumption and no effect on the rate of hospitalisations. Further research is needed to explore the impact of other types of deprescribing interventions led by community pharmacists on hospitalisation or utilisation of care.

Research has shown that payers' perspective of community pharmacist-directed care was positive and that implementation of clinical services at the community pharmacy is financially viable.[58,59] Regarding financial aspects, educational interventions and pre-defined pharmacist-led deprescribing interventions showed the most benefits.[26,32] Other types of interventions explored in this review either noted no difference in costs or did not investigate financial aspects. Son et al. demonstrated that pharmacist-led medication reconciliation also had a positive impact on reducing healthcare cost.[60] The purpose of deprescribing should not be only financial savings; remuneration for healthcare providers is also necessary as deprescribing is a demanding cognitive and time-consuming service. For countries with developing pharmaceutical care, information about cost effectiveness of new aspects of care can be vital for decisions to introduce such care.

The results of this systematic review, exploring the impact of deprescribing led by community-based pharmacists, are similar to those involving pharmacists in secondary and tertiary care settings or long-term care facilities. Deprescribing studies performed in long-term care facilities reported success in reducing medication burden, limited positive effect on mortality (deprescribing in a specific patient population or subgroup analyses), and no effect on outcomes such as cognition, anticholinergic symptoms, rate of falls or hospitalisations.[61–64] The systematic review by Dills et al. indicates that a strong interprofessional collaboration is needed for successful deprescribing.[62] Deprescribing leads to a significant reduction in PIMs, but shows mixed results when it comes to QoL, drug-related problems, rate of falls and changes in functional status.[64] No significant changes were found in mortality and hospitalisations.

4.2 | Strengths and limitations

Inclusion of all types of studies ensured a comprehensive review of available evidence for community-based pharmacist involvement in deprescribing. Most other systematic reviews gathered data on deprescribing in older adults; this review broadened the analysis to include younger adults. With longer life expectancy, availability of preventative medicines and medical procedures, young and middle-aged adults are likely to add medicines to their pharmacotherapy and should be educated on potential future interventions from which they could benefit. Paediatric patients were excluded for several reasons. Even though chronic conditions and polypharmacy are on the rise in paediatric patients as well, distinctions and specificities of this population require a different approach than that given to adults. The same applies to deprescribing interventions. There are only a handful of studies with deprescribing interventions conducted in patients younger than 18 years, and most of them are for psychiatric patients and in inpatient settings.[65–67]

One limitation of this review is the heterogeneity of included studies (study designs, types of interventions, and outcomes), because of which a meta-analysis could not be performed. It is difficult to compare studies across countries due to the differences in healthcare systems and structures of care at the primary level. Generalisability and application of evidence to different healthcare systems could be affected as well by potential differences in the definition of a community-based pharmacist and their role. Sustainability of deprescribing is another important aspect that needs to be explored after successful implementation. The follow-up periods in the selected studies were found to be short (3–12 months), making it difficult to draw any conclusions on long-term effectiveness and on the impacts of the deprescribing interventions themselves. Longer follow-up periods would allow the monitoring of indicators of sustainable deprescribing such as restarting of medication, long-term adverse drug withdrawal events, health deterioration, or changes in quality of life as well as impact on financial or organisational aspects of healthcare systems.

5 | CONCLUSION

All types of interventions within this review demonstrate the outcomes of community-based pharmacist-led deprescribing in terms of decrease in the number of medications and financial benefits, but have limited or no impact on mortality, QoL, falls, hospitalisations or healthcare utilisation. Educational interventions were supported by higher quality of evidence from low-risk RCTs in comparison to other types of interventions; however, they were lacking in reporting more tangible outcomes. A larger body of mixed evidence is available for interventions involving medication review and pre-defined pharmacist-led protocols; these report various outcomes but refrain from giving strong recommendations for everyday practice. Regardless, community-based pharmacists are a valuable partner in deprescribing collaborations, providing necessary monitoring throughout the tapering and post-follow-up stages and ensuring the success of the intervention. Rigorous research is needed to confirm cost-effectiveness of different types of deprescribing interventions, identify the best approach to implement deprescribing in different community settings, evaluate the impact on harder patient outcomes with longer follow-ups, and broaden the patient pool to include younger patients as well as specific patient populations. Additionally, studies with longer follow-ups are needed to evaluate the sustainability of deprescribing interventions. Research combining several types of interventions should be explored as well.

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COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

I.B. was responsible for the conceptualisation and design of the study, conducted the investigation and formal analysis, curated the data, wrote the original draft and reviewed and edited the manuscript, and was also responsible for project administration. I.K. and M.D. conducted the investigation and formal analysis, curated the data and wrote the original draft. M.O.-H. conceptualised and designed the study, was responsible for the resources, wrote the original draft and reviewed and edited the manuscript, and was also responsible for project administration.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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5. EXPLORING PATIENTS' ATTITUDES TOWARD DEPRESCRIBING AND THEIR PERCEPTION OF PHARMACIST INVOLVEMENT IN A EUROPEAN COUNTRY: A CROSS SECTIONAL STUDY

Patient Preference and Adherence

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ORIGINAL RESEARCH

Exploring Patients' Attitudes Toward Deprescribing and Their Perception of Pharmacist Involvement in a European Country: A Cross-Sectional Study

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Purpose: To explore how adult patients perceive deprescribing in a country with developing pharmaceutical care.

Patients and Methods: This was a multicenter cross-sectional study conducted in ten community pharmacies across Croatia. Community-dwelling adults 40 years and older, taking at least one prescription medication long term, were invited to participate. The revised and validated Patients' Attitude Towards Deprescribing Questionnaire was used to investigate community-dwelling adults' opinions on potential medication discontinuation. Questions regarding the patients' perception of pharmacist competences and involvement as well as patients' preferences in deprescribing were added. Collected data were analyzed using IBM SPSS Statistics using descriptive and inferential statistical analysis. Binary logistic regression was used to explore potential predictive factors of willingness to have medication deprescribed. All tests were performed as two-tailed and a $p < 0.05$ was considered statistically significant.

Results: A total of 315 adults aged 40 years and older completed the questionnaire. Majority of participants, 83.81% (95% CI, 79.72% to 87.90%) stated that they were satisfied with their medications, and 83.81% (95% CI, 79.72% to 87.90%) would be willing to deprescribe one or more medications. Participants expressed a positive attitude toward pharmacists' competences (68.89%, 95% CI, 63.75% to 74.03%) and involvement in deprescribing (71.11%, 95% CI, 66.08% to 76.14%). Participants who stated specific medication as deprescribing preference were more likely show dissatisfaction with current medication and show greater willingness to have medication deprescribed. Three factors were found to be associated with a positive attitude towards deprescribing: low concerns about stopping factor score (aOR 0.54, 95% CU=0.35–0.84; p=0.006), low appropriateness factor score (aOR 0.62, 95% CI=0.39–0.98; p=0.039), and a positive opinion on pharmacist involvement (aOR 2.35, 95% CI=1.18–4.70; p= 0.016).

Conclusion: This study showed the patient's willingness for deprescription as well as their positive attitude towards pharmacists being involved in the process. Results favour transition to a patient-centred care and shared-decision making model.

Keywords: stopping medications, patient preference, pharmacist, transition

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Introduction

It is reported that the prevalence of polypharmacy in European's community-dwelling older population ranges from 26.3 to 39.9% and it is expected to rise as the population continues to age.[1,2] There are many definitions of polypharmacy (ie use of five or more

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medication) and many distinguish between appropriate and inappropriate polypharmacy. Appropriate polypharmacy typically indicates use of many medications, all of which may be needed or whose use outweighs the potential risks. Inappropriate polypharmacy represents the use of too many medications and is associated with increased risk of unwanted health outcomes.[2,3] Several factors have been identified to be connected with an increased risk of polypharmacy, such as female sex, lower socioeconomic status, and lower educational attainment.[4,5] Deprescribing can be used as an important and appropriate tool to combat inappropriate polypharmacy. Deprescribing has been described as a process of reducing the dose or withdrawing an inappropriate medication with the aim of reducing polypharmacy and improving health outcomes.[6–9] It is a patient-focused process led by a healthcare provider. As patients are taking up a more active role in healthcare, it is becoming more evident that their opinions, beliefs, and attitudes play a key role in ensuring that the newly introduced aspects of care are beneficial. Community pharmacists are a valuable part of the healthcare team and have specific competences useful for implementing deprescribing in the primary care setting. Pharmacists' competences in deprescribing include performing medicating review and identifying deprescribing possibilities (determining risks and benefits of medications, making evidence-based recommendations), approaching, educating, and monitoring patients during and after deprescribing and collaborating with prescribers. For instance, pharmacist-led educational interventions have proven to be effective in reducing inappropriate prescriptions.[10,11] Patients at risk of polypharmacy might benefit from early familiarization to the concept of deprescribing, and community pharmacist alongside primary care physician could be an ideal healthcare provider to initiate such an important conversation.

Pharmacists from countries with less developed pharmaceutical care in central and eastern Europe (referred to as transition European countries) often find themselves encountering a paradoxical situation. Their desire to keep up to date with current trends in pharmaceutical care as presented by pharmacists from well-developed healthcare systems conflicts with the lack of policy, practice guidelines, and recognition from their own society.[12–14] In Croatia pharmacist-led medication reviews, comprehensive medication management or deprescribing are still seldom used in everyday practice. Currently, comprehensive medication management is available as a pilot project in one primary health care facility,[15] and one university hospital is conducting a project on pharmacist-led medication reconciliation.[16,17] These services are still not supported by health policy nor reimbursed. There are no official reports, studies, or research data on deprescribing in Croatia. A recently published systematic review on community pharmacists' role in deprescribing shows lack of deprescribing research within community pharmacies in central and eastern European countries and reports only one cohort study from Slovenia whose outcomes resulted in deprescribing.[11]

Patients and health care providers from lower income central and eastern Europe are accustomed to a paternalistic decision-making relationship and are making a slow transition to a shared-decision-making model. In everyday practice, it is still evident that when new aspects of care are being introduced, patients tend to escape into the protection of a paternalistic relationship rather than seek information.[18,19] Pharmacists should recognize such patients and lead them towards adapting a patient-centered, shared decision-making attitude. Successful deprescribing requires patient participation and shared-decision making. Patients active involvement in decision-making improves both physical and mental health, and patients with higher decision-making preferences experienced greater increase in treatment satisfaction.[20–22] Research emphasizes the importance of patients' perspective and involvement in deprescribing, and calls for future research to focus on patient perspectives, increasing patient education, engagement and shared-decision making.[23–25] Pharmacists are one potential health care provider who can initiate a conversation about deprescribing. Each health care provider contributes to deprescribing, and the final decision to proceed with deprescribing should include all stakeholders' input. Obtaining insight into patients' attitudes toward deprescribing and their opinion of pharmacist involvement in that process will enable pharmacists to gain momentum to take up deprescribing as part of routine pharmaceutical care. Research on all stakeholders' opinions on new aspects of pharmaceutical care, such as deprescribing, will be useful for future policy making as well.

The objectives of this study are to explore the attitudes and opinions of Croatian patients regarding deprescribing and their perception of pharmacist involvement.

Methods

Ethics approval for this study was granted by the Ethics Committee of City Pharmacies Zagreb (1-7EP/2020 granted on 6th of February 2020). During the research, the principles of the Helsinki Declaration were followed. Written informed consent was obtained from participants.

Study Setting and Sample Size Determination

A multicenter cross-sectional study was conducted in community pharmacies across Croatia. To collect a representative sample of participants, pharmacies from different geographic areas were recruited, including four inner city urban pharmacies located in Zagreb, two suburban pharmacies in Mošćenica near the town of Sisak and Sukošan near Zadar, two rural area pharmacies (in Bedekovčina in Krapina-Zagorje County and Brodski Stupnik in Brod-Posavina County), and two pharmacies located on islands (island of Krk and island of Ugljan).

The sample size was calculated using a single population proportion formula with a 95% confidence level, relative precision of 5%, and the proportion of patients willing to have medicines deprescribed 50% since there were no previous studies in Croatia on this topic. The calculated sample size was 385. Based on available information on Croatian population spatial distribution, the selected ten pharmacies were stratified to collect the following number of participants: 60% for inner city pharmacies (around 230 participants), 30% for suburban pharmacies (around 115 participants) and 5% each for rural and island pharmacies (around 20 participants each).

Participants and Data Collection

Data collection was performed from 15th December 2019 to 15th March 2020. Community pharmacists recruited potential participants while dispensing prescriptions or counseling on the use of prescription medications. All adults 40 years and older who were using at least one prescription medication long term were approached by pharmacist with an inquiry to participate in the study. The choice to include adults 40 years and older was made due to the fact that the most prescriptions for chronic disease medications in the country of study conduction are dispensed to middle-aged and older adults. Involved pharmacist selected the participants using a simple random sampling technique. Informed consent and questionnaires (in paper form) were handed out to interested participants, who were then given the option to complete the questionnaire at home or at the pharmacy, with or without pharmacist assistance (reading questions or filling out the questionnaire for participants with poor eyesight). Participants using medication "as needed", suffering from dementia or unwilling to participate or sign the informed consent were excluded from recruitment.

Survey

The questionnaire was composed of three sections (Supplementary file 1). The first section included personal information (age, sex, list of prescription and over-the-counter medications). The second section employed the revised Patients' Attitude towards Deprescribing Questionnaire (rPATD) developed by Reeve et al which asked participants to answer questions on a 5-point Likert scale.[26] The questionnaire has 22 items; two representing global question on willingness to have medications deprescribed and satisfaction with current pharmacotherapy. Other twenty items explore four factors (five items for each): the perceived appropriateness of medications, burden of medications, concerns about stopping, and involvement in treatment. Questions pertaining to the burden, concerns about stopping, involvement in treatment, and global questions were scored such that a higher total score indicates a greater burden, concern, involvement, or agreement with global questions (5= strongly agree, 4= agree, 3= unsure, 2=disagree, 1= strongly disagree). Questions regarding the appropriateness factor were scored in reverse. In that case, a higher score indicates participants' belief in the appropriateness of their medications. The permission to use and translate the rPATD questionnaire was given in writing by the author. This information was stated in a footnote on the questionnaire given to participants. Following the Brislin translation model, the questionnaire was translated into Croatian and then back-translated to English to ensure no loss of meaning in translation. Two researchers independently translated the questionnaire into Croatian, while two other researchers translated it back into English.

The third section included additional questions, which explored patients' opinions of pharmacists' competences and involvement in potential deprescribing as well as questions regarding personal preferences toward deprescribing medication, as shown in Table 1. These questions were deemed necessary since this is the first research on deprescribing in Croatia and the study intended to explore specific opinions regarding pharmacist involvement. Similar questions were used in research in the original PATD questionnaire used in Australia, Denmark, Italy, and Malaysia.[27–30] A pilot study of the pre-final version of the questionnaire was conducted on 10 participants, whose results were not included in the final analysis, and minor adjustments were made to ensure the ease of use of the final questionnaire.[31]

Table 1 Questions in the Third Section of the Questionnaire

Question	Type of Answer/Possible Answers
How would you feel if a pharmacist was involved in the process of stopping the use of one or more of your regular medications, and provided follow up? (in collaboration with your physician)	5-point Likert scale: very comfortable, comfortable, unsure, uncomfortable, very uncomfortable
If you were to stop using one or more of your regular medication in collaboration with your pharmacist and physician, what follow-up method would you prefer?	Telephone call, pharmacy visit, mail (including e-mail, text message, social media), no follow-up, other
Do you believe your pharmacist has enough knowledge, skills, and information about your medications to suggest deprescribing to you and your physician?	3-point Likert scale: yes, unsure, no
What medication/s would you LIKE to stop taking (that you believe you no longer need, or feel is causing you harm)	Text space to fill
What medication/s you would NOT LIKE to stop taking?	Text space to fill

Statistical Analysis

Collected data were analyzed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA). Frequencies, percentages, medians, and interquartile ranges were used to describe the data. A chi-squared test was used to analyze differences in frequencies between groups. Groups were formed for gender (male or female), age (younger or older than 65 years), and number of medicines (less than five or five and more medications). For analysis purposes, answers to global questions were combined as following: "strongly agree" and "agree" to form "agree", and "unsure", "disagree" and "strongly disagree" to form "disagree". Factor score was calculated by summing the score of each item and dividing by the number of items within the factor. Based on median factor score, two ranks were computed for each factor (low or high). Spearman's rank-order correlation analysis was employed to explore the relationship between factor scores and global questions (using ordinal data for five-point Likert scale data for global questions and continuous data for calculated factor scores). Binary logistic regression was used to explore potential predictive factors of willingness to have medication deprescribed. All tests were performed as two-tailed, and a $p < 0.05$ was considered statistically significant. Internal consistency of all factors was satisfactory, with Cronbach's alpha values as follows: 0.88 for burden factor, 0.81 for appropriateness factor, 0.63 for concerns about stopping factor and 0.83 for involvement factor. The intraclass correlation coefficient (ICC) was used to assess the test–retest reliability of the questionnaire for all items scored with Likert scale. The ICC of each item ranged from 0.69 to 0.96 indicating a good to excellent inter-rater reliability.

Results

Pharmacists distributed 385 questionnaires and received 315 completely answered questionnaires (return rate 82%). Eight returned questionnaires did not have correctly signed informed consent and were thus excluded from the analysis, and 62 questionnaires were not returned. Of the 315 participants, 61.60% were female (194 participants), and the median age was 68 years (IQR: 57–77). Participants were taking a median of four (IQR: 2–6) medications daily and the most commonly prescribed medications included those for the treatment of the cardiovascular system, alimentary tract and metabolism, nervous system, and blood forming organs (Table 2).

About 62% of the participants were elderly (over 65 years of age) and 30.50% were taking five or more medications.

Patients Attitude Towards Deprescribing

Most of the participants reported that they were satisfied with their current medications (n=264, 83.81%, 95% CI, 79.72% to 87.90%). A similar percentage of participants would be willing to stop one or more of their regular medications if their doctor said it was possible (83.81%, 95% CI, 79.72% to 87.90%). Responses to all rPATD questions are represented in Figure 1.

An association between gender and overall satisfaction was observed (χ^2 (1) =6.99; p= 0.008), with women being more satisfied with their current medications than men. There was no statistically significant difference in the willingness toward deprescribing medication between gender.

Participants over the age of 65 years were more willing to have their medications deprescribed (χ^2 (1) =4.06; p=

Table 2 Participants' Characteristics

Participants' characteristics (n=315)	
Age (years)	
Median (IQR)	68 (57–77)
< 65 years (n, % of participants)	121 (38.40%)
> 65 years (n, % of participants)	194 (61.60%)
Gender (n, %)	
Male	121 (38.40%)
Female	194 (61.60%)
Pharmacotherapy characteristics	
Number of medications	
Median (IQR)	4 (2–6)
< 5 medication (n, % of participants)	219 (69.50%)
≥ 5 medication (n, % of participants)	96 (30.50%)
ATC classification (% of participants with prescribed medication)	
Alimentary tract and metabolism	45.40%
Blood and blood forming organs	26.98%
Cardiovascular system	81.27%
Dermatologics	1.59%
Genitourinary system and sex hormones	11.75%
Systemic hormonal preparations	18.10%
Antineoplastic and immunomodulating agents	5.40%
Musculoskeletal system	20.00%
Nervous system	38.10%
Respiratory system	12.38%
Sensory organs	6.35%
Various	0.63%

Abbreviation: IQR, interquartile range.

0.044) than their younger counterparts, but there was no statistically significant difference in overall satisfaction with medications between age groups.

There was no statistically significant difference in patients' willingness to have medications deprescribed or in overall satisfaction with medication between patients currently taking >5 or <5 medications.

Assessed factor scores show that participants experience a moderate medication burden and have moderate concerns about stopping medication. Higher median scores for the involvement and appropriateness factors indicate that participants want to be involved in the management of their medications and find their pharmacotherapy somewhat appropriate (Table 3).

Participants under the age of 65 years were more likely to have the appropriateness factor score below the median (χ^2 (1) =5.96; p= 0.015) than their older counterparts. There were no statistically significant differences in concerns about stopping factor score, burden factor score, involvement factor score, opinion on pharmacist involvement and knowledge, or specific preferences to deprescribing between age groups.

The strongest positive correlation was found between overall satisfaction with medications and belief in appropriateness (r_s = 0.488; p < 0.001). A positive correlation was found between the involvement factor and global questions (r_s = 0.273; p < 0.001 and r_s = 0.243; p < 0.001, respectively), meaning greater involvement in treatment was associated with greater overall satisfaction with medications and greater willingness to have medications deprescribed. There was a weak positive correlation between the involvement factor and the appropriateness factor, and a moderate positive correlation between the burden factor and the concerns about stopping medication factor. A moderate strength negative correlation was found between burden and appropriateness, and burden and overall satisfaction (r_s = −0.556; p < 0.001 and r_s = −0.406; p < 0.001, respectively), indicating that an increased burden correlated with decreased satisfaction and belief in the appropriateness of medications. A weak negative correlation was found between willingness to have medication deprescribed and the concerns about stopping factor.

Perception of Pharmacists' Involvement, Knowledge, and Skills

The majority of participants (71.11%, 95% CI, 66.08% to 76.14%) would feel comfortable if a pharmacist was involved in the deprescribing process, 17.46% were unsure, and 11.43% felt uncomfortable When asked: "Do you believe your pharmacist has enough knowledge, skills, and information about your medications to suggest deprescribing to you and your physician?", 68.89% (95% CI, 63.75% to 74.03%) of participants answered positively, 22.54% were unsure, and 8.57% answered negatively. No difference was found among groups of different ages, sex, and number of medications with regard to their perception of pharmacist competences or involvement.

Regarding the follow-up method, 44.12% of participants preferred a pharmacy visit (appointment with a pharmacist), 34.28% preferred telephone calls, 0.97% preferred mail of any kind, 11.11% would prefer other methods of follow-up (eg, doctor's appointment), and 9.52% would prefer no follow-up. A statistically significant difference was observed in the patients' preference of follow-up method, with participants aged <65 years

Figure 1 Responses to rPATD questions.

preferring telephone calls to pharmacy visits. Younger participants also chose "no follow-up" more frequently than older participants ($\chi^2(4) = 13.05$; p= 0.011).

Patients' Personal Preference to Deprescribing

Two final questions in the questionnaire aimed to gather information on participants' preference on which medication they would or would not like to have deprescribed. When asked which medication they would like to have deprescribed, 31.75% participants gave no answer, 32.69% stated that they would not have any medication deprescribed, and 2.85% stated wanting to have all their medication deprescribed. A small percentage of participants stated the exact medication they would be willing to have deprescribed, with almost 7% of participants wanting to have anti-hypertensive medication deprescribed, 3.50% wanting benzodiazepines or hypnotics and statins deprescribed, while 2.88% wanted NSAIDs deprescribed. Interestingly, four participants (1.27%) stated that they stopped taking medication of their own accord.

Participants gave a more diverse array of responses to the question of which medication they would not like to have deprescribed. About 28.25% did not give an answer,

Table 3 Factor Scores

Factor Scores (N=315)	Burden Factor Score	Appropriateness Factor Score	Concerns About Stopping Score	Involvement Factor Score
Median	2.60	3.60	2.80	4.60
Percentiles	1.60	2.80	2.20	4.00
	2.60	3.60	2.80	4.60
	3.40	4.20	3.40	5.00

24.44% stated "all medication", 15.87% stated antihypertensive medication, 8.57% stated "no medication", 4.76% stated antidiabetic medication, and 3.50% of participants stated not wanting benzodiazepines or hypnotics and thyroid medication deprescribed.

Participants who stated specific medication as deprescribing preference were more likely to answer negative to the question of overall satisfaction with current medicines (χ^2 (1) = 40.38; p < 0.001). Likewise, patients who answered positively to the global question of willingness to have medication deprescribed were more likely to state a specific medication they would be willing to stop taking (χ^2 (1) = 9.07; p = 0.003).

Predictors of the Willingness to Have Medication Deprescribed

A binary logistic regression model was used to analyze potential predictors of the willingness to have medication deprescribed. Participants' age, sex, number of medications, factor scores, and opinions on pharmacist involvement and pharmacist knowledge in deprescribing were included in the model. The results showed that those having a positive opinion about pharmacist's involvement had the odds of 2.35 times greater willingness to participate in deprescription (aOR=2.35; 95% CI=1.18–4.70). The odds ratio for appropriateness factor scores (aOR= 0.62; 95% CI=0.39–0.98) and concerns about stopping factor scores (aOR= 0.542; 95% CI=0.35–0.84) indicates that higher the scores, the less likely the patient will want to have medication deprescribed. (Table 4).

Table 4 Willingness to Have Medication Deprescribed Binary Logistic Regression Analysis

Independent Variable	aOR	95% CI		p value
Appropriateness factor[a]	**0.619**	**0.392**	**0.976**	**0.039**
Burden factor score[a]	1.466	0.954	2.253	0.081
Concerns about stopping factor score[a]	**0.542**	**0.351**	**0.839**	**0.006**
Involvement factor score[a]	1.443	0.885	2.352	0.142
Positive opinion on pharmacist competences[b]	1.370	0.677	2.776	0.381
Positive opinion on pharmacist involvement[b]	**2.351**	**1.176**	**4.699**	**0.016**
Age	0.973	0.924	1.024	0.292
Number of medications	0.945	0.804	1.111	0.496
Female gender	1.307	0.667	2.561	0.436

Notes: The logistic regression model was significant (p < 0.001) with a good model fit (Hosmer–Lemeshow test χ^2 (8) =7.894; p= 0.444). It correctly predicted 84.80% of the results and explained 20.00% of the variance. Variables which are significant for this model are labeled in italics and their values in bold. [a]Possible score range 1–5, [b]participants could have a positive or negative opinion.
Abbreviations: aOR, adjusted odds ratio; CI, confidence interval.

Discussion

This cross-sectional study reported the first data on patients' attitudes on deprescribing in transitioning European country. The results showed that Croatian patients are satisfied with their pharmacotherapy but have nevertheless expressed their willingness to have medication deprescribed. Majority of participants were comfortable with pharmacists' potential involvement in deprescribing and had a positive opinion on pharmacists' competencies regarding deprescribing.

This study is among few to have an accentuated focus on patients' opinions of the role of community pharmacists in deprescribing. The emphasis on community pharmacists' potential involvement in deprescribing stems from research demonstrating that a multidisciplinary approach (including a pharmacist) is essential for successful deprescribing.[10,32–35] A study by Ng et al reported that half of the participants were comfortable with pharmacist involvement.[36] In this study, a larger percentage of participants were identified as having a positive attitude toward the pharmacists' role in deprescribing. Seventy-one percent had a positive opinion on pharmacists' involvement, and 69% believed that pharmacists had appropriate competences for deprescribing Another positive aspect of pharmacist involvement is that majority of patients reported that they preferred face-to-face meetings with a pharmacist as a follow-up method. Schiøtz et al reported comparable results in their study in Denmark.[27]

Patients with multiple chronic comorbidities and repeat prescriptions often visit their community pharmacist more often than their physician. Community pharmacists are well positioned to be physicians' partner in improving patient outcomes. Successful collaboration requires not only mutual trustworthiness,[37,38] but exchange and access to information as well. Studies have proven that pharmacist-led collaborative deprescribing interventions are feasible and effective.[39,40] The accessibility of a community pharmacist should invoke building a trustworthy relationship, and pharmacists could provide the encouragement a patient needs to consider deprescribing.

An association between age and willingness to have medication deprescribed was identified; patients aged 65 years and older were more willing to have medication deprescribed. Other studies have investigated the opinions of older adults in various settings; selecting adults 40 years and older to participate in this study seemed reasonable. With Europeans aging population and rise of inappropriate polypharmacy, deprescribing research in younger patients is limited. Many younger adults with comorbidities will most likely be adding medication to their pharmacotherapy and could benefit from early familiarization with deprescribing. Nevertheless, opinions of older participants from this study are comparable to opinions of older adults worldwide.[26,29,30,36,41–46] While younger participants might not have expressed their willingness to have medication deprescribed through the global question, they were more likely to have lower appropriateness factor score. Low appropriateness factor score was found to be a predictive factor for willingness to have medication discontinued and could indicate younger participants require additional attention and conversation regarding their pharmacotherapy. Middle-aged adults could become an important group for future deprescribing interventions.

Patients from this study have similar appropriateness, burden, and concerns about stopping factor scores as patients from well-developed countries.[44,47] The slight difference in scores could be due to the proportion of younger participants or differences in the healthcare system and participants' healthcare literacy.[48,49] In contrast to patients from the UK and the Netherlands participants from this study expressed greater desire to be involved in management of their treatment.[50,51] We identified patients' readiness for the deprescribing service, which is an important element for the initiation of the deprescribing process. However, the preparedness of the health-care system is equally important for successful implementation with an emphasis on collaboration of different healthcare providers and the availability and sharing of the information. For example, Croatian community pharmacists are in a disadvantageous position with regard to access to patients' healthcare information, where only the currently prescribed and previously dispensed electronic prescriptions in particular pharmacy are accessible. Lack of information for pharmacist could be a missed opportunity to review medication from a different perspective, recognize deprescribing opportunities, and initiate conversation about deprescribing. Participants' desire for involvement in decision-making is an important stepping stone in providing shared-decision-making care. For countries with developing pharmaceutical care high level of patients' involvement could be an indicator of readiness to accept new forms of patient-centered services, such as deprescribing. This finding could be used as a part of implementation strategy. One potential strategy could include initiating conversation between patient interest groups and primary care providers including pharmacist on the topic of inappropriate medicines use and deprescribing.

Many participants did not clearly state which medication they would prefer to stop taking. These results are contradictory to the results to one of the global questions, to which a majority of participants answered positively. Moreover, some participants mentioned that they want all their medications deprescribed, which is not the goal of deprescribing. This could indicate patients' misunderstanding of the deprescribing process, which is not surprising in the country where it is not implemented. Patients' perception of deprescribing could be based on knowledge they gained from a questionnaire but also on their desire to stop all the therapy. In practice, this could be an important finding and allows for the identification of patients who need consultation on their therapy in order to ensure the adherence to the necessary therapy. Overall, patients answers on the question which specific medication they want to be deprescribed could suggest lack of knowledge about their therapy, disguised non-adherence, or uncertainty about the possibilities of informed shared-decision making, and indicate pharmacist educator role is very important. Two recent conceptual deprescribing frameworks emphasize the importance of patients factors when discussing deprescribing, especially attitudes about medications, medication literacy, and experience with medication.[24,25] The final decision to start the deprescribing process should be made equally by all involved parties, pharmacist, physician, and patient. Patients should view deprescribing as a positive intervention in their therapy and their familiarity and opinion on pharmacotherapy is an important factor to consider. For pharmacists, this finding could represent a challenge in deprescribing, and indicates the need for additional time invested in counseling patients. This challenge pharmacists for providing better, more holistic pharmaceutical care; thus, this should be addressed.[52] It is the healthcare providers' role to use their expertise and evaluate the suitability and need for a certain medication, and they should not expect patients to know which medication is no longer necessary. Nevertheless, for patients who have stated specific medication they would want to have deprescribed it would be

prudent to further investigate the deprescribing potential as well as other important patient factors, such as medication adherence or potential adverse reactions. Even though a small number of participants stated the exact medication they would be willing to stop taking, benzodiazepines, NSAID and antihypertensives, for most medication there are available deprescribing guidelines. Knowing which specific medication patients are willing to have deprescribed would allow pharmacist and physician an easier planning of interventions. The diversity of answers could suggest the realistic number of patients who would actually participate in a deprescribing attempt.

Three factors were found to be predictive of a positive attitude toward deprescribing: low concerns about stopping medication factor score, low appropriateness factor score, and a positive opinion on pharmacist involvement. In comparison to other studies, in this study, positive opinion on pharmacist involvement is indicative of the patient's willingness to have medications deprescribed. Pharmacists could take advantage of this information and identify potential candidates who are more willing to deprescribe. A study by Martinez et al investigated the attitudes of middle-aged women and came to a similar conclusion.[53]

This study has limitations. Sociodemographic information may be a predictor of willingness to deprescribe; however, the information provided was limited in this study. This approach was chosen because Croatian patients are not accustomed to participating in research and are often unwilling to participate if personal information is collected or if data collection is time-consuming. For this reason, investigators deemed it more important to focus on the rPATD and added questions to avoid potential participant fatigue. Community pharmacists collecting data could have been prone to selection bias, which may have influenced how questions about pharmacists' involvement and knowledge were answered. Adults who were able to visit the pharmacy were selected to participate; therefore, our results could not be generalized to other community-dwelling patient populations such as frailer adults or patients with disabilities. The majority of participants completed the questionnaire in the pharmacy with the pharmacists' help, and as such, their answers might be prone to bias. Nevertheless, the results could be viewed as the patients trusting the pharmacist and as a good foundation for the successful implementation of deprescribing. The fact that some participants mentioned that they want all their medications deprescribe could indicate their misunderstanding in deprescribing concept and may result in biased responses. However, it also provides additional information on patients' understanding of their therapy and the concept of deprescribing. As intended, this open question gets deeper understanding of patients' attitudes towards the deprescribing and added to the rPADT could inform the health-providers on the needed interventions besides the deprescribing. Further analysis of patient's answers did not show any statistically significant differences between patients' opinion on pharmacist knowledge or involvement in deprescribing and their answers to which medication they would want to stop taking.

It could be helpful to introduce the rPATD questionnaire as standard practice in pharmaceutical care for patients with chronic pharmacotherapy and to have them revisit and retake the survey from time to time as patients' beliefs might change with their age and the appropriateness of their pharmacotherapy. In everyday practice, where pharmacist experience time constraints, it might prove to be useful to ask selected items from the rPATD questionnaire (ie appropriateness factor items) to quickly identify patients who could benefit from additional conversation about deprescribing.

While deprescribing has become a significant research topic, with new and interesting evidence emerging, there is no agreement on the most efficient approach to successful deprescribing. For countries that lack funding for pharmaceutical development, this could be even harder. It is pertinent to explore deprescribing "globally" within such healthcare systems and to include all stakeholders so that the inevitable introduction and acceptance of deprescribing is as seamless as possible. Further research should focus on exploring opinions, barriers, and factors, which enable pharmacists and primary care physicians to fulfill their role in deprescribing, as they might differ from providers in different healthcare systems. Characteristics specific to this country and its healthcare include a relatively small population with little social or racial diversity, predominantly universal (social) healthcare insurance, universally used centralized healthcare information system on the primary healthcare level, and the specific positions of community pharmacists could be important factors that influence deprescribing. Information gained from future research, including planned interventional studies, could help countries with similar characteristics to experience an easier transition into implementing deprescribing in everyday practice. Future interventional studies could be community pharmacist-led, directed at patients with low

appropriateness factor score, patients with higher involvement factor score, or those who state dissatisfaction with certain medication as they are more likely to want to have medicines deprescribed.

Conclusion

Implementation of new aspects of patient-centered care in transition health care systems should be based on research, not only including opinions and capabilities of healthcare professionals, but also the attitudes and expectations of those who are intended to receive the most benefits from those actions. Patients from a country with developing pharmaceutical care would be comfortable with pharmacists' involvement in deprescribing, and this finding should be used in introducing deprescribing and promoting the pharmacists' competences. While transitioning to a shared decision-making mindset may take time, these patients show similar attitudes towards deprescribing as patients from countries with well-developed pharmaceutical care.

Potentially, those with decreased opinion on medication appropriateness could be the first candidates to benefit from deprescribing. Additional interventional studies in transition healthcare systems are necessary.

Abbreviations

rPATD, revised Patients' Attitude towards Deprescribing Questionnaire; NSAID, nonsteroidal anti-inflammatory drug.

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Author Contributions

Iva Bužančić: Conceptualization, Methodology, Software, Formal analysis, Investigation, Data Curation, Writing – Original Draft, Writing – Review & Editing, Visualization, Project administration. Patricia Dragović: Conceptualization, Investigation, Data Curation, Writing – Original Draft, Formal analysis. Tajana Iva Pejaković: Investigation, Data Curation, Writing – Original Draft. Luka Markulin: Investigation, Data Curation, Writing – Original Draft. Maja Ortner-Hadžiabdić: Conceptualization, Methodology, Resources, Writing – Original Draft, Writing – Review & Editing, Visualization, Supervision, Project administration. All authors contributed to data analysis, drafting, or revising the article, gave final approval of the version to be published, agreed to the submitted journal, and agreed to be accountable for all aspects of the work.

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6. DEVELOPMENT AND VALIDATION OF COMPREHENSIVE HEALTHCARE PROVIDERS' OPINIONS, PREFERENCE, AND ATTITUDES TOWARDS DEPRESCRIBING (CHOPPED) QUESTIONNAIRE

pharmacy

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Article

Development and Validation of Comprehensive Healthcare Providers' Opinions, Preferences, and Attitudes towards Deprescribing (CHOPPED Questionnaire)

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Abstract: Successful implementation of deprescribing requires exploring healthcare professionals' opinions, preferences, and attitudes towards deprescribing. The aim of this study was to develop and validate the questionnaire exploring healthcare providers' opinions preferences and attitudes towards deprescribing (CHOPPED questionnaire). This was a cross-sectional on-line survey. A comprehensive 58-item questionnaire, in two versions (for pharmacists and physicians), was developed through an extensive literature review and interviews with experts. The questionnaire was validated, and its reliability was assessed through data collected from 356 pharmacists and 109 physicians. Exploratory factor analysis was performed, and 37- and 35-item questionnaires were developed. Ten factors were identified: knowledge, awareness, patient barriers and facilitators, competencies barriers and facilitators, collaboration barriers and facilitators, and healthcare system barriers and facilitators. The CHOPPED tool has satisfactory face, content (CVR > 0.62) (content validity ratio), construct, and criterion validity. The reliability statistics of all factors in both versions was acceptable with Cronbach's alpha > 0.6. Test–retest reliability analysis showed that gamma rank correlations of total factor scores were strong and very strong (between 0.519 and 0.938). The CHOPPED tool can be used as a valid and reliable tool to explore healthcare providers' opinions and attitudes toward discontinuing medications in the primary care setting in Croatia.

Keywords: deprescribing; questionnaire; barriers; facilitators; primary care

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1. Introduction

Increasing life expectancy of populations and availability of medical care lead to inappropriate prescribing, polypharmacy, and poor health outcomes, especially in the elderly [1–3]. Healthcare practitioners and researchers have many tools available to combat this ever-growing problem, one of them being deprescribing. Deprescribing can be described as an essential part of prescribing and involves identifying inappropriate medicines that should be reduced or discontinued as their continuing use brings more harm than benefit to the patient [4]. Research shows that most problems in deprescribing arise from a lack of well-established and implemented services in standard practice. Even though deprescribing as a clinical intervention has been in focus in the past decade and many feasibility trials and protocols have been developed, there is still a lack of implementational studies and strategies. Several authors and publications have accentuated this particular problem and declared it as a priority in future research [5–7]. Ailabouni and co-authors in their commentary from 2022 address the current limitations of implementing deprescribing guidelines into practice and policy, and how implementation science can be of service [8].

Deprescribing requires thoughtful engagement of all stakeholders, patients, and their healthcare providers, including physicians, specialist doctors, and pharmacists. The introduction and implementation of deprescribing in everyday clinical practice, for both

primary care physicians and community pharmacists, are demanding and are influenced by many factors. While patient characteristics might be considered most important, a number of qualitative health research studies show a variety of barriers for healthcare providers to identify when considering deprescribing [9]. In each healthcare system, unique determinants that influence the ability to provide deprescribing can be identified. Gathering information and determining factors from first-line healthcare providers in those systems can aid in creating implementational strategies [8,10].

Qualitative research is valuable in identifying concepts and themes of a new service but is often limited by the number of participants or excludes participants less familiar with the topic. Most commonly identified themes or concepts include patient expectations, medical culture, fear of damaged reputation, ethical, legal, and financial dilemmas, lack of organization, uncertainty in skills or abilities and professional identity, and access to information to name a few [7,11–14]. To reach a larger and more diverse population of healthcare providers, surveys can be used. Until recently, only a few attempts were made to develop and validate a tool that could explore barriers and facilitators of deprescribing. Linsky et al. developed an instrument valuable for exploring prescribers' perceptions of medication discontinuation [15]. The instrument was used on healthcare providers familiar and versed in deprescribing. For healthcare systems with developing pharmaceutical care, as well as for different levels or settings within a healthcare system unfamiliar with deprescribing, it is essential to explore healthcare providers' perceived barriers and enablers of deprescribing to ensure successful implementation of a novel service [5]. Therefore, the aim of this study is to develop and validate a Comprehensive Healthcare providers' OPinions, Preferences, and attitudEs towards Deprescribing questionnaire (CHOPPED questionnaire). The questionnaire is developed considering both prescribers and those without prescribing benefits as their viewpoints might differ, as well as those who do not provide deprescribing as standard practice.

2. Materials and Methods

2.1. Design

A cross-sectional survey was conducted on registered community pharmacists and primary care physicians in Croatia.

2.1.1. Development of the CHOPPED Questionnaire

For item development, both deductive and inductive methods were used [16]. An extensive literature examination was performed, including qualitative design studies, commentaries, letters to the editors, expert opinions, and systematic reviews on the topic, in order to identify key concepts, themes, and factors [9,14,15,17–27]. Authors identified three frequently appearing themes: patient, profession, and organisation. For each theme, the most commonly occurring concepts were systematized. These included professional accountability, system support, communication, finance and legal, prescribing, patient wishes and desires, beliefs about medication appropriateness and harm, and relationships and perceptions. One-on-one interviews with ten primary health care providers (six pharmacist and four physicians) were conducted on the topic of medication stopping, and potential obstacles and motivators needed for providing such a service were identified. To help guide the interviews for each concept, researchers formulated prompts (Table 1). Involved healthcare providers came from different clinical backgrounds and had diverse and complementary skills in pharmaceutical care. During interviews, researcher eliminated prompts considered unnecessary or those that were not mentioned by the interviewees and formulated preliminary items. Highly similar items were then merged or removed. Based on interview data and proposed themes and domains, a comprehensive 58-item questionnaire was prepared by two researchers, in two versions, one for physicians and one for pharmacists (Supplementary File S1) All questions from this part of the questionnaire used a 5-point Likert scale (1 = strongly disagree, 2 = disagree, 3 = neither agree nor disagree, 4 = agree, 5 = strongly agree) as possible answers.

Table 1. Themes, concepts, and prompts used to develop the questionnaire items.

Patient		Profession		Organization
Wishes and desires • burden • desire to stop • involvement • duration of pharmacotherapy • health perception • wellbeing expectations • resistance to change • candidates for medication review • candidates for medication discontinuation	*Prescribing* • pressure to prescribe • pressure to dispense • reluctance to change medications • justification of illness • overprescribing • overconsumption	*Professional accountability* • knowledge • opinion • capabilities and confidence • opportunities to act • indifference • uselessness • fear or hesitation	*Communication* • fragmentation of care • access to information • transfer of care	*System support* • time • space • guidelines • system alerts • education • technology utilization
Relationships and perceptions • loss of trust • feeling of abandonment • shared decision making • prior positive experience • positions of authority	*Beliefs about medication appropriateness and harm* • better safe than sorry attitude • side effects • end of life • comfort	*Relationships and perceptions* • inter-professional • intra-professional • professional courtesy • division of responsibilities • shared-decision making • hierarchy		*Finance and legal* • reimbursement • penalties • repercussions • ethics • policy

The CHOPPED questionnaire was further extended by the inclusion of a case vignette based on a real-life patient. The case vignette was intended to assess pharmacists' and physicians' agreement on deprescribing decisions (File S2). In the pharmacists' version, respondents had to indicate which medication they would suggest for deprescribing and state the rationale behind their answer. In the physicians' version, respondents had to indicate which pharmacist deprescribing suggestion they would agree with. The patient in the vignette was a community-dwelling older adult with 15 medications, four comorbidities, low activity of the daily living score, and high willingness to have medication deprescribed.

2.1.2. Participants

LIMESurvey® software was used to design and distribute the questionnaire. Dillman's guiding principles for mail and internet surveys were used to help with the survey design [28]. The survey was sent via email to available community pharmacies and physicians' practices from the directory of the health insurance fund and professional affiliations (national chamber of pharmacists and national chamber of physicians). In the invitation email, potential participants were asked to forward the link to the survey to fellow pharmacists or physicians. Two email reminders, four and eight weeks after the initial email, were sent. All responses were anonymous. Informed consent was included in the survey and was set as a required response to ensure all participants were informed on all aspects of the study. Potential participants who did not digitally authorise the informed consent could not access the survey. The study was conducted between October 2021 and January 2022 in Croatia. It was approved by the Ethics Committees of City pharmacies Zagreb and Health Centre Zagreb. Participants could save the answers of the unfinished questionnaire and complete the questionnaire at a later time. To ensure there were no duplicate inputs, each unique IP address was marked in the responses. If a single IP address had multiple inputs, cross-checking was performed for socio-demographic information. Duplicate unfinished or answerless questionnaire entries from duplicate IP addresses were discarded. Participants' inputs were included in the validation analysis if all of the questions were answered.

As literature reports for adequate sample size for validity analysis vary, a general rule of subject to item ratio of 2:1 to 10:1 was considered, and 4:1 ratio was employed [29,30]. For test–retest reliability, a sample size of 20 was chosen, and for exploratory factor analysis, a sample size of 200 was considered adequate [31]. The response rate was expected to be around 20%; therefore, the questionnaire was sent to at least 1000 email addresses.

2.2. Validation

Face validity, content validity, construct validity, criterion validity, internal consistency, and test–retest reliability were the chosen methods of validation.

2.2.1. Face Validity

Healthcare providers involved in item generation, described above, participated in the face validity assessment. They were invited to a group discussion to review and comment on prepared preliminary versions of the questionnaire. Each item was examined and rated on clarity, relevance, and importance. Finally, panellists assessed whether appropriate phrasing was used, and necessary changes were made before validation and widespread administration.

2.2.2. Construct Validity

Exploratory factor analysis (EFA) was performed to identify factors and to refine the questionnaire length [32]. The analysis was performed concurrently for both versions of the questionnaire. Promax rotation was chosen as a rotation method of EFA since there was correlation between factors. The criteria to retain the number of factors included the eigenvalue, the scree plot test, the proportion of total variance accounted for, and the interpretability criterion. The eigenvalue signifies the amount of variance in all of the values for which the factor accounts for. A value > 1 implies that the factor accounts for more variance than an average single item [33]. For the proportion of the total variance, factors explaining 60% to 70% of total variance were retained. Sampling adequacy was confirmed using the Kaiser–Meyer–Olkin statistic and the suitability for reduction using the Bartlett's test of sphericity. Additionally, parallel analysis was used to compare and confirm proposed number of factors. During EFA item reduction was performed as well, analysing inter-item and item-total correlations. Items with loading value <0.3 and those loaded on two or more factors (>0.32) were removed first. Before item removal the research team discussed the potential impact of the item, and the final decision was made based on reached consensus. Several variations of the EFA were performed to ensure the best possible combination of items formed the final versions of the questionnaire (considering loading values, variance, internal consistency, and practical matters). The model was considered having a good fit if less than 50% of the non-redundant residuals had absolute values >0.05. The pharmacists' data was randomly split into two groups (60% and 40% of participants to ensure adequate sample size) and the factors were developed on the 60% of the data. To confirm the proposed factors, 40% of pharmacists' data was used and forced factors extraction method was utilized. Physicians' data was insufficient to split and repeat the EFA.

2.2.3. Content Validity

Content validity was assessed employing Lawshe's method [34]. A panel of ten healthcare providers, which have not been involved in item development, scored post-EFA items as ''essential", ''useful but not essential", and ''not necessary". For each item content validity ratio (CVR) was calculated. Responses ''essential" and ''useful but not essential" were combined. Items with CVR < 0.62 (value of at least 0.62 equals > 80% of panellists considering the item to be essential or useful but not essential) were reviewed and removed.

2.2.4. Scoring of the Questionnaire

As a 5-point Likert scale was used the following scoring system was proposed: each item could be scored from 1 to 5. Factor score was calculated by summing all item scores and averaging with the number of items in that factor. That way each factor could have a score from 1 to 5. The overall factor theme determined the direction of scoring.

2.2.5. Criterion Validity

Criterion validity was established exploring this proposed hypothesis: items or factors associated with higher positivity towards deprescribing will be correlated with higher knowledge and awareness about deprescribing. Factors associated with obstacles towards deprescribing will be negatively correlated with willingness to suggest deprescribing, while facilitators of deprescribing will be positively correlated willingness to suggest deprescribing.

2.2.6. Reliability

The reliability of the final versions of questionnaire was assessed by determining internal consistency of the questionnaire and performing a test–retest. Internal consistency was determined for each factor via Cronbach's alpha testing. Items that increased Cronbach's alpha when deleted were removed from the questionnaire. For test–retest reliability new twenty healthcare providers were recruited. They were given hard copies of the final versions of the questionnaire to complete. Retest was scheduled two weeks later. Test–retest reliability of individual items was determined using linear-weighted Cohen's kappa. A Cohen's kappa coefficient of <0.20 was considered poor, 0.2–0.4 fair, 0.41–0.60 moderate, 0.61–0.80 good, and >0.80 very good [35]. Gamma rank correlation was used to determine the test–retest reliability of factor scores.

2.3. Case Vignette

The case was reviewed by a clinical pharmacy specialist and academic researcher to ensure proposed answers agreed with available guidelines in prescribing and deprescribing of potentially inappropriate medications.

2.4. Data Analysis

Sociodemographic data was analysed using descriptive statistics. For all analyses, a value of $p < 0.05$ was considered statistically significant. All analyses were performed using IBM SPSS Statistics for Windows, Version 26.0. (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Participants

Pharmacists' version of the CHOPPED questionnaire was sent to 1108 email addresses, and physicians' version was sent to 773 addresses. Response rate could not be estimated as there was no way to collect the precise number of email addresses the survey was sent to via the snowball sampling. For pharmacists' version 784 inputs were registered and for physicans' version 330. Overall, 356 pharmacists' and 109 physicians' complete inputs were available for validation analysis (Figure 1). Pharmacist who provided sociodemographic information but did not complete the survey were not statistically different in terms of age, years of experience, level of educational attainment or type of pharmacy practice to those who completed the survey. There was no statistically significant difference in characteristics (age, years of experience, practice characteristics, number of patients, or number of elderly patients in practice) among physicians who completed the survey and those who did not.

Both pharmacists and physicians were mostly female (86.23% pharmacists and 68.80% physicians). Pharmacists had a median age of 35 years (IQR 28–43), a median professional experience of 10 years (IQR 3–19.75) while physicians had a median age of 51 (IQR 33–59), a median professional experience of 23 years (IQR 7–31.50). Majority of healthcare providers worked in an urban area (58.43% pharmacists and 42.20% physicians) (Table 2) Based on surveys time stamp, the median time to complete the first part of the questionnaire was 8 min (IQR 3–16) for both pharmacists and physicians. Pharmacists spent a median of 16 min (IQR 5–24) completing the case vignette, while physicians spent a median 4 min (IQR 0.5–12).

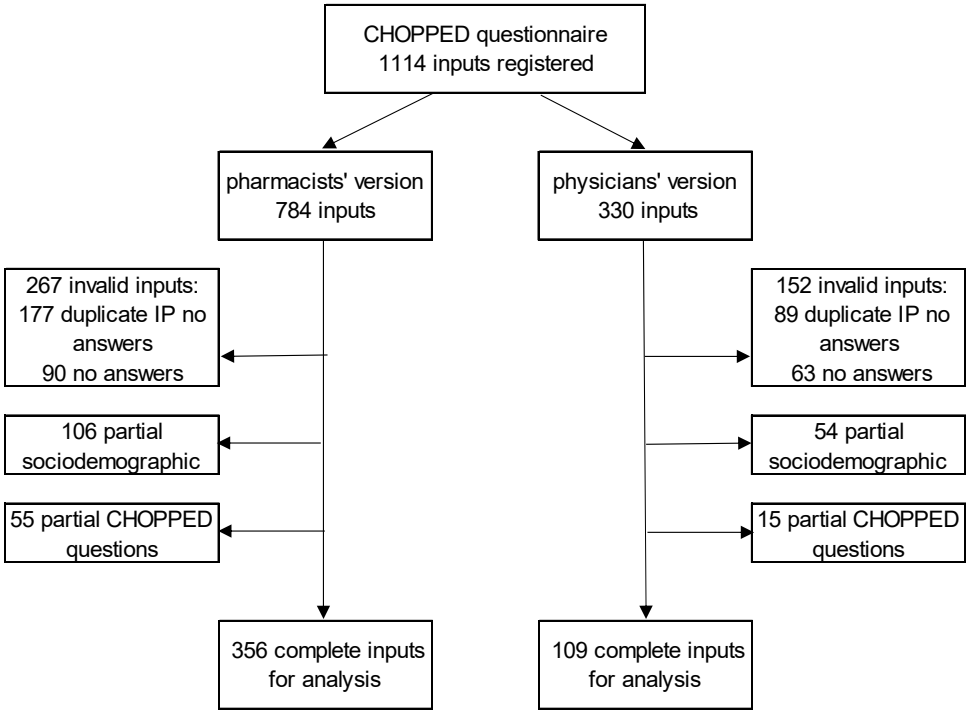

Figure 1. Participant recruitment and data selection.

Table 2. Participant characteristics.

Characteristics	Pharmacists	Physicians
Sex female (n, %)	307 (86.23%)	75 (68.80%)
Age (median, IQR)	35 (28–43)	51 (33–59)
Professional experience (median, IQR)	10 (3–19.75)	23 (7–31.5)
Practice location (n, %)		
urban	208 (58.43%)	46 (42.20%)
suburban	114 (32.02%)	38 (34.86%)
rural	34 (9.55%)	25 (22.93%)
Practice placement (n, %)		
within another healthcare facility	61 (17.13%)	75 (68.81%)
near another healthcare facility	140 (39.33%)	N/A
within a shopping facility	19 (5.34%)	N/A
displaced (not near any facility)	136 (38.20%)	34 (31.19%)
Patient population (median, IQR)		
number of patients	N/A	1600 (1216–1860)
percentage of elderly patients (>65 years)	N/A	35% (28.50–47.50)

3.2. Questionnaire Validation and Item Reduction

3.2.1. Construct Validity

The sampling adequacy of the 60% of the pharmacists' sample (n = 214) was confirmed using the Kaiser–Meyer–Olkin measure (0.834); Bartlett's test of sphericity ($p < 0.001$) confirmed the factorability. The scree plot indicated 12 factors that accounted for 40.67% of variance when all items were used in the analysis. After final extraction analysis, 37 items were retained and grouped into 10 factors. The final 10 factors accounted for 53.87% of the variance. There were 3% nonredundant residuals with absolute values greater than 0.05. When repeating the EFA on the remaining 40% of the sample (n = 142) and using the forced

factor extraction, all items loaded on the same factors. Five questions showed cross-loading with respect to other factors (loading values < 0.3200) but loaded the most strongly on the original factor. Parallel analysis confirmed 10 factors.

For the physicians' version of the questionnaire, the Kaiser–Meyer–Olkin measure of sampling adequacy was 0.759, and Bartlett's test of sphericity ($p < 0.001$) confirmed the factorability. The scree plot indicated 12 to 14 factors explaining 43.27% and 46.48% of the variance when all items were analysed. Several models were explored by removing and adding items in the analysis to achieve factors similar to those in the pharmacists' version. Finally, 35 items formed 10 factors, which accounted for 58.07% of the variance. The 10 factors were equal to those in the pharmacists' version and were confirmed with parallel analysis. There were 7% nonredundant residuals with absolute values greater than 0.05. There were certain differences in item loadings in the two versions. Questions, "*I worry that stopping medications could lead to adverse drug withdrawal effects or worsening of patient's health*", "*A decision support tool within healthcare providers software would enable me to suggest stopping medications more*", and "*I believe there is a disproportion between available guidelines on prescribing and stopping medications which makes it difficult for me to suggest deprescribing*" did not significantly load on any factors in the physicians' version of the questionnaire. Questions "*Having the possibility to contact a task force or a professional network when I am having doubts regarding stopping or reducing medications, would encourage me to suggest such changes*" and "*Lack of direct in-real-time communication with other healthcare providers (hospital doctors or specialists, pharmacist, nursing home care teams...) makes it difficult for me to suggest stopping or reducing medications*" did not significantly load on any factors in the pharmacists' version.

The retained 10 factors were grouped into three domains best described as: Knowledge and awareness about deprescribing, Barriers to deprescribing, and Facilitators of deprescribing. Knowledge and awareness about deprescribing contain seven items in two factors. In Barriers to deprescribing and Facilitators of deprescribing, four factors can be identified: patient factor, competencies factor, collaboration factor, and healthcare system factor. Each factor was explored with three or four items (Table 3).

The question "*I am willing to suggest deprescribing to a patient if appropriate*" was removed during EFA as it did not significantly load on any factor but was retained in both final versions of the questionnaire due to its overall importance.

Two versions of the questionnaire and differences in items can be seen in Table 3, and the source of questions and the initial version of the questionnaire can be seen in File S1.

Table 3. Questionnaire validation and reliability analysis.

Factor	Item	Factor Loading			Item: Total Correlation		Test–Retest Reliability [c]	
		Pharmacists'Version Development	Pharmacists' Version Repeatability	Physicians' Version	Pharmacists' Version	Physicians' Version	Pharmacists' Version	Physicians' Version
Knowledge factor Cronbach's α 0.684/0.703	tapering or reducing a dose	0.707	0.894	0.421	0.519	0.339	0.85	0.74
	changing medication to a safer alternative	0.720	0.543	0.633	0.519	0.339	0.47	0.57
	method of discontinuing a drug	0.624	0.540	0.671	0.505	0.541	0.59	0.52
Awareness factorCronbach's α 0.783/0.811	important as prescribing medication	0.378	0.786	0.769	0.505	0.665	0.38	0.61
	reduces health care expenditures/costs	0.707	0.735	0.549	0.644	0.472	0.36	0.43
	improve patient adherence	0.793	0.719	0.808	0.596	0.721	0.51	0.51
	patient outcomes	0.771	0.434	0.764	0.561	0.654	0.88	0.80
Patient Facilitators factorCronbach's α 0.776/0.713	patient desire to reduce	0.852	0.697	0.646	0.585	0.580	0.61	0.49
	successful prior stopping of medication	0.818	0.788	0.839	0.654	0.624	0.25	0.29
	easily available patient materials	0.436	0.718	[b]	0.501	[b]	0.51	[b]
	patients with greater involvement	0.571	0.798	0.361	0.611	0.585	0.44	0.39
Collaboration Facilitators factorCronbach's α 0.787/0.744	collaboration with pharmacist//collaboration with physician	0.572	0.506	0.730	0.542	0.558	0.48	0.48
	physicians contact pharmacists regarding patient care	0.589	0.428 [a]	[b]	0.548	[b]	0.57	[b]
	evidence-based pharmacists' rationale	[b]	[b]	0.803	[b]	0.641	[b]	0.59
	a public health project	0.808	0.378	0.854	0.649	0.763	0.49	0.36
Competencies Facilitators factorCronbach's α 0.870/0.861	continuing education on the rationale	[b]	[b]	0.686	[b]	0.585	[b]	0.50
	guidelines or algorithms	0.562	0.600 [a]	0.884	0.706	0.788	0.36	0.58
	how to approach patients	0.824	0.884	0.925	0.746	0.804	0.36	0.70
	medication review and management	0.682	0.884	0.872	0.713	0.801	0.47	0.69
	reminder/decision support tool	0.817	0.721	[b]	0.700	[b]	0.52	[b]
Healthcare systems Facilitators factorCronbach's α 0.694/0.629	reimbursement	0.454	0.593	0.781	0.463	0.447	0.48	0.54
	contact a task force or a professional network	[b]	[b]	0.510	[b]	0.351	[b]	0.37
	patients' medical records access	0.409	0.543	[b]	0.520	[b]	0.37	[b]
	additional staff members	0.591	0.441 [a]	0.363	0.507	0.407	0.30	0.54

Table 3. *Cont.*

Factor	Item	Factor Loading			Item: Total Correlation		Test–Retest Reliability [c]	
		Pharmacists'Version Development	Pharmacists' Version Repeatability	Physicians' Version	Pharmacists' Version	Physicians' Version	Pharmacists' Version	Physicians' Version
Patient Barriers factorCronbach's α 0.668/0.730	patients using medications for a long time	0.684	0.564	0.697	0.486	0.465	0.86	0.53
	harm my relationship with my patient	0.600	0.624	0.448	0.436	0.502	0.64	0.62
	patients with low understanding of their therapy	0.482	0.540	0.604	0.390	0.509	0.64	0.55
	insisting on continuing prescribing	[b]	[b]	0.829	[b]	0.583	[b]	0.45
	adverse effects or worsening of patient's health.	0.416	0.338	[b]	0.501	[b]	0.72	[b]
Collaboration Barriers factorCronbach's α 0.899/0.635	pharmacists suggestions are inappropriate	0.652	0.632	0.736	0.644	0.553	0.40	0.36
	lack of direct communication	[b]	[b]	0.405	[b]	0.643	[b]	0.44
	negatively influence relationship with prescribers//inappropriate to stop medications prescribed by other physicians	0.816	0.873 [a]	0.403	0.810	0.632	0.41	0.60
	physicians not understanding pharmacist//inappropriate for another physician to stop medications	0.843	0.926	0.442	0.823	0.515	0.50	0.34
	physicians find pharmacist unknowledgeable	0.940	0.865	[b]	0.825	[b]	0.67	[b]
Competencies barriers factor Cronbach's α 0.713/0.687	unable to identify potentially inappropriate medicines	0.630	0.711	0.333	0.460	0.495	0.48	0.38
	lack of confidence	0.657	0.580	0.891	0.580	0.549	0.48	0.82
	disproportion of guidelines	0.609	0.481	[b]	0.479	[b]	0.37	[b]
	apprehensive to stop preventative medication.	0.470	0.518 [a]	0.452	0.489	0.455	0.31	0.38
Healthcare systems Barriers factorCronbach's α 0.642/0.741	lack of time	0.521	0.889	0.788	0.569	0.573	0.29	0.66
	additional documentation	0.455	0.442	0.797	0.383	0.501	0.22	0.53
	lack of space//fragmented patients care	0.480	0.442	0.527	0.558	0.481	0.52	0.52
	lack of policy and legislation	0.613	0.440	0.501	0.387	0.591	0.49	0.49
Willingness	willing to suggest deprescribing	NA	NA	NA	NA	NA	0.77	0.69

[a] questions showing cross-loading with respect to other factors (loading values < 0.3200); loading was the most strongly related to the original factor, [b] questions not in the pharmacists' or physicians' version, [c] Cohen's kappa.

3.2.2. Content Validity

During the content validity assessment, the CVR for all items was calculated as >0.62, and as such, no items were removed (Table S1). The majority of items had a CVR of 1, and around 36% of items had a CVR of 0.8.

3.2.3. Scoring of the Questionnaire

A simple unweighted approach was chosen. Factors were scored so that the higher score indicated higher knowledge and awareness of deprescribing, as well as a greater effect of barriers or facilitators on deprescribing. Willingness to deprescribe was not scored, and a total score for the complete questionnaire was not developed.

In the pharmacists' version, the mean value of factor scores was knowledge 4.04 ± 0.88, awareness 4.57 ± 0.57, patient facilitator 3.63 ± 0.81, collaboration facilitator 4.51 ± 0.58, competencies facilitator 4.45 ± 0.65, healthcare system facilitator 4.22 ± 0.78, patient barrier 3.21 ± 0.72, collaboration barrier 3.65 ± 1.01, competencies barrier 3.42 ± 0.74, and healthcare system barrier 3.89 ± 0.75. In the physicians' version, the mean value of factor scores was knowledge 3.71 ± 0.84, awareness 4.19 ± 0.77, patient facilitator 3.77 ± 0.67, collaboration facilitator 3.78 ± 0.93, competencies facilitator 3.95 ± 0.84, healthcare system facilitator 3.90 ± 0.80, patient barrier 3.11 ± 0.81, collaboration barrier 3.16 ± 0.76, competencies barrier 2.87 ± 0.82, and healthcare system barrier 3.84 ± 0.81. A detailed table with minimum and maximum values can be found in Table S2.

3.2.4. Criterion Validity

Greater knowledge and awareness were correlated with greater willingness to suggest deprescribing in both pharmacists' and physicians' data (G = 0.228; $p < 0.001$ and G = 0.292; $p = 0.002$, respectively). In the pharmacists' data, an increased perception of barriers of deprescribing was inversely correlated with the willingness to suggest deprescribing to patients (G = −0.182, $p = 0.001$). Facilitators of deprescribing were statistically significantly associated with the willingness to suggest deprescribing (G = 0.298, $p < 0.001$). In the physicians' data, a greater perception of facilitators of the deprescribing score was associated with greater willingness to suggest deprescribing (G = 0.213, $p = 0.026$). There was no correlation between physicians' willingness to deprescribe and barriers (G = 0.115, $p = 0.193$).

3.2.5. Reliability

Internal consistency was assessed by analysing Cronbach's alpha, which showed satisfactory scores for all factors in both versions of the questionnaire [36]. In the pharmacists' version, competencies facilitators and the collaboration barriers had exemplary internal consistency (>0.8), while awareness, patient facilitators, collaboration facilitators, and competencies barriers had extensive internal consistency (>0.7). Internal consistency for knowledge, healthcare system facilitators, patient barriers, and healthcare system barriers was moderate (>0.6) [37]. In the physicians' version, awareness and competencies facilitators had exemplary internal consistency (>0.8). Knowledge, patient facilitators, collaboration facilitators, patient barriers, and healthcare system barriers had extensive internal consistency (>0.7). Moderate internal consistency was found for healthcare system facilitators, collaboration barriers, and competencies barriers, with Cronbach's alpha levels >0.6 (Table 1). No individual item of each factor increased the alpha score when deleted; therefore, no item was deleted for the respective factors.

Repeatability based on the analysed linear-weighted Cohen's kappa was fair for two questions, moderate for 36, good for 14, and very good for four questions (Table 3). Gamma rank correlations of total factor scores were strong and very strong. In the pharmacists' version, the knowledge factor had a G value of 0.938, the awareness factor had G = 0.519, patients' facilitators had G = 0.552, collaboration facilitators had G = 0.929, competencies facilitators had G = 0.531, and the healthcare systems facilitators had G = 0.881. In the barriers theme, patients' barriers had G = 0.826, collaboration barriers had G = 0.544,

competencies barriers had G = 0.789, and healthcare system barriers had G = 0.645. In the physicians' version, the G values were as follows: knowledge factor 0.864, awareness factor 0.565, patients' facilitators 0.695, collaboration facilitators 0.812, competencies facilitators 0.559, healthcare system facilitators 0.844, patients' barriers 0.902, collaboration barriers 0.623, competencies barriers 0.682, and healthcare systems' barriers 0.545. All factor score correlations were statistically significant, with $p < 0.001$.

4. Discussion

This study describes the development and validation of a novel tool that can explore healthcare providers' opinions and preferences regarding deprescribing. Validation analysis demonstrated that a psychometrically rational questionnaire was developed. Factors such as knowledge and awareness, as well as facilitator factors, were correlated with a greater willingness to suggest deprescribing. At the moment, there are several attempts in the development of a questionnaire suitable for healthcare providers [15,38–40]. This accentuates the global need for tools to widely investigate important deprescribing factors that might influence implementation in everyday practice. The tool developed by Shrestha and colleagues, designed to explore healthcare professionals' attitudes towards deprescribing in older adults with limited life expectancy (HATD tool), identified factors named concerns and assurance, which have a similar construct to the CHOPPED competencies barriers and facilitators [40]. The Brazilian Desmedica Study protocol describes a conceptual framework with similar themes such as the health system or patient context [38]. These similarities additionally confirm not only universally recognized barriers, but also that the CHOPPED questionnaires' factors have the potential to be applied to different healthcare systems around the world. The questionnaire proposed in this study is one of the first tools to be validated and used amongst healthcare providers inexperienced in deprescribing. The tool explores general barriers and facilitators, regardless of the type of patient or medication aimed to deprescribe. The CHOPPED questionnaire contains 10 factors meaningful for potential deprescribing. Adequate knowledge and awareness of the benefits of a service, such as deprescribing, are an important basis for future implementation [41]. An extensive literature review helped to generate potential questionnaire items, showing the complex background of deprescribing, as well as the impact it has on healthcare providers' attitudes [6,13,14,19,23,25,42–46]. This questionnaire aimed to quantitatively capture these barriers and facilitators. Patient factor items explore the connection between healthcare providers' willingness and hesitancies to deprescribe and a patient's involvement with medication, as well as the influence of deprescribing on their relationship. Items from the collaboration factors explore how inter- and intra-professional collaboration can affect potential deprescribing decisions. The competencies factors examine healthcare providers' necessary skills and intrinsic motivation needed to suggest deprescribing. Healthcare system factors explore how policy, legislation, renumeration, access to information, or workplace organization affect deprescribing initiatives. Certain similar concepts were explored in qualitative studies [47–49]. Item: "I am willing to suggest deprescribing to a patient if appropriate" was kept in the questionnaire even though it did not load significantly on any factor. It was deemed to be essential by all the panellists as it could potentially quantitatively define the true willingness to suggest deprescribing and could potentially be correlated with the suggested deprescribing factors.

A case vignette ensured participants were given a clinical conundrum similar to those seen in everyday practice. Case vignettes can be a useful learning and implementational tool, but a detailed analysis was out of scope for this manuscript [50,51]. Future in-depth analysis of the case vignette answers could be correlated with the questionnaire factor scores. This could help outline types of healthcare providers who are keener to suggest deprescribing. It can also be used to identify common deprescribing misconceptions.

Two versions were developed, one for pharmacists and one for physicians. This, alongside a case vignette, additionally distinguishes CHOPPED from other tools. One tool enables easier identification of common barriers and facilitators within the same

healthcare system, while two versions allow finer understanding of professional specific viewpoints. The majority of the developed items (regarding patients, competencies, or healthcare systems) were appropriate for both pharmacists and physicians. When it came to differences between professions or their responsibilities, equivalent items were developed. For example, items regarding collaboration were formulated from the position of a certain healthcare provider. The main item of willingness to suggest deprescribing remained the same for both professions. Deprescribing is first and foremost a patient-centred process, and each different healthcare provider can substantially contribute to effective deprescribing. Focus groups, semi-structured interviews, and case vignettes are the most commonly used research methods, and general practitioners and healthcare providers with prescribing privileges are the most common research participants [11,26,27,52–56]. Healthcare systems are recognizing pharmacists as valuable deprescribing partners, and research shows pharmacist-led or collaborative deprescribing interventions are effective and safe [57–61]. Examining profession-specific viewpoints can be beneficial for achieving the multi-disciplinary approach deprescribing requires. The CHOPPED questionnaire has the potential to be used in primary care settings where other healthcare providers, such as nurses (nurse practitioners' practices, mobile nursing practices), have prescribing rights or participate in deprescribing. Recently, there has been a surge of research publications regarding nurses' positions and perspectives in deprescribing, especially in terms of geriatric patients [62–64]. Depending on the particular nursing professionals' responsibilities, both versions of CHOPPED could be used. The pharmacists' version of the questionnaire with minor changes might be a good starting point to explore nurses' perceptions of deprescribing, especially for those without prescribing rights. For those with prescribing rights, the adjusted physicians' version could be used. In healthcare systems with a GP-nurse–pharmacist team care for the same patient, it would be prudent to educate and involve nurses in deprescribing as well.

Analysis showed that the developed tool has satisfactory face, construct, and content validity for both versions. Criterion validity was established for both versions as well, but additional research is needed to confirm other types of criterion validity, especially concurrent validity using other scales.

Strengths and Limitations

The test–retest subjects had a median age of 33 years (IQR 26–40), and a median of seven years of professional experience (IQR 2–14), being somewhat younger than the participants in the validation samples (Additional information on test–retest participants' characteristics is provided in Supplementary Table S3). This could have influenced the values of the reliability analysis. Lower Cohen's kappa for certain items might be due to changes in perception of items in the questionnaire as well as changes in knowledge and opinion when retesting. Deprescribing is a relatively new topic amongst the test–retest participants. There was no significant difference in the test–retest scores between the two professions. The range of scores implies the scales have the ability to capture differences in opinion and could indicate that participants have not merely provided a satisfactory answer. Moderate internal consistency was found for four factors in the pharmacists' version and for three factors in the physicians' version. Regardless, reliability analysis showed satisfactory internal consistency and adequate repeatability.

Additional limitation could concern the participants in the validation samples. A less age-diverse sample of pharmacists completed the questionnaire compared to physicians. Potential reasons could include younger participants having higher computer literacy or being more prone to using internet tools. During questionnaire development, several panellists commented on the possibility to distribute the survey in paper form, as many mature healthcare providers still prefer such surveys. Due to the COVID-19 pandemic and a lack of face-to-face events, where such a method could be used, it was viewed that the internet distribution was a more wholesome option as it could reach healthcare providers in displaced and rural areas as well. More mature pharmacists could have had different

opinions, which could have affected the correlation analysis. Furthermore, the physicians' sample was three times smaller than the pharmacists' sample, and a larger percentage of physicians' inputs was invalid. The reasons for this lower participation rate could include a lack of time or interest in participation due to the pandemic. Further studies should include more experienced healthcare providers or different distribution methods to gain a more in-depth view of the topic. Most participants in both samples were female, which might be viewed as a limitation as well. Based on data from the Croatian Institute of Public Health and Croatian chamber of pharmacists, more than 60% of all physicians are female and more than 80% of all pharmacists are female [65,66]. The sample of healthcare providers in this study adequately represents the population of healthcare providers in Croatia.

While there is substantial qualitative research regarding barriers and facilitators of deprescribing [67], this study brings a novel tool that can be used in different healthcare systems and in different levels of healthcare. Underdeveloped or developing healthcare systems are confronted with different barriers than developed healthcare systems with implemented and widely accepted pharmacists' interventions. Gaining knowledge on potential barriers or facilitators can help such a system in policy and legislation development and in finding the best implementation strategy of a service such as deprescribing. For instance, a healthcare system's barriers in certain settings might be greater than competencies barriers and could indicate changes in information access or an increase in personnel is needed.

The length of the questionnaire could be viewed as a potential limitation. It was developed and validated on a population of healthcare providers new to deprescribing. The main aim of the CHOPPED questionnaire is to comprehensively and thoroughly explore all latent traits connected to deprescribing. Awareness of deprescribing was correlated with willingness to deprescribe. Raising awareness amongst inexperienced healthcare providers could potentially initiate deprescribing engagement. For healthcare providers familiar with deprescribing, only barrier and facilitator factors can be used. It would be beneficial to use the tool for such healthcare providers and compare and contrast barriers and facilitators.

The CHOPPED questionnaire has the potential to be universally used in the primary care setting. As evidence on deprescribing is growing, future revision of the questionnaire will most likely be necessary. Future research should include using the suggested questionnaire or its factors as a part of a deprescribing intervention.

5. Conclusions

A comprehensive questionnaire exploring healthcare providers' attitudes towards deprescribing was developed. Ten factors were identified: knowledge, awareness, patient barriers and facilitators, competencies barriers and facilitators, collaboration barriers and facilitators, and healthcare systems' barriers and facilitators. The tool has the potential to help identify obstacles and enablers of deprescribing in the primary care setting and facilitate implementation of the deprescribing process.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/pharmacy10040076/s1, File S1: The preliminary 58 items and source of items; File S2: CHOPPED case vignette; Table S1: Content validity assessment (number of panellist's responses). Table S2: Distribution of factor scores; Table S3: Test–retest participants' characteristics. References [68–80] are cited in the supplementary materials.

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7. DIFFERENCES IN FACTORS INFLUENCING DEPRESCRIBING BETWEEN PRIMARY CARE PROVIDERS: CROSS-SECTIONAL STUDY

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Differences in Factors Influencing Deprescribing between Primary Care Providers: Cross-Sectional Study

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Abstract: Deprescribing is a notable approach to improve medication management, but few healthcare systems recognize it. To introduce a new practice, it is important to examine the factors influencing the provision of a new or elaborate cognitive service within the desired setting. This study explores the perceived barriers and facilitators of deprescribing by primary healthcare providers, and identifies the factors associated with a willingness to suggest deprescribing. A cross-sectional survey was conducted (in Croatia, between October 2021 and January 2022) using a validated comprehensive healthcare providers' opinions, preferences, and attitudes towards deprescribing (CHOPPED) questionnaire. A total of 419 pharmacists and 124 physicians participated. Participants showed a high willingness to deprescribe, with significantly higher scores in physicians than in pharmacists (5.00 (interquartile range—IQR 5–5) vs. 4.00 (IQR 4–5), $p < 0.001$). Pharmacists had significantly higher scores in seven out of ten factors (knowledge, awareness, collaboration facilitators, competencies facilitators, healthcare system facilitators, collaboration barriers, competencies barriers) while in the remaining three factors (patient facilitators, patient and healthcare system barriers) there was no difference in scores. The strongest positive correlation with willingness to suggest deprescribing was found with the collaboration and healthcare system facilitators factors for pharmacists (G = 0.331, $p < 0.001$, and G = 0.309, $p < 0.001$, respectively), and with knowledge, awareness, and patient facilitators factors for physicians (G = 0.446, $p = 0.001$; G = 0.771, $p < 0.001$; and G = 0.259, $p = 0.043$, respectively). Primary healthcare providers are willing to suggest deprescribing but face different barriers and facilitators. For pharmacists, the most important facilitators were extrinsic, while for physicians they were more intrinsic and patient related. The stated results provide target areas which one could focus upon to help to engage healthcare providers in deprescribing.

Keywords: deprescribing; barrier; facilitator; primary healthcare; questionnaire

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1. Introduction

Inappropriate polypharmacy (the use of five or more medicines concurrently), is a well-known risk factor for negative health outcomes, including increased healthcare costs, adverse drug events, drug interactions, decline in functional status, medication non-adherence, or cognitive impairment [1]. This problem is especially worrisome in regard to the elderly. As the global population is aging, it is expected that increasing rates of unnecessary polypharmacy will lead to inadequate care for a large number of sensitive elderly patients. Many countries are recognizing this problem and reforming policy paths in order to keep a sustainable healthcare system [2–4].

In recent years, deprescribing, the planned and supervised process of medication withdrawal or dose reduction with the intent to manage polypharmacy and improve outcomes [5], is becoming a noticeable approach to help healthcare providers resolve both existing and potential medication-related problems [6].

Different healthcare providers can uniquely contribute to deprescribing [7]. It has been shown that pharmacist-led or -initiated deprescribing interventions are successful and

useful [8–11]. Pharmacists can identify candidates, initiate conversations on deprescribing, or suggest deprescribing interventions to physicians, as well as monitor and follow up on patients. Physicians' knowledge and relationship with patients can contribute to the easier adoption of suggested deprescribing [12]. Even though deprescribing is considered a part of good prescribing practice, and good clinical or pharmaceutical care, in many healthcare settings and systems it is still a novel approach. For instance, at the time of the study there were no official workflows, guidelines, or recommendations regarding providing deprescribing at the primary healthcare level in Croatia, nor was deprescribing defined as a part of any diagnostic–therapeutic approach. There were no official data on the topic of deprescribing at any healthcare level, and healthcare providers were not reimbursed for deprescribing. Suggesting deprescribing and providing adequate follow-up to patients were still matters of healthcare professionals' discretion. Both pharmacists and physicians suggest deprescribing to their patients as a part of their routine work, but this often depends on a collaborative approach. Due to a lack of access to the entirety of patients' medical records and the inability to make significant inputs into electronic records, pharmacists contact the primary care physician to discuss comprehensive interventions. Primary care physicians often discuss deprescribing with fellow specialist doctors when it comes to specialist-prescribed medications. Similarly to Croatia, in the majority of European countries, proactive deprescribing policies, frameworks, and workflows are still being formed [13]. Evidence is being gathered on how to successfully identify the challenges of implementation of deprescribing across healthcare systems and settings [14,15], as well as how to enhance deprescribing interventions both in research and in everyday practice [16,17].

In order to introduce a new practice, it is important to examine potential barriers and facilitators within the desired setting. Exploring opinions and attitudes towards new or elaborate cognitive services often requires time, experienced researchers, financial support, and readily available participants. To help reduce the costs of research and reach a larger number of important stakeholders who will provide the service and whose opinions, perceptions, experiences, and attitudes effect the provision of a service, a validated tool can be used for the identification of barriers and facilitators for deprescribing.

The aim of this study was to explore the perceived barriers and facilitators of deprescribing by primary care physicians and pharmacists inexperienced in every day deprescribing, and to identify whether any factors were associated with a willingness to suggest deprescribing.

2. Materials and Methods

A cross-sectional online survey was used to collect data, with LimeSurvey® software being used in the design and the distribution of the survey (LimeSurvey Version 2.67.1 + 170626; LimeSurvey GmbH, Hamburg, Germany. URL: http://www.limesurvey.org, accessed on 15 September 2021). The software used is part of the services, data, and collaboration system tools available from the University of Zagreb Computing Centre (SRCE). The survey consisted of three parts: sociodemographic questions, a comprehensive healthcare provider's opinions, preferences, and attitudes towards deprescribing questionnaire (CHOPPED), and a case vignette (analysis not included herein). The development and validation of the CHOPPED questionnaire have been described elsewhere [18]. Two versions of the questionnaire are available, one for pharmacists (with 38 items) and one for physicians (with 36 items). Each questionnaire consists of ten factors, knowledge, awareness, patient barriers/facilitators, competencies barriers/facilitators, collaboration barriers/facilitators, and healthcare system barriers/facilitators, and one question regarding the willingness to suggest deprescribing. Items within the knowledge factor, awareness factor, and willingness to suggest deprescribing are equal in both versions. For each facilitators factor, there was a difference in one item between the versions. For the barriers factor, the difference between the two versions was in one item for all factors except for the collaboration barrier factor, which had three profession-specific items that

were unique in each version. All of the questions within the CHOPPED questionnaire were scored on a 5-point Likert scale ("strongly disagree", "disagree", "neither agree nor disagree", "agree", and "strongly agree"). Details on items and the differences between the two versions are available in Supplementary File S1.

The link to the survey was sent to community pharmacists and primary care physicians (general practitioners or family physicians) as their professional email addresses were publicly available on the national chambers of pharmacists and physicians. Participants were asked to forward the link to the survey to potential participants (*snowballing method*). At the beginning of the survey, the participants had to read and digitally authorize the informed consent, without which they could not access the survey. All data were collected anonymously. Participants could save the answers of the unfinished survey and complete it at a later time. Two reminders to complete the survey were sent four and eight weeks after the initial email. The study was conducted in Croatia, between October 2021 and January 2022. To ensure there were no duplicate inputs, each unique IP address was marked in the responses. If a single IP address had multiple inputs, they were cross-checked for the uniqueness of the socio-demographic information. Duplicate unfinished or answerless questionnaire entries from duplicate IP addresses were discarded, as were other invalid or incomplete inputs.

Since there were no data or studies in Croatia on the topic of healthcare providers' attitudes towards deprescribing, a single population proportion formula was used, with a 95% confidence level and relative precision of 5%, and the proportion of primary care providers willing to suggest deprescribing was 50%. Sample size was determined based on the number of registered primary care physicians and community pharmacists. Data were available from the Croatian health statistics yearbook and the Croatian chamber of pharmacists states than in 2021 there were 2180 registered primary care physicians and 2870 registered community pharmacists [19,20]. Therefore, the calculated sample size was 339 for pharmacists and 327 for physicians.

Sociodemographic data were analyzed using descriptive statistics. The factor score was calculated by summing the score of each item and dividing it by the number of items within the factor. A chi-squared test was used to analyze differences in frequencies between groups. The Mann–Whitney U test was used to determine differences in CHOPPED factor scores between professions. Gamma rank correlation was used to analyze potential associations between factor scores and the willingness to deprescribe (using ordinal data for both factors' scores and willingness to suggest deprescribing). For all analyses, a value of $p < 0.05$ was considered to be statistically significant. All analyses were performed using IBM SPSS Statistics for Windows, Version 26.0. (IBM Corp., Armonk, NY, USA).

3. Results

In total, 419 pharmacists' and 124 physicians' inputs were available for analysis. No statistically significant differences, in any characteristics, were found for both the pharmacists' and physicians' samples when comparing those who completed the survey and those who completed just a part of it.

3.1. Participants Characteristics

Healthcare providers who participated in the study were mostly female at 82.32% (86.62% among pharmacists and 74.30% among physicians). They had a median of 36 years of age (interquartile range (IQR) 29–48), and a median of 11 years of professional experience (IQR 4–22). More than half of them worked in an urban area (55.99%), 32.04% worked in suburban areas, and 11.97% provided healthcare services in rural areas across Croatia. Detailed characteristics of participants and differences between professions can be found in Table 1. Practices were almost equally placed either near other healthcare facilities (34.26%) or defined as a displaced/standalone practice (35.54%), while 25.78% of practices were within another larger healthcare facility, and 4.42% were within a shopping center.

Table 1. Participants' characteristics.

Characteristic	Pharmacists (*n* = 419)	Physicians (*n* = 124)
sex (female gender, %)	86.62	74.30
age (median, IQR)	35 (28–43)	50 (33–60)
years of experience (median, IQR)	10 (3–19)	24 (6.75–33)
highest educational attainment		
graduate degree	83.94	26.16
postgraduate specialist course [a]	11.44	n/a
health specialization [b]	3.41	72.80
master's degree (MSc)	0.48	0.72
doctoral degree (PhD)	0.73	0.32
location		
urban	59.85	43.58
suburban	31.15	38.54
rural	9.00	17.88
practice location		
within another healthcare facility	16.55	59.78
near another healthcare facility	40.15	11.17
within a shopping center	5.59	n/a
displaced/not near another healthcare facility	37.71	29.05
practice ownership		
private/concession	54.00	23.20
public	46.00	76.80
type of ownership		
single practice	13.12	n/a
chain pharmacy <10 units	28.00	n/a
chain pharmacy >10 units	58.88	n/a
number of patients in practice (median, IQR)	n/a	1650 (1250–1946)
percentage of elderly patients in practice (median, IQR)	n/a	35 (28.75–50)

[a] 1-year course, [b] 3-year healthcare residency including postgraduate specialist course, IQR—interquartile range; n/a- not applicable.

3.2. Knowledge and Awareness of Deprescribing

When it came to knowledge about deprescribing, pharmacists were more likely to agree with statements that deprescribing involves tapering and reducing the dose of a medication or that it represents changing medication to a safer alternative than physicians (71.59% vs. 52.42%, $\chi^2(4) = 25.64$, $p < 0.001$, and 61.09% vs. 43.49%, $\chi^2(4) = 15.16$, $p = 0.004$, respectively).

Even though the majority of all healthcare providers agreed with all of the statements in the awareness factor, pharmacists were more likely to find deprescribing as being as important as prescribing medication compared to physicians (94.98% vs. 83.87% $\chi^2(4) = 17.64$, $p = 0.001$). Physicians were less likely to be aware of the deprescribing benefits, including a reduction in healthcare expenditures, an improvement in outcomes, or adherence, than pharmacists (91.88% vs. 75.86%, $\chi^2(4) = 40.02$, $p < 0.001$, 86.87% vs. 66.13%, $\chi^2(4) = 35.05$, $p < 0.001$, and 80.44% vs. 77.41% $\chi^2(4) = 29.01$, $p < 0.001$, respectively).

3.3. Facilitators and Barriers of Deprescribing

Four factors pertaining to the facilitators and barriers of deprescribing were examined: patient, collaboration, competencies, and healthcare system.

In the patient facilitators factor, participants agreed the most with the statement "*I am keener to suggest stopping medications to patients who show greater involvement in their medication*" with 83.74% being positive answers. Conversely, only 39.22% of participants agreed that they would suggest deprescribing to patients if patients expressed their desire to have their number of medications reduced. There was no difference in agreement between professions for any of the statements.

In the collaboration facilitators factor, both professions agreed that a public healthcare project on deprescribing would be encouraging (81.30% of all participants). In the physicians' version, 77.19% considered having pharmacists' evidence-based deprescribing rationale to be useful for suggesting deprescribing, and more than half (57.89%) found a close collaboration with a pharmacist encouraging. A greater majority of pharmacists agreed that a close collaboration with a physician would encourage them to suggest deprescribing (92.59%).

The majority of participants (85.34 of physicians and 89.82% of pharmacists) agreed that they needed incentives when it came to their competencies. Physicians were less likely to state that they needed education on medication review, how to approach patients regarding deprescribing, or guidelines and algorithms than pharmacists (69.45% vs. 93.32%, $\chi^2(4) = 62.69$, $p < 0.001$; 70.83% vs. 87.83%, $\chi^2(4) = 34.19$, $p < 0.001$; 69.44% vs. 92.36%, $\chi^2(4) = 52.39$, $p < 0.001$, respectively).

Even though more than 60% (64.15%) of all participants believed that reimbursement for deprescribing is needed, physicians were more likely to disagree with this statement than pharmacists (36.11% vs. 13.60%, $\chi^2(4) = 42.53$, $p < 0.001$). There was no difference in agreement between professions for other items in the healthcare system facilitators factor.

In the patient barriers factor, healthcare providers were the least worried about deprescribing suggestions negatively influencing their relationship with patients, with 15.04% of participants agreeing with this statement. On the other hand, the majority of healthcare providers (83.69%) found it difficult to suggest deprescribing to patients with low involvement in medication decision-making. Pharmacists were more likely to find this statement to be a barrier than physicians (88.07% vs. 49.06%, $\chi^2(4) = 58.73$, $p < 0.001$).

In the collaboration barriers factor, pharmacists were most concerned about physicians finding their suggestions inappropriate (70.80%), while physicians found the biggest barrier being a lack of real-time communication with other healthcare providers (70.64%).

Competencies barriers differed amongst healthcare providers. Pharmacists found recommending deprescribing preventative medications a higher barrier than physicians (44.63% vs. 13.21%, $\chi^2(4) = 38.46$, $p < 0.0001$). Pharmacists indicated that they had lower confidence and found it more difficult to identify potentially inappropriate medications than physicians (32.22% vs. 13.20%, $\chi^2(4) = 12.46$, $p = 0.014$, and 57.28% vs. 33.96%, $\chi^2(4) = 11.94$, $p = 0.018$, respectively).

Within a healthcare system, participants perceived a lack of time and lack of legislation as being the biggest barriers (72.25% and 78.39%, respectively). Physicians were less hindered by a lack of legislation than pharmacists (49.06% vs. 82.10%, $\chi^2(4) = 43.52$, $p < 0.001$). Pharmacists considered a lack of time to be a higher obstacle than physicians (74.46% vs. 54.72%, $\chi^2(4) = 10.80$, $p = 0.029$).

Detailed answers to all of the questions within both versions of the CHOPPED questionnaire can be seen in Supplementary Figure S1.

When analyzing differences in factor scores between pharmacists and physicians, it was found that pharmacists had statistically significantly higher scores in all factors except for patient facilitators, patient barriers, and healthcare system barriers (Figure 1).

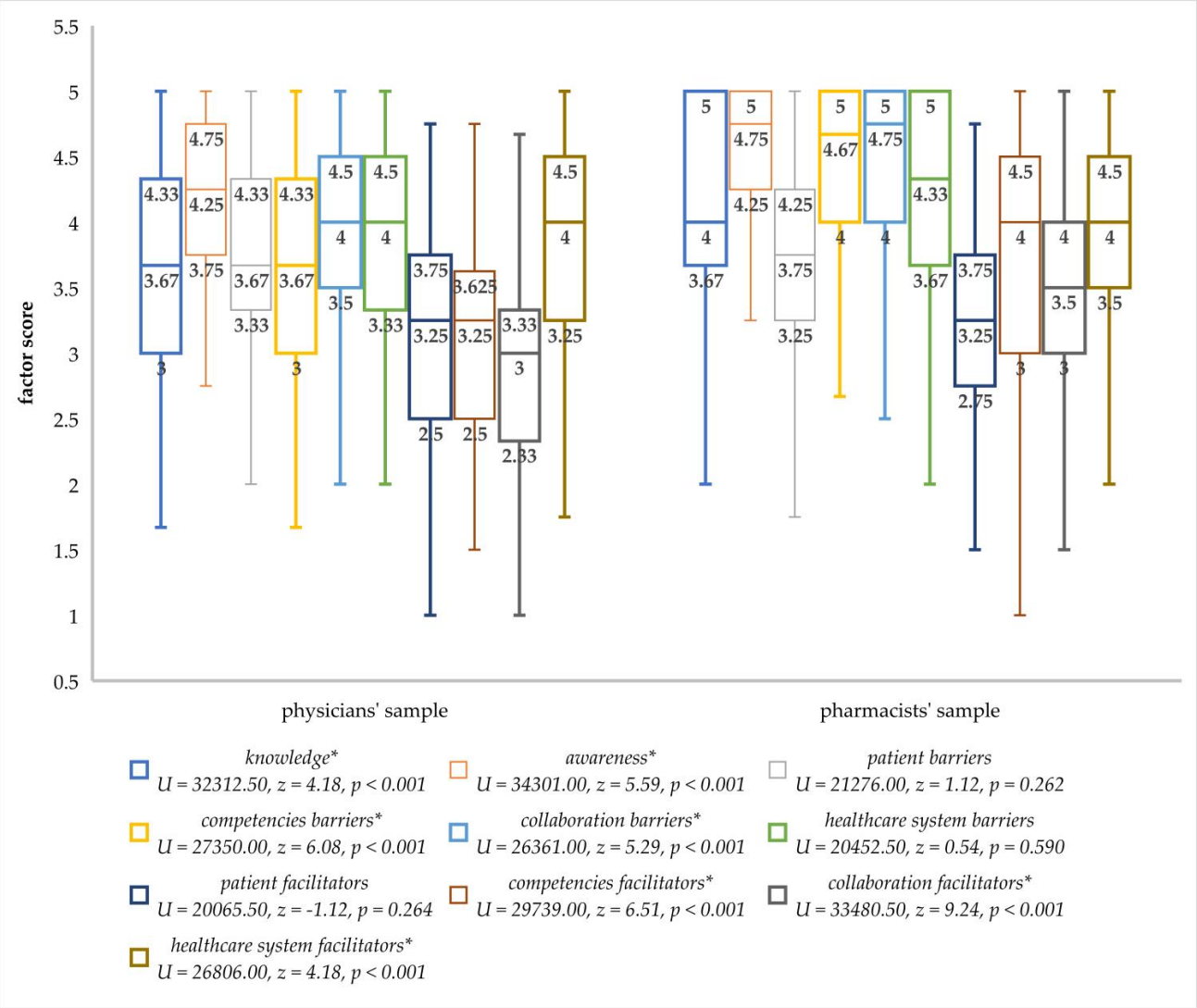


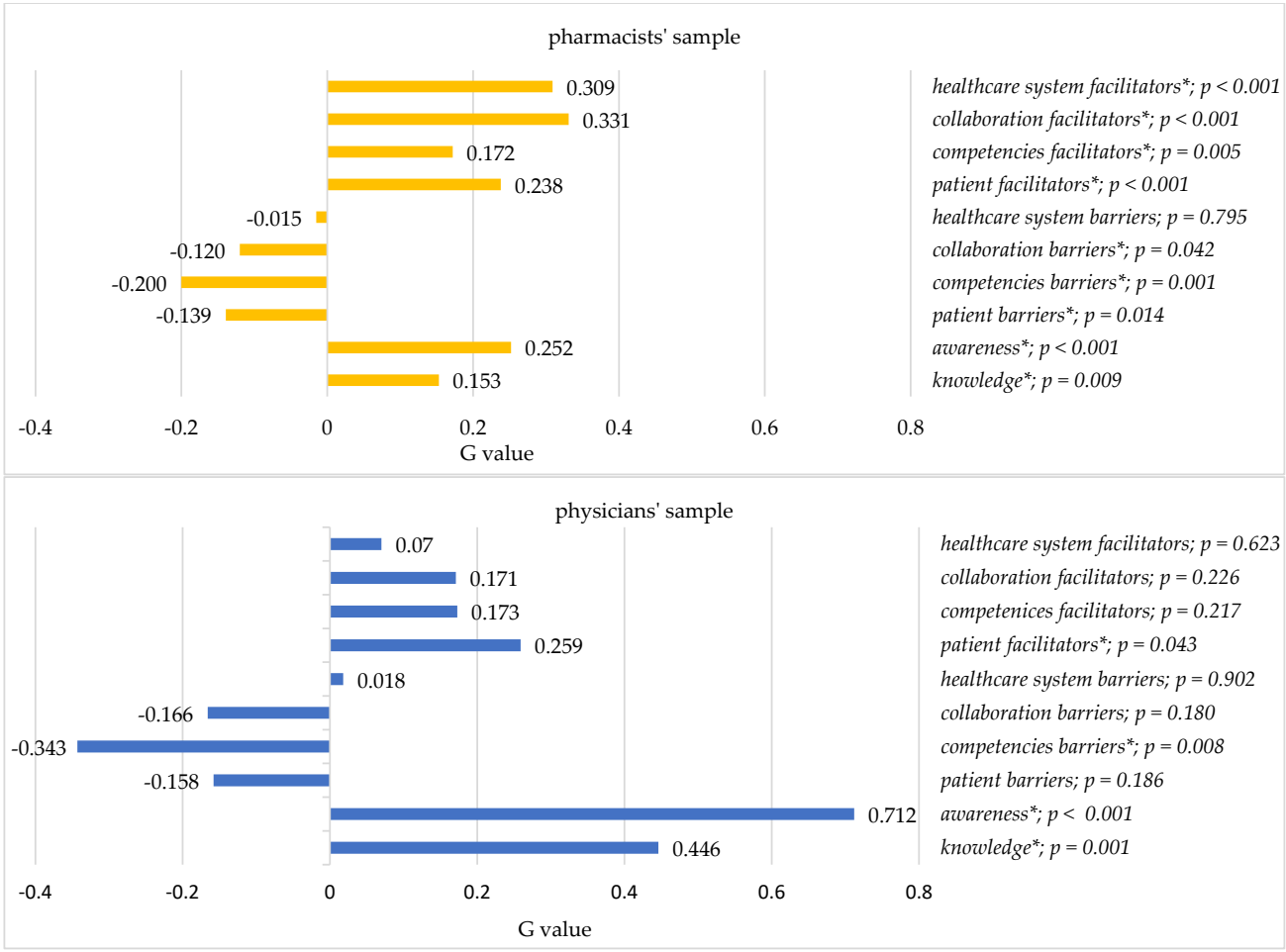
Figure 1. Differences in factor scores between pharmacists and physicians (Mann–Whitney U test).

3.4. Willingness to Suggest Deprescribing

More than 80% (n = 473, 87.12%) of all healthcare providers stated that they would suggest deprescribing to a patient if this was appropriate. Pharmacists were more likely to show uncertainty, with 11.97% of them stating "neither agree nor disagree" in comparison to 3.36% of physicians ($\chi^2(4) = 44.93$, $p < 0.001$). In both the pharmacists' and the physicians' samples, there was no difference in willingness to suggest deprescribing between participants based on age, years of experience, education, location, or practice characteristics. The median willingness to suggest deprescribing score was statistically significantly higher in physicians than in pharmacists (5.00 (IQR 5–5) vs. (4.00 (IQR 4–5)), U = 15293.00, z = −6.62, $p < 0.001$).

Several factors were associated with an increased willingness to suggest deprescribing in both samples. In the pharmacists' sample, all factors, except healthcare system barriers, were statistically significantly associated with a willingness to suggest deprescribing. The strength of association was weak to moderate, with collaboration facilitator and healthcare system facilitator factors showing the strongest correlation in the pharmacists' sample. In the physicians' sample, four factors were associated with a willingness to suggest deprescribing. The knowledge factor was very strongly associated with a willingness to suggest deprescribing, while the awareness factor exhibited a strong correlation. Patient

facilitators and competencies barriers factors were moderately associated with a wiliness to suggest deprescribing. The negative correlation found between a willingness to suggest deprescribing and the competencies barriers factor indicates that an increased perception of a lack of personal competencies was associated with a lower willingness to suggest deprescribing. Additional information on the correlation between the willingness to suggest deprescribing and the CHOPPED factors can be found in Figure 2.



*statistically significant correlation

Figure 2. Gamma rank correlation.

4. Discussion

Healthcare providers are willing to suggest deprescribing, with pharmacists showing more uncertainty than physicians. Contrariwise, pharmacists showed higher knowledge and awareness of the deprescribing benefits than physicians. An Irish study on community pharmacists highlights a similar finding, where pharmacists express high knowledge, but their willingness is hindered by different obstacles [21]. Pharmacists' uncertainty could be attributed to the lower confidence that they expressed in comparison to physicians. These results are in line with research confirming that the majority of physicians feel comfortable and self-assured with deprescribing [22,23], as well as that pharmacists often feel less confident in their role in deprescribing [24].

There is a noticeable distinction between pharmacists and physicians when it comes to the correlation between the willingness to suggest deprescribing and other factors. For pharmacists, it was the collaboration facilitators and healthcare system facilitators factors, and for physicians it was knowledge, awareness, and patient facilitators factors. This not

only accentuates the differences between professions, but also highlights the possible target areas which one could focus upon to help to engage healthcare providers in deprescribing.

Each healthcare system is different and needs a customized implementational strategy in order to deliver an intervention. Analyzing determinants which affect this implementation is a critical step in ensuring the success of a clinical intervention [25]. The decision to suggest deprescribing is complex and influenced by a number of factors, and some of which can be overlooked when only explored through the viewpoint of those involved in qualitative studies. Having a tool which can help measure the willingness to deprescribe in a larger number of healthcare providers can give a more realistic insight into the readiness of the setting to implement deprescribing. Tools similar to the CHOPPED questionnaire are being developed, which underlines the need for and importance of exploring deprescribing factors within healthcare systems [26,27]. Most qualitative research has focused on the opinions, beliefs, and attitudes of physicians, with pharmacists and other healthcare providers being less represented [22,28–35]. It is sensible to involve those who prescribe medication in deprescribing; nevertheless, research shows that other healthcare providers can be important stakeholders and facilitators of deprescribing [10,11,36]. Deprescribing is an intricate intervention often more successful if a multidisciplinary approach is satisfied [37,38]. The CHOPPED questionnaire explores, among others, collaboration barriers and facilitators in both versions, with the increased collaboration facilitators factor score being associated with an increased willingness to suggest deprescribing in the pharmacists' version for this sample. Furthermore, increased knowledge and awareness of deprescribing were associated with an increased willingness to suggest deprescribing, while a decreased perception of competencies was associated with a decreased willingness to deprescribe in both versions. Continuous professional education and early introduction to the concept of deprescribing as a part of pharmacy or medical curricula could help future generations of pharmacists and physicians to increase their involvement in proactive deprescribing [8,39,40]. Taking actions to involve patients or the public in deprescribing, such as having open discussion days on medication optimization actions with patient advocacy groups or visiting nursing homes to talk to patients about healthcare, can have multiple benefits. On the one hand it can increase the patient facilitator factor score which is important for healthcare providers to increase their willingness to suggest deprescribing, and on the other hand it creates opportunities for patients to help guide healthcare providers in creating interventions tailored to their specific needs. Finally, the CHOPPED questionnaire as a tool has the potential to help characterize differences in factors influencing deprescribing among healthcare providers and to help recognize target areas needing improvement.

4.1. Limitations

Several limitations of this study should be stated. Nonresponse bias, as a type of selection bias when using an online survey as the method of data collection, could be viewed as a limitation of this study. The true response rate could not be determined since the exact number of healthcare providers reached by the snowballing method is unknown. Additionally, unknown number of email addresses could have been incorrect, duplicated, or unavailable. Differences in sample sizes, age and experience of participants, or female-dominated participation could be viewed as a shortcoming. Regardless, selection bias can be considered to be minimal since the characteristics of both samples of involved healthcare providers (gender, educational attainment, and practice location) correspond to those of the population of interest [19]. The survey reached around 15% of the overall community of the pharmacists' population and around 6% of the population of primary care physicians in Croatia, which can be considered satisfactory, especially in the circumstances of the pandemic. Based on the number of respondents, the crude estimation of the targeted population for each profession, and the defined confidence interval of 95%, a satisfactory margin of error was determined: 4.43% for the pharmacists' sample and 8.56% for the physicians' sample. The results of this study could not be generalized and do not apply to different study populations aside from ours. The study was carried out in Croatia, a small

country with a developing healthcare system based on social solidarity. It is important to state that deprescribing is very new concept in the investigated setting and this may have led to healthcare providers being more familiar with the concept being the ones willing to participate in the study, creating a bias. Nevertheless, a significant advantage of this research is a strong methodology for the development and validation of the tool used in this research with confirmed face, content, construct, and criterion validity [18].

4.2. Implications for Research Practice

One advantage of CHOPPED as a tool is that it can be reused to re-evaluate healthcare professionals' viewpoints as providers as the system changes or adapts. The two versions of the tool allow for a more tailored approach to each profession, yet the universal and shared factors ensure that systematic changes can be achieved where necessary. Optimizing workload, giving access to important patient information, providing patient deprescribing materials, improving knowledge on the advantages of deprescribing, and creating opportunities for inter- and intra-professional communication and collaboration are the possible goals for overcoming the hurdles recognized by the CHOPPED tool. For instance, within a health center, a multidisciplinary workshop focusing on increasing collaborative practice and awareness on deprescribing benefits could be of help to both professions. Studies including more mature pharmacists, a larger sample of physicians, and healthcare providers less interested or aware of deprescribing, as well as studies in countries with different types of healthcare systems and different experiences with deprescribing interventions, should be carried out to additionally confirm the appropriateness and usefulness of the CHOPPED questionnaire. Future research can combine the use of the CHOPPED questionnaire with a model intervention to investigate whether or not the tool can help to identify obstacles prior to and during deprescribing.

5. Conclusions

Primary care physicians and pharmacists are willing to suggest deprescribing but are faced with different barriers and facilitators. For pharmacists, the most important facilitators were extrinsic factors (collaboration and healthcare-system-related), while for physicians these were more intrinsic (knowledge and awareness) and patient-related. This study highlights the differences in determinants influencing deprescribing between professions, and also accentuates the possible target areas upon which one could focus to help to engage healthcare providers in deprescribing.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/ijerph20064957/s1: File S1: Questions within the CHOPPED questionnaire; Figure S1: Answers to the CHOPPED questionnaire. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. All participants digitally signed the informed consent form at the beginning of the study.

Data Availability Statement: The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflicts of Interest: The authors declare no conflict of interest.

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8. DEPRESCRIBING IN A MULTIMORBID OLDER ADULT: A CASE VIGNETTE STUDY AMONG COMMUNITY PHARMACISTS AND PRIMARY CARE PHYSICIANS

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Deprescribing in a multimorbid older adult: A case vignette study among community pharmacists and primary care physicians

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Abstract

Collaborative deprescribing can include pharmacists' medication review with identification and suggestion of potential deprescribing targets to physicians. Case vignettes can be a valuable method for researching variations in clinical decision making, especially in settings unaccustomed to newer clinical approaches such as deprescribing. This study aimed to explore if pharmacists can identify deprescribing targets and if physicians would accept pharmacist's deprescribing rationales. A cross-sectional study was performed using an online case vignette based on a real-life elderly patient. Pharmacists were asked to indicate which medicines they would recommend deprescribing, alongside a rationale. Physicians were asked to state their acceptance of the proposed pharmacist's deprescribing suggestion. Pharmacists gave 1275 deprescribing rationales, and most were given for deprescribing opioids, NSAID and diuretics. Physicians would accept rationales to deprescribe a median of 10 medicines, while pharmacist would recommend deprescribing a median of six medicines. Most difference lays in deprescribing of preventative medicines. Healthcare providers share agreement on deprescribing targets, but pharmacists show hesitancies in making recommendations that could hamper potential collaboration. Action is needed to improve pharmacists' skills in recognizing deprescribing targets and confidence in making suggestions, which could lead to opening of possibilities for joint patient care.

KEYWORDS
case vignette, deprescribing, multimorbidity, polypharmacy, primary care

1 | INTRODUCTION AND BACKGROUND

Ageing leads to the decline in a number of human body functions. To help slow down the effects of ageing, prolong life expectancy and increase quality of life, medications are often used. Use of five and more and 10 and more medications concomitantly (polypharmacy and hyperpolypharmacy, respectively) is frequent among older persons, especially those who are prefrail or frail.[1] Commonly used and safe medications can become unsafe in such adults, due to, among other, age-related changes in pharmacokinetics and pharmacodynamics.[2] Negative outcomes, including increase in mortality, decrease in or

loss of adherence, falls or hospitalizations, are associated with inappropriate polypharmacy.[3–5] Optimizing pharmacotherapy to combat inappropriate polypharmacy or hyperpolypharmacy can include approaches, such as suggesting deprescribing. Deprescribing is described as a thoughtful process of dose reduction or withdrawing of medication, which is no longer of benefit to the patient with intent to improve outcomes.[6–9]

Older multimorbid patients are often cared for by a number of different healthcare providers, including primary care physician, specialist physicians, nursing staffs and pharmacists. Different healthcare providers can contribute to deprescribing and guide the patient through the process. Research shows a collaborative deprescribing (i.e. pharmacist and physician collaboration) model in different settings is feasible and results in improved outcomes.[10–12] Medication review and/or medication optimization with pharmacists' suggestions for physicians can be a good starting point for multidisciplinary and joint patient care.[13,14] An important foundation for successful collaborative deprescribing is sharing agreement on planned patient care, which could be initiated by pharmacists' identification and suggestion of potential deprescribing targets to physicians.[10,15] Providing deprescribing can be hindered by different barriers, such as those related to the patient (patient resistance, differences in care goals, lack of shared decision making), healthcare provider (knowledge, awareness or competences) or the healthcare system (policy and regulations, practice environment or characteristics).[16–19] Besides exploring obstacles and enablers of deprescribing, getting insight into healthcare providers' decision-making process while identifying deprescribing targets can be a useful step before implementation. To aid in decision making, prescribing and deprescribing guidelines are available to clinicians.[20,21] For each patient, the risk–benefit ratio of using a particular medication should be assessed based on their overall health, which may not always comply with or be supported by the available guidelines, potentially leaving the healthcare provider feeling unsupported or unsure how to reach a suitable decision.[22]

Case vignettes can be a valuable method for researching variations in clinical decision making, and a useful teaching tool as well,[23,24] especially in settings unaccustomed to a clinical approach such as deprescribing. Therefore, the aim of this study was to explore whether or not community pharmacists can identify deprescribing targets and recommend rationales for deprescribing and whether or not primary care physicians would accept pharmacist's deprescribing rationales in a case vignette of a multimorbid older adult.

2 | MATERIALS AND METHODS

This observational study utilized cross-sectional internet-based surveys administered to two independent samples of healthcare providers: community pharmacists and primary care physicians. The survey consisted of three parts: (a) sociodemographic characteristics, (b) comprehensive healthcare providers' opinions, preferences and attitudes towards deprescribing (CHOPPED) questionnaire and (c) case vignette. For the purpose of this analysis, first (sociodemographic data) and third parts of the survey (patient case vignette) were used, while analysis of CHOPPED questionnaire is presented elsewhere (in press). Our analysis of the patient vignette aimed to investigate pharmacists' deprescribing recommendations and to determine physicians' acceptance of proposed pharmacist's rationale on deprescribing particular medication from the patient vignette.

Details on the study design were described in a previous publication.[25] Primary care physicians and pharmacists were sent an invitation (with two remainder invitations 4 and 8 weeks after the initial invite) and the link to the survey containing the case vignette via email. Participants were asked to digitally authorize the informed consent before accessing the survey and the case vignette. Link to the study was open between October 2021 and January 2022. Duplicate, invalid or incomplete inputs were discarded.

The case vignette was based on a real-life community-dwelling patient. In collaboration, a community pharmacist and a clinical pharmacy specialist/academic researcher refined and adapted the case vignette for study purposes. Additionally, the clinical pharmacy specialist/academic researcher reviewed the proposed answers ensuring they agreed with guidelines on prescribing and deprescribing of potentially inappropriate medications. Details on patient's medical history as well as recent laboratory findings were presented. Patient's chronic multimorbidity included hypertension, gout, anxiety disorder, benign prostatic hyperplasia and overactive bladder. Patient's pharmacotherapy included 16 prescription and over-the-counter medication (18 substances in total of which two were multidrug medicines). Additionally, the vignette included their recent health complaints, such as falls, dizziness, feeling of tiredness and the desire to have the number of medications and pills reduced. Two different surveys were developed for each cohort. Pharmacists were asked to recommend potential medication to be deprescribe and were offered 17 choices (16 medications and the last choice was 'no medication to be deprescribed'). Hereafter, pharmacists were asked to state the rationale/evidence for their choices. Physicians were asked to state whether or not they would accept and

potentially implement the deprescribing suggestions proposed by the pharmacists based on pharmacists' rationales. To express acceptance of the proposed pharmacist's deprescribing suggestion a 5-point Likert scale was offered (*strongly disagree*, *disagree*, *neither agree nor disagree*, *agree*, *strongly agree*). When examining physicians' answers, positive answers (strongly agree, agree) indicated acceptance of proposed deprescribing suggestion. Negative answers (neither agree nor disagree, disagree, strongly disagree) indicated a physician would not accept the proposed suggestions. Details of the case vignette can be found in Data S1.

To ensure the healthcare providers' samples were representative of Croatian pharmacists and physicians population, enrolment targets included ≥80% female participation in the pharmacist sample and ≥60% female participation in the physician sample.[26] Inputs were included in the analysis if the participants completed both the sociodemographic and the case vignette portions of the questionnaire.

Sociodemographic data were analysed using descriptive statistics. A chi-squared test was used to analyse differences in frequencies between groups. Qualitative conceptual content analysis of pharmacists' deprescribing suggestions was performed in the following way. Firstly, the collected data were sorted based on each medication and corresponding participant input. During data sorting, one researcher engaged in data familiarization to ascertain an interactive set of codes. Interactive set of codes included codes such as tapering, stopping, lack of indication, interactions, adverse effects and pro re nata use. When necessary, additional codes were introduced to ensure no loss of meaning, such as patient monitoring, prioritizing or use of non-pharmacologic measures. For each medication and each registered input (one line of data), one researcher completed manual coding, for both presence and frequency. Manual coding was performed to correctly categorize potential errors (i.e. spelling mistakes, repetitive inputs such as 'answer like before' or 'same as prior input') or implicative codes. For each medication and corresponding code, frequency was calculated. Codes were then grouped into two appropriate categories named DEPRESCRIBING and CONTINUING. Tapering, stopping medication, reducing dose, deprescribing due to lack of indication or due to prolonged use of medicine intended for short-term use, due to adverse effects or interactions, and deprescribing with introduction of non-pharmacologic measures were grouped under DEPRESCRIBING, and suggestions such as monitor the patient or do not deprescribe were grouped under CONTINUING. The second researcher checked the coding and the grouping. Any discrepancies were solved through discussion and consensus. Physicians' answers were collated in the following manner: 'strongly agree' and 'agree' were considered as 'agree' with the proposed deprescribing suggestion, while all other answers ('neither agree nor disagree', 'disagree' and 'strongly disagree') were considered as 'disagreeing', for the purposes of comparison to pharmacists' answers. We believe the answer 'neither agree nor disagree' could be viewed as showing uncertainty to act, and in practice, this type of inertia usually does not lead to accepting deprescribing. Proportion of pharmacists that proposed particular medication for deprescribing and proportion of physicians that accepted the proposed rationale was presented as percentage. For all analyses, a value of $p < 0.05$ was considered statistically significant. All analyses were performed using IBM SPSS Statistics for Windows, Version 26.0. (IBM Corp., Armonk, NY, USA).

The study was conducted in accordance with the *Basic & Clinical Pharmacology & Toxicology* policy for experimental and clinical studies.[27]

3 | RESULTS

A total of 363 inputs (272 pharmacists' and 91 physicians') were ready for analysis after incomplete, invalid, and duplicate inputs were discarded. Participants who completed the case vignette did not differ in any characteristic from those who did not.

3.1 | Participant characteristics

The majority of participants were female (81%), with median age of 36 years (IQR 29–49) and a median of 12 years working as a healthcare provider (IQR 5–22). A little more than half of all participants practiced in an urban setting (55%). Characteristics of participants and differences between pharmacists and physicians are presented in Table 1.

3.2 | Pharmacists' deprescribing rationales

For the 16 medications and supplements the patient in the case vignette is taking, pharmacists gave 1275 rationales with various reasons for deprescribing. Three medications for which pharmacists gave the most deprescribing recommendations included opioid analgetic ($n = 163$, 13%), non-steroidal anti-inflammatory medications (NSAID) ($n = 163$, 13%) and diuretic (furosemide) ($n = 129$, 10%). Least number of recommendations was given for urinary antispasmodic, solifenacin,

TABLE 1 Participants characteristics.

Characteristic	Pharmacists (n = 272)	Physicians (n = 91)
Sex (female,%)	86	68
Age (median, IQR)	36 (28–43)	51 (33–59)
Years of experience (median, IQR)	10 (4–19)	25 (7–32)
Highest educational attainment (%)		
Graduate degree	84	27
Postgraduate specialist course[a]	12	n/a
Health specialization[b]	3	71
Master's degree (MSc)	0.5	1
Doctoral degree (PhD)	1	n/a
Location (%)		
Urban	58	45
Suburban	32	32
Rural	10	23
Practice location (%)		
Within another healthcare facility	16	56
Near another healthcare facility	41	14
Within a shopping centre	6	n/a
Displaced/not near any healthcare facility	37	30
Practice ownership (%)		
Privately/concession	51	23
Publicly	49	77
Number of patients in practice (median, IQR)	n/a	1600 (1200–1870)
Percentage of elderly patients in practice (median, IQR)	n/a	40 (30–50)

[a]1-year course.
[b]3-year healthcare residency including postgraduate specialist course.

TABLE 2 Number of deprescribing rationales for each medication.

Medication	Number of suggestions
NSAID	163 (13%)
Opioid	163 (13%)
Furosemide	129 (10%)
Alprazolam	122 (10%)
Zolpidem	102 (8%)
PPI	102 (8%)
ASA	93 (7%)
Lactulose	78 (6%)
Moxonidine	66 (5%)
Allopurinol	66 (5%)
Bisoprolol	44 (3%)
Amlodipine/valsartan	43 (3%)
Vitamin	43 (3%)
Escitalopram	26 (2%)
Solifenacin	20 (2%)
tamsulozin	15 (1%)

Abbreviations: ASA, acetylsalicylic acid; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor.

with 20 suggestions (2%), and alpha-1 receptor blocker, tamsulosin, with 15 suggestions (1%). Table 2 shows the total number of deprescribing rationales for each medication. On average, 77% of deprescribing recommendations were supported by a rationale (61% suggestions for deprescribing solifenacin as the lowest and 92% suggestions for deprescribing bisoprolol as the highest). Participants' examples of rationales for deprescribing recommended medications can be seen in Table 3. Rationales under deprescribing were recommended the most, with 97% of all suggestions falling into this category. The least number of suggestions, 4%, was in regard to keeping the medication. A small percentage of participants, 4% ($n = 11$), added comments expressing their concern their recommendations would not be accepted by neither the physician nor the patients. Five pharmacists stated this worry for deprescribing alprazolam, three for deprescribing zolpidem, and one each for ASA, vitamin and all medicines.

When examining the types of deprescribing rationales, almost one-fifth of all were deprescribing due to lack of indication/lack of justification to continue treatment ($n = 254$, 20%), followed by suggestions to reduce dose or dosing ($n = 215$, 17%), to stop medication without additional reasoning provided ($n = 159$, 12%) and to deprescribe due to potential or existing adverse effects ($n = 140$, 11%) all falling into the DEPRESCRIBING category. Some participants recommended deprescribing with certain measures such as medication be used as needed ($n = 141$, 11%), recommending short-term use ($n = 102$, 8.00%), deprescribing after prioritizing ($n = 63$, 5%) or recommending non-pharmacological measures ($n = 41$, 3%). Recommendation to monitor patient was the least given rationale, suggested only four times (<1%). Table 4 contains details on all types of recommendations and for which medication they were given.

TABLE 3 Pharmacists' deprescribing rationales with examples for each medication.

Medication	Deprescribing rationales (*n*)	Participant's example
NSAID	Pro re nata use (26)	'patient should take it as needed, not every day'
	No indication (37)	'Is there a justifiable indication to use? Last acute gout exacerbation was two years ago. I did not see any report of pain'
	Reduce dose/dosing (17)	'It is not recommended that older adults take such high doses all the time, I would first suggest reducing the dose'
	For acute/short-term use only (19)	'Patient should be taking it only when there is acute pain present, this is a common problem … patients taking acute medicines chronically'
Opioid	No indication (41)	'Patient is not reporting any pain, I see no reason to take this strong pain medicine. This type of medicine is not for that type of pain'
	Adverse effects (26)	'Half of the patient's problems are due to this medication: constipation, drowsiness, vertigo … probably falls as well!' 'Opioid should be stopped because it causes vertigo, falls, sedation, hypotension …'
	Pro re nata use (26)	'I would suggest taking it as needed, or in case gout is really bad'
	Interaction (6)	'It's inappropriate for older adults, especially in combination with alprazolam, zolpidem and all the antihypertensives'
Furosemide	No indication (60)	'I would suggest stopping, I don't see any reasons for taking a diuretic, and the blood pressure levels are low' 'There are no oedemas present, so the diuretic should be stopped' 'The latest ESC guidelines first line treatment should include an ACE inhibitor and calcium channel blocker; diuretic should be added if the patient is not well controlled or has heart failure … I do not see any information on that, so I would suggest stopping'
	Reduce dose/dosing (22)	'I would suggest reducing the dosing to every other day and continue to monitor the blood pressure' 'Blood pressure is lower than recommended for persons their age, so I would suggest reducing the dose to half, or taking it every other day'
	Adverse effects (21)	'It is evident that the falls and vertigos are because of hypotension' 'Furosemide can worsen constipation and drowsiness'
Alprazolam	Tapper and stop (27)	'Slowly tapper and stop, I would suggest reducing the dose every two weeks and then stopping completely after six weeks'
	For acute/short-term use only (21)	'Alprazolam should be used for four weeks until the full effect of'
	Pro re nata use (21)	'Alprazolam should be used once daily and only if needed, if the patient is experiencing anxiety attacks'
	Adverse effects (16)	'It causes sedation, and could be an additional reason the patient experienced falls. It is also causing tolerance and addiction, there are more reasons to stop this than to continue'
Zolpidem	Pro re nata use (20)	'Z-drugs should only be used when needed, but I know this suggestion will not be accepted by this, or any patient'
	Adverse effect (14)	'It can cause forgetfulness, memory loss, drowsiness and many other side effects which are huge problem in older adults, it should be stopped'
	For acute/short-term use only (17)	'The patient information leaflet states it should be used no longer than four weeks, so I would try to suggest a shorter course of therapy'
	Change to different medication (10)	'Maybe try with melatonin, or herbal remedies, such as valerian root' 'There are better therapeutic options for this patient, a sedative antidepressant could be a way to go … kill two birds with one stone'
PPI	Reduce dose/dosing (38)	'I think a dose reduction is a possibility, I think 20 mg a day should be enough for gastroprotection'

(Continues)

TABLE 3 (Continued)

Medication	Deprescribing rationales (*n*)	Participant's example
		'There is no need for such a high dose, 40 mg 1x a day is enough, or even 20 mg a day'
	After deprescribing other medications (33)	'If we could get the patient to stop taking all the NSAID then I think we could stop the PPI'
		'I think it was prescribed for gastroprotection for one of the NSAIDs, so if consider that ibuprofen is inappropriate, when ibuprofen is stopped, this PPI can be stopped as well'
ASA	No indication (74)	"I have read that older patients should not take ASA if they have a CV incident, so I think there is no indication for this medication"
		'Obviously this should be stopped, it could cause more harm than good for this patient, and it is intended for primary prevention, not secondary'
Lactulose	After deprescribing other medications (27)	'The patient needs the laxative because of the constipation caused by the opioid and other medication, if he could stop the opioid, I think there would be no need to continue the laxative'
	Non-pharmacologic measures (16)	'Council the patient on dietary measures, fibre intake, exercises and maybe suggest a visit to a dietitian'
Moxonidine	Adverse effect (17)	'It is causing orthostatic hypotension and falls, it should be stopped!'
Allopurinol	Reduce dose/dosing (30)	'The last exacerbation was two years ago, if urate levels are ok, I would at least lower the dose, and then if the patient is still ok stop the medicine'
	Non-pharmacologic measures (21)	'I think the dose could be reduced if he changes the diet and controls meat intake'
		'Dietary measures are enough to control the condition, I would suggest monitoring the urate levels, continue with the diet, and stop the allopurinol. It could be one less pill the patient is taking'
Bisoprolol	Reduce dose/dosing (12)	'I would reduce the dose, there are too many antihypertensives in therapy, and beta blocker is not first choice'
Amlodipine/valsartan	Reduce dose/dosing (29)	'I think his blood pressure levels are too low, half of the dose should be enough'
Vitamin	For acute/short-term use only (23)	'Patient should be taking vitamins only during the winter months, or couple of times a year, not all the time'
Escitalopram	Tapper and stop (7)	'I think the patient is taking this medicine too long, slowly reduce the dose and stop, it has been three years'
Solifenacin	Adverse effect (4)	'I think the dose should be reduced because this medication is causing constipation, and blurred vision'
Tamsulozin	Adverse effect (3)	'This medicine can cause the blood pressure to drop, especially in the morning, so maybe it could be stopped'

3.3 | The comparison of pharmacists' and physicians' answers

On average, pharmacists recommended deprescribing a median of six medicines (IQR [3–8]), while physicians would accept the proposed recommendation to deprescribe a median of 10 medicines (IQR [9–11]; $U = 4124.50$, $z = -9.56$, $p > 0.0001$).

Physicians would accept recommendation to deprescribing furosemide the most ($n = 84$, 92%), followed by opioid and NSAID analgesics (both $n = 81$, 89%) and central antihypertensive, moxonidine ($n = 80$, 88%). Least acceptance was found for deprescribing multivitamin ($n = 48$, 53%), solifenacin ($n = 59$, 65%) and acetylsalicylic acid ($n = 62$, 68%). Pharmacists recommended deprescribing NSAID and opioid the most ($n = 210$, 77%, and $n = 209$, 77% respectively), followed by recommending alprazolam and furosemide (both $n = 156$, 57%). Pharmacists were least willing to recommend deprescribing tamsulozin and escitalopram ($n = 18$, 7% and $n = 32$, 12% respectively).

For four medications, amlodipine/valsartan, bisoprolol, tamsulozin and escitalopram, there were no reasons for deprescribing offered in the physicians' version, but

TABLE 4 Analysis of deprescribing rationales.

Category and type of deprescribing rational	Number of rationales (percentage)	Medication (number of rationales)
DEPRESCRIBING		
No indication/lack of prescribing justification	254 (20%)	ASA (74), furosemide (60), opioid (41), NSAID (37), PPI (15), lactulose (6), zolpidem (6), bisoprolol (5), multivitamin (4), alprazolam (3), moxonidine (2), solifenacin (1)
Reduce dose/dosing	215 (17%)	PPI (38), allopurinol (30), amlodipine/valsartan (29), furosemide (22), NSAID (17), alprazolam (16), moxonidine (16), bisoprolol (12), opioid (10), zolpidem (9), solifenacin (7), ASA (4), lactulose (3), escitalopram (2)
Stop medication[a]	159 (12%)	Opioid (32), moxonidine (25), furosemide (25), NSAID (19), bisoprolol (15), allopurinol (10), lactulose (7), zolpidem (5), PPI (5), alprazolam (4), escitalopram (4), amlodipine/valsartan (4), ASA (3), tamsulozin (1)
Adverse effects (potential or existing)	140 (11%)	Opioid (26), furosemide (21), moxonidine (17), alprazolam (16), zolpidem (14), NSAID (14), PPI (6), ASA (5), amlodipine/valsartan (5), bisoprolol (5), solifenacin (4), tamsulozin (3), lactulose (3), escitalopram (1)
Tapper slowly and stop[a]	55 (4%)	Alprazolam (27), zolpidem (15), escitalopram (7), opioid (6)
Interaction (potential or existing)	20 (2%)	Opioid (6), ASA (4), moxonidine (3), NSAID (2), solifenacin (2), zolpidem (1), alprazolam (1), escitalopram (1)
Patient has other medication for control	15 (1%)	Alprazolam (8), NSAID (4), opioid (2), zolpidem (1)
Pro re nata use	141 (11%)	NSAID (47), opioid (26), alprazolam (21), zolpidem (20), lactulose (13), multivitamin (8), PPI (4), allopurinol (1), bisoprolol (1)
Medication for acute/short-term use	102 (8%)	Multivitamin (23), alprazolam (21), NSAID (19), zolpidem (17), opioid (14), escitalopram (4), allopurinol (2), lactulose (2)
Deprescribe after deprescribing other medications first (prioritizing)	63 (5%)	PPI (33), lactulose (27), tamsulozin (1), solifenacin (1), amlodipine/valsartan (1)
Non-pharmacological measures	41 (3%)	Allopurinol (21), lactulose (16), multivitamin (4)
Change to different medication/supplement	23 (2%)	Zolpidem (10), NSAID (4), alprazolam (3), escitalopram (2), multivitamin (2), allopurinol (1), amlodipine/valsartan (1)
CONTINUING		
Consult physician/prescriber	18 (1%)	Zolpidem (4), escitalopram (4), bisoprolol (3), moxonidine (2), alprazolam (2), tamsulozin (1), ASA (1), furosemide (1)
Do not deprescribe	14 (1%)	ASA (2), solifenacin (2), tamsulozin (2), bisoprolol (2), amlodipine/valsartan (1), moxonidine (1), allopurinol (1), escitalopram (1), lactulose (1), PPI (1)
Keep use but change formulation	11 (1%)	Tamsulozin (7), solifenacin (2), multivitamin (2)
Monitor patient	4 (<1%)	Amlodipine/valsartan (2), bisoprolol (1), solifenacin (1)

Abbreviations: ASA, acetylsalicylic acid; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor.
[a]No other information was given, no additional rationale given.

physicians were given the possibility to add additional medications they were willing to deprescribing. No additional comments were given for any of the four medications.

Overall, physicians were more likely to accept proposed deprescribing recommendations than pharmacists were to make, and it applied to every medication in case vignette (Table 5).

TABLE 5 Pharmacists' deprescribing recommendations and physicians' acceptance of deprescribing proposal.

Medication	Pharmacists	Physicians	Chi-squared test
Furosemide	57%	92%	$\chi^2(1) = 37.189$; $p < 0.0001$
Moxonidine	31%	88%	$\chi^2(1) = 88.298$; $p < 0.0001$
Allopurinol	28%	80%	$\chi^2(1) = 75.782$; $p < 0.0001$
NSAID	77%	89%	$\chi^2(1) = 5.976$; $p = 0.014$
Opioid	77%	89%	$\chi^2(1) = 6.289$; $p = 0.012$
Alprazolam	57%	78%	$\chi^2(1) = 12.433$; $p < 0.0001$
Zolpidem	46%	87%	$\chi^2(1) = 47.013$; $p < 0.0001$
Solifenacin	12%	65%	$\chi^2(1) = 100.098$; $p < 0.0001$
ASA	43%	68%	$\chi^2(1) = 15.259$; $p < 0.0001$
PPI	44%	86%	$\chi^2(1) = 48.384$; $p < 0.0001$
Lactulose	33%	53%	$\chi^2(1) = 11.184$; $p = 0.001$
Vitamin	19%	53%	$\chi^2(1) = 38.637$; $p < 0.0001$

Abbreviations: ASA, acetylsalicylic acid; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor.

4 | DISCUSSION

In this study, community pharmacists unaccustomed to deprescribing were able to recognize potential deprescribing targets. On inspection suggested deprescribing rationales were in line with prescribing and deprescribing guidelines.[28–30] They were comfortable in suggesting most commonly potentially inappropriate medicines, opioid analgesics and NSAIDs, for which they gave the most rationales. Interestingly, about 20% of all rationales were for benzodiazepine receptor agonists, yet only around 50% of all pharmacists agreed with deprescribing these medications, suggesting pharmacists have knowledge and awareness of potentially inappropriate medications, but show hesitancy in recommending deprescribing. Equally can be said for, furosemide, one of the most used diuretics and for proton pump inhibitor (PPI). In the physicians' sample, the acceptance of the proposed rationale for the majority of medications was high (more than 80% for seven medications and 50%–80% for the other five medications). The lowest acceptance rate was to deprescribe ASA and solifenacin, possibly due to prescribing specificities. In the vignette, solifenacin was prescribed by a specialist physician that might have influenced the decision not to accept the particular deprescribing rationale. Qualitative research reports physicians' hesitancy to interfere with colleagues prescribing.[31,32] This may be even harder in settings where patient care is fragmented or there is a lack of in-real-time communication possibilities for healthcare providers. Additionally, participants might not have attributed patient's reported side effects to the anticholinergic effects of solifenacin. For ASA, the quandary of deprescribing preventative medications could be the main reason for less acceptance. Appropriateness of long-term use of preventative medications (i.e. cardiovascular medications) in older population, such as the patient presented in the case vignette, is questionable and can lead to clinical decision-making inertia.[33,34]

Both healthcare providers gave less attention to two over-the-counter medicines, lactulose and multivitamin. When it comes to potential deprescribing, supplements and over-the-counter medicines are often overlooked in patients' pharmacotherapy but silently contribute to medication burden and could even be inappropriate in certain patients.[35,36] Even though, from a clinical perspective, they may not be a deprescribing priority, it is important to consider and suggest deprescribing of such medicines as well. Physicians should routinely ask patients on usage, and pharmacists should attentively counsel patients when recommending any over-the-counter medication, herbal or dietary supplements. Efforts have been made to explore physicians and patients' willingness to deprescribe dietary and herbal supplements.[37]

Overall physicians were more likely to accept deprescribing rationales than pharmacists were to give them, what applied to all medications from the patient vignette. Reasons could include, for instance, age and experience or confidence in therapy decisions. Physicians in this study were older and had more professional experience than pharmacists. A study on general practitioners' deprescribing decisions in older adults with polypharmacy suggests older physicians were more likely to make deprescribing decisions.[38] While pharmacists' role in patient care has grown from dispensing to developing

and providing services based on clinical skills, pharmacists still report lack of confidence, particularly when it comes to adopting new practices or approaches such as deprescribing.[39,40] This can be especially evident in healthcare systems with developing pharmaceutical care, such as this study's setting. Pharmacists are used to taking a more passive role in patient care and could feel uncomfortable or harbour a feeling of crossing professional boundaries by taking the lead in proactive deprescribing.[32,40] Several pharmacists added comments regarding their rationales and stated they know a particular medication should be discontinued but fear the patient and the physician would not accept their suggestion. This could additionally explain why pharmacists recommended deprescribing less often than physicians stated they would accept it and why almost a quarter of deprescribing suggestions were not supported by a rationale. Australian study by Page et al reports a similar finding, with pharmacists deprescribing less than physicians,[41] indicating pharmacists' barriers to deprescribing are shared across the world regardless of how advanced or developed pharmaceutical care is in a particular setting. Majority of physicians are motivated and self-assured to suggest deprescribing, with only some reporting reluctance when it comes to certain type of medications.[42,43] Even though physicians could have been encouraged to accept potential deprescribing suggestions since they were presented with a sound pharmacist's rationale, for certain medications there was a lower level of acceptance. Research confirms physicians welcome pharmacists' participation[44] but fear that sometimes pharmacists lack patient information or that pharmacists' position in patient care may not comply to their standards and care plans.[45,46] Nonetheless, physicians would accept the majority of pharmacist's suggestions indicating a collaborative approach is possible. For any collaboration to be successful, all involved stakeholders need to be equally engaged. Pharmacists' reluctance to suggest deprescribing could hamper the possibility of a joint care action, resulting in missed opportunities to improve patient outcomes. Steps should be taken to encourage pharmacists to engage in pharmacist–physician communication irrespective of outcome. Collaborative deprescribing interventions are feasible in primary care settings versed in deprescribing,[47] and such experiences could be used to foster similar action in healthcare systems still adopting a deprescribing approach.

Several elements in this study could be viewed as a limitation. Pharmacists' sample was larger than physicians. This could be accounted to the lack of time and changed working conditions due to the COVID-19 pandemic. Regardless, based on available data, both samples adequately represent primary care providers and account for around 9% of primary care physicians and 10% pharmacists registered in the setting's country.[26] Even though both researchers agreed while coding and aggregating pharmacists' recommendations, and did not find any of the recommendations problematic, shortly written or incomplete rationales could have been misunderstood. On average, for each medication, 75% of deprescribing suggestions were supported with a rationale indicating that pharmacists carefully considered their answers. Physicians were presented with a pharmacist's deprescribing rationale, which could have biased their responses; nonetheless, variety of potential acceptance rates implies physicians used a mindful approach when selecting their answers. Furthermore, as this was an observational case vignette study, it is difficult to generalize that these healthcare providers would indeed suggest and accept recommendations to deprescribing any medicines in real life. There is lack of data on Croatian healthcare providers offering, leading and providing deprescribing. Steady yearly increase in use of medication,[48] especially those potential inappropriate such as benzodiazepines, could indicate the opposite, increase in prescribing and very little deprescribing. Only one case vignette was presented, which could be viewed as a limitation. Even though several simpler cases might have been easier for participants of the study to fulfil the survey, the rather complex vignette was chosen with intent to give a clinical conundrum as similar to everyday practice as possible. Complexity of decision making while providing and counselling a patient on deprescribing could have been underestimated; nevertheless, results suggest inexperienced healthcare providers have the knowledge to recognize potential deprescribing targets but need incentives to initiate collaboration. Possible advantage of this presented case vignette is that it included not only known potentially inappropriate medicines used in older adults but also medicines considered safe, which are often prescribed and used in this population.

It would be useful to compare responses, to this case vignette, of healthcare providers more accustomed to deprescribing, as well as to compare different healthcare providers' deprescribing rationales and its effect on a potential collaborative intervention. Further research evaluating case vignette studies and real-life medical-records data could be valuable in gaining additional understanding of the decision-making process when it comes to deprescribing.

5 | CONCLUSION

Primary care physicians would accept pharmacist's deprescribing rationales indicating multidisciplinary collaboration is possible. Pharmacists can identify potential deprescribing targets but show reluctance in suggesting deprescribing rationales. To ease into collaborative deprescribing, alongside physicians' acceptance of pharmacists' proposals, first targets should be medicines both healthcare providers share most agreement on, such as opioids, NSAIDs or diuretics. Action should be taken to engage healthcare providers in joint care for the patient with intent to increase deprescribing practice in order to improve patient safety and rationalize pharmacotherapy.

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None.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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9. DEPRESCRIBING POTENTIAL OF COMMONLY USED MEDICATIONS AMONG COMMUNITY-DWELLING OLDER ADULTS: INSIGHTS FROM A PHARMACIST'S GERIATRIC ASSESSMENT

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Deprescribing potential of commonly used medications among community-dwelling older adults: insights from a pharmacist's geriatric assessment

Iva Bužančić[1,2,6], Margita Držaić[1,2,6], Ingrid Kummer[3], Maja Ortner Hadžiabdić[2]✉, Jovana Brkić[3,4] & Daniela Fialová[3,5]

Pharmacist's geriatric assessment can provide valuable insights into potential deprescribing targets, while including important information on various health-related domains. Data collected from a geriatric assessment questionnaire, for 388 patients, from the Croatian cohort of the EuroAgeism H2020 ESR 7 international project, along with guideline-based deprescribing criteria, were used to analyse potentially inappropriate prescribing of four medication groups (benzodiazepines (BZN), proton pump inhibitors (PPI), opioids, and non-steroidal anti-inflammatory drugs (NSAID)), and to assess the deprescribing potential. Binary logistic regression was used to explore the effects of age, gender, number of medicines and diagnoses, self-reported health, frailty score, and healthcare utilization on the likelihood of needing deprescribing. More than half of participants (n = 216, 55.2%) are candidates for deprescribing, with 31.1% of PPI, 74.8% of NSAID, 75% of opioid, and 96.1% of BZN users meeting at least one criterion. Most common criteria for deprescribing were inappropriately long use and safety concerns. Women (aOR = 2.58; $p < 0.001$), those reporting poor self-reported health (aOR = 5.14; $p < 0.001$), and those exposed to polypharmacy (aOR = 1.29; $p < 0.001$) had higher odds of needing to have medicines deprescribed. The high rate of deprescribing potential warrants prompt action to increase patient safety and decrease polypharmacy. Pharmacist's geriatric assessment and deprescribing-focused medication review could be used to lead a personalised approach.

Keywords Deprescribing, Healthy ageing, Geriatrics, Geriatric assessment, Polypharmacy

In an aging world, healthy aging is a priority for all stakeholders, including older adults, healthcare providers, policy makers, and social care professionals. Healthy aging is defined as the process of developing and maintaining the functional ability that enables well-being in older age[1]. Use of medication to improve health and increase life expectancy is ubiquitous, especially in older adults, but prescribed medication can in some individuals become potentially inappropriate leading to undesirable outcomes such as adverse drug events, hospitalizations, and increased morbidity and mortality[2–4].

Commonly prescribed and used medications, such as, proton pump inhibitors (PPI), non-steroidal anti-inflammatory drugs (NSAID), opioid analgesics (OPI), or benzodiazepine receptor agonists (BZN) can be inappropriate for older adults[2,3]. To help reduce the risk of use of potentially inappropriate medications (PIMs) and improve outcomes, patients should be introduced to the concept of deprescribing, the healthcare provider-led process of dose reduction or withdrawal of medication which are no longer of benefit to the patient[5,6]. Deprescribing, as a patient-centred process besides taking into consideration patient-related factors, should encompass

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comprehensive medication history, identifying of potential targets for deprescribing, prioritising and determining which medication can be ceased, planning and initiating the withdrawal process, and providing follow-up care to the patient[7]. Each step in deprescribing requires adequate information, time, clinical experience and knowledge, as well as patient involvement. Conducting comprehensive geriatric assessment can provide valuable insights into potential deprescribing targets, while also including crucial information from various health-related domains[8,9]. Comprehensive geriatric assessment involves a systematic evaluation of older persons, provided by a team of health professionals, which identifies medical, psychosocial, and functional capabilities in order to develop a coordinated plan to maximize overall health with ageing[10]. The content of the assessment varies depending on settings of care (outpatient, hospital, long term care facilities), and can be completed by different members of a multidisciplinary team. Geriatric syndromes, identified during comprehensive geriatric assessment, are often worsened by medicines. Pharmacists, as a part of a multidisciplinary team, can be well placed to help provide pharmacist's geriatric assessment, prevent potentially inappropriate prescribing and support deprescribing in the management of geriatric syndromes[11,12].

The aim of this study is to analyse potentially inappropriate prescribing, and the deprescribing potential of four commonly used medicines (prescription and over-the-counter PPI, prescription and over-the-counter NSAID, and restricted prescription OPI and BZN) among community-dwelling older adults. Additionally, we aimed to explore potential factors associated with increased likelihood of needing to have medicines deprescribed.

Methods

Data collection and participants

Data were collected as a part of the EuroAgeism H2020 ESR 7 international project entitled ''*Inappropriate prescribing and availability of medication safety and medication management services in older patients in Europe and other countries*"[13], using a standardized, and piloted 17-part research questionnaire for comprehensive geriatric assessment. Participants' input, as well as available medical records (medical history, laboratory values), and dispensing data were used to complete the questionnaire. Questionnaire included sociodemographic, clinical, medication-related, and service-use related domains, with core clinical components of comprehensive geriatric assessment examined with questions on nutritional status (Mini Nutritional Assessment-short form[14]), mobility and strength (SARC-F questionnaire[15]), activities of daily living (Activities of Daily Living Hierarchy scale[16]), frailty (Clinical Frailty scale[17]), cognitive status (Cognitive Performance scale[18]), mood (self-reported mood items based on Minimum Data Set-based depression rating scale[19]), self-reported health, falls, pain frequency and control (short-form McGill questionnaire[20]), diagnoses, and symptoms. The choice of scales used in the questionnaire was carefully selected by a multidisciplinary team consisting of clinical pharmacists, gerontologists, geriatricians, and academic researchers with the background in clinical pharmacy and geriatrics. Pharmacist's geriatric assessment included the use of aforementioned questionnaire and assessment of deprescribing potential described below.

This was an observational, cross-sectional study, conducted in Croatia, from June 2019 to December 2020. Community pharmacists, trained in the use of geriatric clinical scales which comprised the questionnaire, from three geographically different regions (north-western (City of Zagreb) and north-eastern continental (Slavonia), and coastal region (Istria)) approached community-dwelling older adults with the invitation to participate in the project. Pharmacists used convenience sampling when approaching potential participants. Participants were included if they were 65 years or older, of stable health (no palliative or terminal care, no acute worsening of health requiring hospitalization or emergency department visit in the last 3 days, and with life expectancy longer than 1 year), using at least one medication, willing to give informed consent, and without sever communication disorders (unable to speak or hear) or dementia. Pharmacists conducted the interviews, in a separate part of the community pharmacy to ensure privacy and comfort. On average interviews lasted between 45 and 75 min. To avoid participant fatigue, or when medical documentation was needed to support participants' recall, pharmacist and participant arranged subsequent meetings to complete the questionnaire.

For this analysis, parts of collected data were used: sociodemographic, data on lifestyle (smoking, alcohol intake, diet), frailty score (examined using the clinical frailty scale from "very fit" (1) to "terminally ill" (9)), changes in cognitive status (no changes, improvement or worsening of cognitive status), healthcare utilization (hospitalizations and emergency departments visits within the last 12 months), diagnoses, symptoms (present in the past 7 days), self-reported health score (scale from "very poor" (0), "poor"(1), "moderate" (2), "good" (3), "very good" (4)), pain frequency and control (examined using the short form McGill pain questionnaire and diagram with frequency scale from "multiple times a day" (0), "once daily" (1), "couple of time a week" (2) to "rarely" (3) and numeric pain intensity scale from "no pain" (0) to "worst possible pain" (10)), history of falls, and detailed information on the use of, and adherence to prescription and over-the-counter medicines as well as herbal and dietary supplements.

Sample size was determined based on census data on the number of adults 65 years and older in Croatia, using a single population proportion formula, with a 95% confidence level and relative precision of 5%, and was calculated to 385 participants[21]. This aligned with the EuroAgeism H2020 ESR 7 projects protocol on number of participants from each participating country. Ethical approval was obtained from the Ethical committees of the Charles University (Czech Republic, EuroAgeism H2020 ESR7 study centre) and University of Zagreb (Croatia, national study centre). Participating subjects signed the informed consent prior to data collection and were free to decline participation any time during the study. To ensure anonymity and data confidentiality, all data were collected and stored under specific codes. All methods were carried out in accordance with relevant project guidelines and regulations.

Outcome measures and statistical analysis

The primary outcome was deprescribing potential of four commonly used medications in the community setting. To assess the deprescribing potential, deprescribing criteria for each medication were developed. Criteria were created based on available prescribing and deprescribing guidelines[22–24]. These included evidence-based explicit prescribing tools such as Beers[23], LESS-CHRON[25], START/STOPP criteria[26], STOPPFrail[27], and STOPP-Fall criteria[28], PRISCUS 2.0 list[24], as well as available medication-specific deprescribing guidelines[29–34], clinical practice guidelines on treatment choices in older adults[35,36], and summary of product characteristics[37]. Table 1 showcases deprescribing criteria for each of medication groups, while more detailed description of deprescribing criteria is available in Appendix file 1. The research team which participated in the EuroAgeism H2020 ESR 7 project, assessed the deprescribing potential. All researchers were familiarized with deprescribing criteria and their appropriate application. Junior researchers (community pharmacists with clinical background) collected and analysed the data. Senior researchers (clinical pharmacists with geriatric background) supervised the data analysis and application of criteria, and were available for discussion and final assessment of challenging cases. To ensure deprescribing potential was assessed in a standardized way at least two researchers needed to share agreement on selected criteria. For each patient, deprescribing potential was assessed by applying the deprescribing criteria while performing medication review and analysing the aforementioned collected data (pharmacist's geriatric assessment). At least one deprescribing criterion had to be met for medication in question, for the patient to be considered a potential deprescribing candidate. Both potential clinically significant drug-drug interactions and adverse drug effects which could be associated with inappropriate use of certain medication were taken into account when considering safety concerns as deprescribing criteria. Detailed list of considered potential adverse drug effects can be found in Appendix 1. Reported symptoms, changes in cognitive status, falls, pain frequency and control, and diagnoses were assessed for analysis of potential adverse drug effects. For patients who reported *pro re nata* (PRN) use of medications; diagnoses, and the frequency and severity of symptoms (i.e. pain control, insomnia, reflux) was reviewed to determine the frequency of PRN use. Those reporting symptom frequency of less than couple of times a week were considered as true PRN users. Patients who did not know for how long they were using a certain medication (stating *"I do not know/remember"*(IDK)), were considered to be long-term users after diagnoses and symptoms review (i.e. reports symptoms of chronic pain but does not know when opioid/NSAID was started). Potentially clinically significant drug-drug interactions included analysis of interactions categorized by Lexicomp® as D (therapy modification should be considered) and X (combination should be avoided) to avoid potential overestimation of the deprescribing potential due to safety concerns. Category C interactions, while clinically significant usually do not require dosage adjustments, and benefits of concomitant use usually overweigh the potential risks[38,39], and therefor were not included in the analysis. If a patient was prescribed certain medication for other approved indications (i.e. diazepam/clonazepam for epilepsy, or muscle spasms) or for off-label indications, appropriateness for deprescribing was assessed based on diagnosis, safety criteria and frequency of use. In instances where data was missing, clinical assessment was unclear, or conflicting data was present, the application of specific deprescribing criteria was discussed. If feasible, a consensus was reached regarding the application of criteria, or if deemed impossible to assess, the case was identified as unassessable.

Descriptive statistics were used to analyse sociodemographic data, and a chi-squared test was used to analyse differences in frequencies between groups. To explore the effects of age, gender, number of medicines, number

Criteria	PPI	NSAID	OPI	BZN
Lack of indication	appropriate indications: GERD, *H.pylori* eradication, ulcer disease, hypersecretory conditions, gastritis	Appropriate indications: chronic rheumatoid or short-term non-rheumatoid musculoskeletal pain	Resolution of pain/ definitive pain relieving intervention, lack of improvement in pain control	appropriate indications: insomnia disorders, anxiety disorders
	GI protection indicated, but no clear need/ low risk patient			
Inappropriately long use	> 4 weeks for symptomatic GERD > 8 weeks for reflux oesophagitis or peptic ulcer > 12 weeks for *H. pylori* ulcer disease	> 1 week for acute pain > 6 months for chronic pain[a]	> 6 months for non-cancer pain	> 4–8 weeks for insomnia disorders > 12 weeks for anxiety disorders
Inappropriate dose[b]	Use of higher than recommended gastroprotective dose	Use of higher than recommended daily dose	Use of more than 50 mg oMME for frail patients	Use of higher than recommended daily dose
	Prescribed for NSAID gastroprotection, but NSAID used PRN		Use of more than 90 mg oMME for non-frail patients	
Safety concerns*	Potentially clinically significant drug-drug interactions[c]	ADE associated with use	ADE associate with use	ADE associate with use
		Risk factors which could be exacerbated by NSAID use		Potentially clinically significant drug-drug interactions
		Potentially clinically significant drug-drug interactions[c]	Potentially clinically significant drug-drug interactions[c]	Frail patients

Table 1. Deprescribing criteria. PPI—proton pump inhibitors, NSAID—nonsteroidal anti-inflammatory drugs, OPI—opioid analgesics, BZN—benzodiazepine receptor agonists, GI—gastrointestinal, GERD—gastroesophageal reflux disease, PRN—pro re nata use, ADE—adverse drug effects, oMME—oral morphine milligrams equivalent, [b]inappropriate dose of each medication can be found in Appendix file 1 (inappropriate dose included inappropriate dosing regimen such as dosing too frequently), [c]potential clinically significant drug-drug interactions identified as D or X as assessed by Lexicomp®, [a]more than 6 months for patients prescribed adequate gastroprotection, *Included contraindications for use.

of diagnoses, self-reported health, frailty score, and healthcare utilization on the likelihood of deprescribing potential a binary logistic regression was performed. For the purposes of the logistic regression, nominal variables self-reported health, healthcare utilization, and frailty score were dichotomised. Categories "very poor" and "poor" formed "poor", and "moderate", "good", and "very good" formed "good" for the variable self-reported health. Variable frailty score was dichotomised into "frail" (frailty score from 4 to 9) and "non frail" (frailty score from 1 to 3), while healthcare utilisation (combined variable of hospitalisations and emergency department visits) was dichotomised into "utilisation within the last 12 months" and "no utilisation in the last 12 months". For all analyses, a value of $p < 0.05$ was considered statistically significant. All analyses were performed using IBM SPSS Statistics for Windows, Version 26.0. (IBM Corp., Armonk, NY, USA).

Ethics approval and consent to participate

Ethical approval for this study was obtained from the Ethical committees of the Charles University (Czech Republic, EuroAgeism H2020 ESR7 study centre) and University of Zagreb (Croatia, national study centre). Participating subjects signed the informed consent prior to data collection, and were free to decline participation any time during the study. To ensure anonymity and data confidentiality, all data were collected and stored under specific codes. All methods were carried out in accordance with relevant project guidelines and regulations.

Results

Participants characteristics

In total 388 older adults participated, of which 269 (69.3%) used at least one of the medications of interest. Almost one third of all participants used a proton pump inhibitor (n = 122, 31.4%), and almost 40% used a BZN (n = 154, 39.7%). Use of NSAID and opioid analgesics was noted in 111 (28.6%) and 60 (15.5%) participants, respectively. Most commonly used medication combinations were a PPI and a BZN (n = 32, 8.2%), PPI, NSAID and BZN (n = 24, 6.2%), and a combination of a NSAID and a BZN (n = 23, 5.9%). Only three participants used all four types of medications simultaneously. Additional information on participants' characteristics can be found in Table 2.

Potential for deprescribing

Based on deprescribing criteria more than half of patients (n = 216, 55.7%) would be candidates for deprescribing, with 33.5% for one medicine, 18.8% for two medicines, and 3.4% for three medicines. When it comes to specific type of medicine, 31.1% of PPI users, 74.8% of NSAID users, 75% of opioid users, and 96.1% of BZN users would be candidates for deprescribing. Information on criteria which participants satisfied for deprescribing of particular medicine can be found in Table 3 and more detailed descriptive statistics is available in Appendix file 2. In 52.6% (n = 55) of BZN users, 30% (n = 18) OPI users, and 6.3% (n = 7) NSAID users adverse effects could be associated with use of other medicines. Half of PPI users reported gastrointestinal symptoms regardless of PPI use, and 17.2% (n = 21) should use a PPI for gastroprotection but had it prescribed for another diagnosis.

In a univariate analysis, several factors were found to be associated with a higher potential for deprescribing, namely female gender, six or more diagnoses, and poor self-reported health status. Women (71.3%) were more likely to need to have medicines deprescribed than men (28.7%)(χ^2 (1) = 12.283, $p < 0.001$), and those with six or more diagnosis (58.9%) were more likely to need to have medicines deprescribed than those with five or less (46.2%) (χ^2 (1) = 7.088, $p = 0.008$). Those who reported being of poor health (88.1%) were more likely to need to have medicines deprescribed than those who reported being of good health (51.9%)(χ2 (1) = 19.907, $p < 0.001$). Healthcare utilization was more prevalent in those needing to have medication deprescribed, with those who needed to have one or more medicines deprescribed being more likely to experience emergency department visit in the previous 12 months (31.2% vs.17.4%; χ^2 (1) = 9.578, $p = 0.002$) or experience a hospitalisation (χ^2 (4) = 12.206, $p = 0.016$). No statistically significant difference was found in deprescribing potential between different age groups or regions.

Predictors of potential for deprescribing

A binary logistic regression model was employed to examine potential predictors for an increased deprescribing potential. The model included several variables: age, number of medicines, number of diagnoses, gender, healthcare utilization, frailty score, and self-reported health. Among these variables, gender, number of medicines and self-reported health emerged as statistically significant predictors of deprescribing potential. Women had 2.58 times higher odds (aOR = 2.58; 95% CI = 1.59–4.18) of requiring deprescribed than men. The odds ratio for the number of medicines (aOR = 1.29; 95% CI = 1.17–1.44) indicated that the higher the number of medicines taken by a patient, the higher the likelihood of needing deprescribing. Participants who reported poor health had 5.14 times higher odds (aOR = 5.14; 95% CI = 1.73–15.25) of needing deprescribing compared to those who reported good health (Table 4).

Discussion

More than half of all participants were candidates for deprescribing, and the most common criteria for deprescribing were inappropriately long use followed by safety concerns, and lack of indication. Similar patterns were found for pharmacists' deprescribing recommendations in the tertiary hospital in Singapore and long term care facilities settings in Australia[40,41], highlighting consistent inappropriate prescribing patters in older adults' pharmacotherapy regardless of setting and geographical location.

The lowest number of deprescribing candidates were PPI users due to high number of patients reporting symptoms regardless of PPI use. Even though older adults often require pharmacotherapy with PPIs, evidence suggests low-dose, or on-demand use can be a reliable strategy to reduce the rate of unnecessary high-dose or

Characteristic	N = 388 participants
Age (median, IQR)	73 years (IQR 69–79.75)
Gender (women, n; %)	247; 63.7%
Region (n; %)	
North–west continental	144; 37.1%
North–east continental	125; 32.2%
Coastal	119; 30.7%
Number of medicines (median, IQR)	6 (IQR 4–8)
Number of diagnosis (median, IQR)	5 (IQR 3–8)
Last hospitalization (n; % of participants)[a]	
Within the last 12 months	51; 13.9%
More than 12 months ago	317; 86.1%
Emergency department visits (n; % of participants)[a, b]	
Yes	97; 25.1%
No	290; 74.9%
Utilization of other healthcare services (n; % of participants)[a, b]	
Yes	54; 14.1%
No	328; 85.9%
Self-reported health status (n; % of participants)[a]	
Very poor	6; 1.6%
Poor	36; 9.4%
Moderate	151; 39.0%
Good	142; 36.7%
Very good	52; 13.4%
Frailty score (n; % of participants)	
Non frail (score 3 or less)	285; 74.2%
Frail (score 4 or higher)	99; 25.8%
Length of medicine use (median, IQR)[c]	
PPI	4 years (IQR 2–6)
NSAID	3 years (IQR 2–5 years)
OPIOID	2.5 years (IQR 2–5 years)
BZN	5 years (IQR 2–10 years)

Table 2. Participants' characteristics. IQR—interquartile range, [a]calculated from non-missing values (missing values less than 5%), [b]within the previous 12 months (other healthcare services include services such as physiotherapy, palliative care, rehabilitations, home care…), [c]patients stating IDK for length of medication use: 41 for PPI, 52 for NSAID, 22 for opioids, and 61 for BZN.

Criteria[a]		PPI	NSAID	OPI	BZN
Total number of deprescribing candidates (n, % of users)		n = 38/122 (31.1%)	n = 83/111 (74.8%)	n = 45/60 75.0% (75.0%)	96.1% n = 148/154 (96.1%)
Lack of indication (n, % of users)		n = 9/122 (7.4%)	0	18.3% n = 11/60 (18.3%)	n = 38/154 (24.7%)
Inappropriately long use (n, % of users)		n = 32/122 (26.2%)	n = 58/111 (52.3%)	n = 42/60 70.00% (70.00%)	n = 94/154 (61.0%) for insomnia use n = 73/154 (47.71%) for anxiety use
Inappropriate dose (n, % of users)		n = 20/122 (16.4%) inappropriately high gastroprotective dose	n = 19/111 (17.1%) higher than recommended daily dose	0	n = 26/154 (17.0%) higher than recommended daily dose
Safety concerns (n, % of users)	Potential clinically significant DDI	n = 3/122 (2.5%)	n = 36/111 (32.4%)	n = 31/60 (51.7%)	n = 39/154 (25.5%)
	Presence of ADE		n = 45/111 (40.5%)	n = 32/60 (56.3%)	n = 81/154 (52.6%)
	Pther safety concerns		n = 35/111 (30.97%) with factors which could be exacerbated by NSAID use	0	n = 56/154 (36.6%) frailty score 4 and above

Table 3. Analysis of deprescribing criteria for each therapeutic class. [a]Patient could meet multiple deprescribing criteria for a single therapeutic class, PPI—proton pump inhibitors, NSAID—nonsteroidal anti-inflammatory drugs, OPI-opioid analgesics, BZN—benzodiazepine receptor agonists, DDI—drug-drug interaction, ADE—adverse drug effects, pro re nata use was noted in 4.09% (n = 5/122) PPI users, 18.92% (n = 21/111) NSAID users, 23.33% (n = 14/60) OPI users, and in 26.80% (n = 41/154) BZN users. Siginificant values are in bold.

Independent variable	aOR	95% CI		*p* value
Age	1.00	0.98	1.00	0.813
Number of medicines	**1.29**	**1.17**	**1.44**	**<0.001**
Number of diagnoses	0.93	0.84	1.02	0.128
Women	**2.58**	**1.59**	**4.18**	**<0.001**
Utilization of healthcare in the previous 12 months[a]	1.30	0.78	2.16	0.322
Frail patients[b]	1.22	0.67	2.22	0.506
Poor self-reported health	**5.14**	**1.73**	**15.25**	**<0.001**

Table 4. Deprescribing potential binary logistic regression analysis. The logistic regression model was significant ($p < 0.001$) with a good model fit (Hosmer–Lemeshow test χ^2 (8) = 3.037 $p = 0.932$). The model explained 24.20% of the variance in deprescribing potential and correctly predicted 68.0% of cases. [a]dichotomized variable with categories: utilization in the previous 12 months and utilization more than 12 months ago, [b]dichotomized variable with categories: score 1–3 indicating non frail patients and score 4–9 indication frail patients, aOR—adjusted odds ratio, CI—confidence interval. Significant values are in bold.

prolonged PPI therapy while providing adequate symptom control[42,43]. Although reducing existing or potential harm is one of the main goals of deprescribing, when it comes to analgesics, it is important to maintain pain control even after medication withdrawal. Large number of NSAID users were candidates for deprescribing due to safety concerns, and opioid users were confronted with a twofold setback, of inappropriately long use and safety concerns. Pharmacist-led deprescribing interventions can lead to a decrease in use of NSAIDs and still effectively manage pain[44,45]. Opioids can be efficient in improving pain in the short-term, but long-term therapy may actually worsen the impact of chronic pain on quality of life due to low efficacy and adverse effects[46]. Multidisciplinary care programmes seem to be effective in opioid deprescribing[47], but additional evidence is needed to assess the most suitable type of intervention. An overwhelming number of BZN users are candidates for deprescribing, mostly due to inappropriately long use and adverse effects. Deprescribing BZN can be challenging for both patients and healthcare providers, but when provided with a non-pharmacological support can be successful[48,49]. For each medication group analysed in this study, there are substantial evidence and guidelines at healthcare providers' disposal, which should be tailored to individual patient's needs and utilized during patient care.

Several factors were identified as potential predictors for increased need to have medicines deprescribed, including female gender, reporting poor health, and using multiple medications. Besides keeping in mind pharmacodynamic and pharmacokinetic differences between men and women, healthcare providers should consider other factors which could influence adequate provision of healthcare to men and women. A review by Rochon et al. explores the importance of sex and gender differences in providing care when it comes to polypharmacy and potential deprescribing, highlighting how women are more likely reach to old age, be exposed to inappropriate prescribing and polypharmacy, and be at risk or drug-related adverse events[50]. Women are also more likely to consider the impact of medication when it comes to the decision to agree with deprescribing, while men find the impact of physician more important[51]. Self-reported health, which is negatively associated with polypharmacy[52], can be used in predicting short-term mortality risk among older adults[53], and has been identified as one of the priority outcomes in deprescribing research[54,55]. There is lack of evidence on the effect of deprescribing on self-reported health, but results of one study suggest that deprescribing can have a positive effect on increasing and/or sustaining levels of self-reported health[56]. Deprescribing can have a positive impact on other clinical outcomes which can then affect self-perception of health, such as mental health status, function, or frailty[57]. Furthermore, higher the use of medications, higher the odds participant will need medications deprescribed. When examining the deprescribing potential of four medication groups, more than one fifth of participants were suitable candidates for deprescribing multiple medications. Polypharmacy has been recognised as a risk factor for negative outcomes, and where appropriate polydeprescribing (the simultaneous deprescribing of multiple medications) could be recommended to quicken the process without compromising patient safety[58]. For healthcare providers polydeprescribing enables tackling multiple medications at once as deprescribing priorities, which can potentially lead to earlier improvement in outcomes for those eligible patients who are comfortable with accepting discontinuation of multiple medications. Healthcare providers should carefully consider patients who exhibit multiple factors associated with increased deprescribing potential.

As deprescribing is a patient-centred process and requires shared decision-making, it is important to evaluate patients' opinions and attitudes before suggesting deprescribing. Evidence suggests patients are willing to have medicines deprescribed[59,60], but actual number of patients who accept deprescribing could be lower[61]. No difference was found between different age groups regarding deprescribing potential in this study, and every eligible patient should be offered deprescribing. Nevertheless, there is a potential difference in acceptance of deprescribing suggestions among different age groups, with very old adults expressing satisfaction with pharmacotherapy and not seeing any need for medication withdrawal[62,63], which should be taken into account when providing care for older adults.

Several limitations need to be stated. Analysis of safety concerns, namely the effect of found potentially clinically significant interactions needs to be interpreted with caution, as interactions should be assessed and confirmed at point-of-care and include detailed clinical interpretation with extensive clinical data, which could not have been collected in its entirety with the used questionnaire. For those reasons, the research team focused on interactions which could be interpreted based on collected data and patient context. Another limitation in this

study is the lack of a shared medical electronic records across different healthcare levels, and lack of electronic medical record available in the community pharmacy. As a result, the accuracy of the data used for analysis relied on information collected directly from the patient and the medical documentation provided by the participant to the researchers. Potential for deprescribing was assessed for four medication groups, which could be viewed as a limitation, as true need for deprescribing is underestimated. Whereas it would have been interesting to explore the deprescribing potential of other commonly used medications, such as antihypertensives, antidepressants, antipsychotics, or other fall risk increasing medications, the data did not present enough clinical information to adequately assess disease control and subsequent deprescribing potential. Nevertheless, these four medication groups represent most commonly used medicines in the sample's population[64], and were most commonly recognised as inappropriate medications needing deprescribing[2,65]. On the other hand, use of pharmacist's geriatric assessment as well as medication review with detailed deprescribing criteria ensured deprescribing potential was judged considering all important aspects of patients' health. Results of pharmacist's geriatric assessment with the analysis of deprescribing potential should be a part of a more encompassing interdisciplinary approach, involving general practitioners and specialists such as geriatricians, in order to verify and position the findings in a clinical context of the patient in question to reach the desired therapeutic goal. Comprehensive geriatric assessment has been proven to be a useful method for identifying deprescribing targets, and a combination of clinical geriatric assessment and collaborative medication review can result in positive effects on health-related quality of life[66,67].

Additional limitations include analysis performed on data collected for one participating country from the EuroAgeism H2020 project, and cross-sectional study design for which causal relationships cannot be confirmed. However, this sample adequately represents patients from this high-income Central and Eastern European country, with relatively high use of potentially inappropriate medications among older adults in the community setting[68] and average frailty prevalence[69]. The lack of data on deprescribing potential in community-dwelling older adults in Central and Eastern Europe, including other participating countries, further emphasizes the importance of the results obtained from this study. While this study explores the potential for deprescribing in the community-dwelling adults, it can be assumed the need for deprescribing is even more pronounced in secondary or tertiary settings, and in long-term care facilities. Deprescribing potential assessed using available deprescribing guidelines in a retrospective study on hospitalized older patients showed almost three quarters of patients were deprescribing candidates[70]. There is a need for additional research and comparative studies (within Europe and worldwide) to get a better insight: into the deprescribing potential among vulnerable patient groups, as well as to assess the availability of medication management services, particularly in healthcare settings unfamiliar with deprescribing. This can help identify differences and variations in prescribing practices, as well as highlight the opportunities and challenges for implementing deprescribing into everyday practice. Results of this study additionally highlight the importance of community pharmacists' involvement in providing safe and personalized multidisciplinary geriatric care and underscore the possibilities of implementing a more active role of community pharmacists in achieving better outcomes for older adults.

Further research is necessary to establish how identified factors influence provision and success of a deprescribing intervention, especially when it comes to clinical and patient-related outcomes, such as self-reported health status. Potential target subpopulation could be women who are exposed to inappropriate polypharmacy and are expressing poor self-reported health.

Conclusion

A significant proportion of older adults are eligible candidates for deprescribing one or more medicines, with a particular emphasis on the deprescribing potential of benzodiazepines. followed by analgesics. Polypharmacy and poor self-reported health, as well as being a woman, have been identified as factors contributing to increased deprescribing potential. Timely action towards reducing the use of commonly prescribed potentially inappropriate medications is needed to increase patient safety and contribute to healthy ageing. Personalised approach can be achieved through pharmacist's geriatric assessment and deprescribing-focused medication review.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

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Author contributions

M.O.H., J.B. and D.F. conceptualized and designed all works on the paper. I.K., M.D. and I.B. collected the data, managed data collection and prepared the dataset for analysis. I.B. and M.O.H. conducted initial and statistical analyses. I.B. and M.O.H. prepared the first draft of manuscript. All authors contributed to the analyses and interpretation of results. All authors contributed significantly to the study design, data collection and preparation of the study dataset, or to the critical appraisal of statistical works or works on the manuscript. M.O.H. and D.F. supervised all the work. All authors read, critically reviewed, corrected and approved the final version of the manuscript.

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Competing interests

The authors declare no competing interests.

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10. GENERAL DISCUSSION

10.1. Overview, positioning and novelty of findings

The four-phased research on the potentials and opportunities, as well as needs and challenges of deprescribing in the primary care setting elucidated the following novel findings:

A thorough systematic review conducted during the first phase of this research revealed community-based pharmacists can successfully lead deprescribing interventions. Through educational interventions aimed at patients, medication review or management, or through pharmacist-led collaborative interventions, pharmacists can be valuable partners in deprescribing. They can identify potential candidates, recommend a tailored deprescribing plan and intervention, which suites the patient, to the prescriber, monitor the patient throughout tapering and medication withdrawal, and provide necessary follow-up to ensure the success of deprescribing.

Furthermore, the second phase cross-sectional study on 315 adults, 40 years and older in community pharmacies revealed that more than 80% of participants would be willing to deprescribe one or more medications, with older adults (65 years and older) being more willing to have medications deprescribed than younger adults. Research shows varying range of percentages of patients (41%-93%), namely older adults, expressing their willingness to have medications deprescribed (97–104). Reasons for variation could be attributed to differences in health literacy and health-related culture, accessibility of healthcare, and the understanding of deprescribing process (105). Different patient determinants influence the decision to accept deprescribing. In this research, it was found that greater involvement in treatment was associated with greater willingness to have medications deprescribed. Besides involvement, studies reported medication burden, and concerns about stopping medications, being correlated with willingness to deprescribe (101–103,106). Often opposing and conflicting preferences and attitudes are conveyed when it comes to medication and deprescribing (107). For instance, in the oldest of old (those ≥ 80 years) with increased frailty score, and high medication regimen complexity index (MRCI) and medication burden, lower willingness to deprescribe was found (108). Moreover, majority of participating adults (more than 70%) would feel comfortable with pharmacist's involvement in deprescribing, and almost equal majority (around 69%) believes (their) pharmacist has enough knowledge, skills, and information to suggest deprescribing. Positive opinion on pharmacists' involvement was assessed as a predictive factor for positive attitude towards deprescribing for Croatian adults. This research was first to report patients' preference on pharmacists' involvement in deprescribing, initiating other research groups to explore the same aspect. Indonesian researchers found patients were less likely to accept

deprescribing if it were initiated by a pharmacist in comparison to a general practitioner, however patients with low educational attainment were more likely to find pharmacists' deprescribing recommendation acceptable (109). As pharmacists can be valuable partners in deprescribing, it is important to further explore in which circumstances pharmacists can be healthcare provider of choice to lead the deprescribing intervention.

While it could be argued that patients should not be making the decision which medication should be deprescribed, and that rather that decision should be made by a healthcare provider leading the potential intervention, patients' opinion is crucial for the success of the intervention (110). For those reasons, a wholesome approach to the exploration of patients' opinions and attitudes towards deprescribing was taken as a part of the second phase of research, with added questions on patients' preferences to deprescribing specific medications from their pharmacotherapy. Participating adults expressed uncertainty when answering the questions about deprescribing preference. Around one third of participants did not answer preference related questions, and only a small percentage stated specific medications (AHTN, BZN, statins, and NSAID) they would be willing to stop taking, or would not be willing to stop taking (AHTN, antidiabetics, and BZN). Those who stated a specific medication they would be willing to stop taking, were more likely to positively answer the question about willingness to deprescribe. In a Dutch study on patients' preferences toward deprescribing cardiometabolic medications, older adults stated antihypertensives and insulin to be more appropriate medication than statins or sulfonylureas (103), while Indonesian researchers found that older type II diabetic patients are more likely to be willing to stop taking antidiabetic medications, if they are using a single glucose-lowering medication than if they are taking multiple (109). Patients' preference is basis for shared decision-making, and such information can be used for, not only, easier planning of a deprescribing intervention, but for discussions on potential non-adherence, adverse reactions, or missed treatment goals as well. These findings additionally highlight the importance of conscientious and continuous examination of patients' preferences and attitudes towards deprescribing, which could change as patients' health status, including pharmacotherapy, changes.

Successful implementation and sustainability of deprescribing into everyday clinical practice heavily depends on healthcare providers readiness to engage in this novel approach. Qualitative research, based on one-on-one interviews or focus groups, reveals important domains, concepts, and themes, but often fails to encompass opinions of a larger number of healthcare providers (95,111–113). Theoretical domains frameworks, Behaviour Change Wheel framework, and

Normalisation Process Theory are repeatedly used to inform qualitative research on deprescribing (114–117). Often similar or identical concepts are categorised as different domains of different frameworks, making it not only increasingly more difficult to distinguish between new and existing knowledge in the field of deprescribing (89), but also to position ones' finding for comparison to others, and use it for further implementation. Comprehensive Healthcare providers' OPinions, Preferences, and attitudEs towards Deprescribing questionnaire was developed, during the third phase of research, to aid in exploration of healthcare providers' determinants important for implementing and providing deprescribing regardless of their familiarization with deprescribing. The tool, developed in two versions, contains ten factors grouped in three domains, Knowledge and awareness about deprescribing, Barriers to deprescribing, and Facilitators of deprescribing. Barriers to deprescribing, and Facilitators of deprescribing each contain four thematically similar factors, Patient factor, Competencies factor, Collaboration factor, and Healthcare system factor. Two versions allow for the capturing of profession-specific viewpoints, while one comprehensive tool enables easier recognition of shared barriers and facilitators within a healthcare system, or its single component (*i.e.,* primary healthcare centre). Two other, more narrow intended, tools are available, one developed by Linsky et al, aimed at healthcare providers with prescribing privileges, and one by Shrestha et al, aimed at healthcare providers deprescribing in older adults with limited life expectancy (118,119). Huffmyer et al, state "communication" as principal and shared barrier and facilitator concerning deprescribing, in their research on community-based primary care healthcare providers when using adapted Linsky et al tool (120). Given the complex nature of healthcare systems and the deprescribing approach, it is improbable that different healthcare providers serving within the same system are perceiving only one barrier or facilitator, as research reports various barriers and facilitators, as well as differences among different stakeholders (121–123). This potentially suggests that the tool adaption was lacking and that it cannot comprehensively explore barriers and facilitators. CHOPPED has satisfactory face, construct, content, and criterion validity for both versions, making it one of the first validated tools in this field exploring general barriers and facilitators, regardless of healthcare provider, patient, or medication type. Use of CHOPPED tool can help move the focus of research on barriers and facilitators forward from small qualitative studies, enabling for an easier translation of recognised challenges, into more straightforward implementation strategies on a larger scale.

The CHOPPED tool was used to identify factors associated with willingness to suggest deprescribing. On the whole, majority of healthcare providers (87%) stated they would suggest deprescribing to a patient if appropriate, with pharmacists showing more uncertainty than physicians. Whilst for pharmacists most important factors were collaboration facilitators and healthcare systems facilitators, for physicians most prominent correlation was found for knowledge, awareness, and patient facilitators factors. For both pharmacists and physicians, a negative correlation between willingness to suggest deprescribing and competencies barriers factor was found, indicating that those with increased perception of lack of personal competencies express lower willingness to deprescribe. Results from this phase of research elucidate CHOPPED's ability to characterise differences and similarities in factors influencing deprescribing among different healthcare providers within the same healthcare system, and help recognise agents and targets for improvement.

Evaluation of the level of agreement on deprescribing suggestions between pharmacists and physicians was assessed using a case vignette study, as a part of the third phase of research. Pharmacists were able to identify potential deprescribing targets and state balanced deprescribing rationales (most commonly suggested for OPI, NSAID, and diuretic), although reluctance and diffidence were expressed for certain suggestions (BZN, preventive and specialist prescribed medications). Even though there was a difference in number of medications physicians and pharmacists would deprescribe (physicians indicated they would accept a recommendation to deprescribe ten, and pharmacists recommend deprescribing six medications), there was strong matching in class and type of medication which should be suggested for deprescribing (diuretic, OPI, NSAID) indicating a collaborative deprescribing approach is possible for Croatian primary healthcare providers. Australian study found comparable discrepancies in number of selected deprescribing targets between pharmacists and physicans, bringing to light the notion that regardless of advancement of the healthcare system and healthcare providers' awareness of deprescribing, there are globally similar potential obstacles to collaborative deprescribing (124). While there is positive evidence on physicians' acceptance of pharmacists' deprescribing recommendations, additional efforts are needed to implement and sustain such interventions as part of everyday practice (71,99). In addition, when examining the entirety of CHOPPED and case vignette findings, a more wholesome formative evaluation into healthcare providers' attitudes, preferences, and opinions emerges. Croatian primary healthcare providers are skilled in recognising deprescribing targets, willing to suggest

deprescribing to patients, and open for a collaborative pharmacist-led deprescribing intervention, but require different incentives.

Assessment of the deprescribing potential of commonly used medications among community-dwelling older adults, as the fourth phase of research, was performed using data from a Croatian cohort of the EuroAgeism H2020 project and guideline-based deprescribing criteria. Four medication groups (PPI, NSAID, BZN, OPI) were chosen to evaluate the deprescribing potential, using pharmacist's geriatric assessment and medication review. More than half of patients were identified as deprescribing candidates of one or more medications, with emphasis on need for deprescribing benzodiazepines and analgesics. Several factors, identifying as a woman, polypharmacy, and poor self-reported health status, were recognized as predictive for increased need for deprescribing. Four-country research using patient typology found several overlapping factors associated with decision-making and management of medications and deprescribing, with excellent health being associated with decreased, and being female associated with increased opportunities for deprescribing (30). A Danish study on a chronic care model involving deprescribing found that self-reported health status increased following deprescribing (125), contributing to findings of this research, that effect on self-reported health could be used as potential leveraging outcome when discussing deprescribing interventions with potential candidates.

10.2. Implementation strategy based on research findings

Utilising the qualitative and quantitative findings of this multiphase research, given the complexity of a healthcare system, and specificity of the deprescribing approach, a promising multifaceted implementation strategy and an interventional protocol can be proposed. Designing an implementation strategy and interventional protocol completes the developmental formative evaluation necessary for the success of an intervention (126). To aid in the development, several frameworks should be reviewed and appropriately adapted such as, the integrated Promoting Action on Research Implementation in Health Services (i-PARIHS), the Active Implementation Frameworks (AIF), the UK Medical Research Council's framework for complex interventions, the Consolidated Framework for Implementation Research (CFIR) and the Expert Recommendations for Implementing Change (ERIC) thematic clusters (127–133). A hybrid effectiveness-implementation typology with dual testing of clinical effectiveness and implementation strategies (134) can be used to describe the findings-guided implementation strategy (shown in Figure 3) and protocol (shown in Figure 4 and described in section 10.2.1.)

of a collaborative deprescribing approach, which are presented on an example of a primary care health centre setting including physicians' practices and community pharmacies.

Patient-oriented discrete strategies should elicit two complementary changes in patients, changes in awareness of, and engagement in deprescribing (Figure 3). These strategies can include public and private communication tools (*i.e.* infographics, handouts, or web-based tools) to upsurge awareness and provide information on the concept and benefits of deprescribing with intent to increase patient engagement. While there are number of communication tools available to initiate deprescribing, a limited number is tested and validated (59). For this proposed implementation strategy to become viable, adapted communications tools are necessary for both patients and healthcare providers. Positive patient experiences were reported in the "EMPOWER" trail regarding medication safety information being sent via mail which resulted in increase in number of patients who broached the subject of deprescribing with their healthcare provider (135,136). Patient-oriented engagement tools should encompass, direct-to-consumers strategies, which should target not only patients, but also families, informal caregivers, and all other members of the public who might benefit from such services directly or indirectly (137).

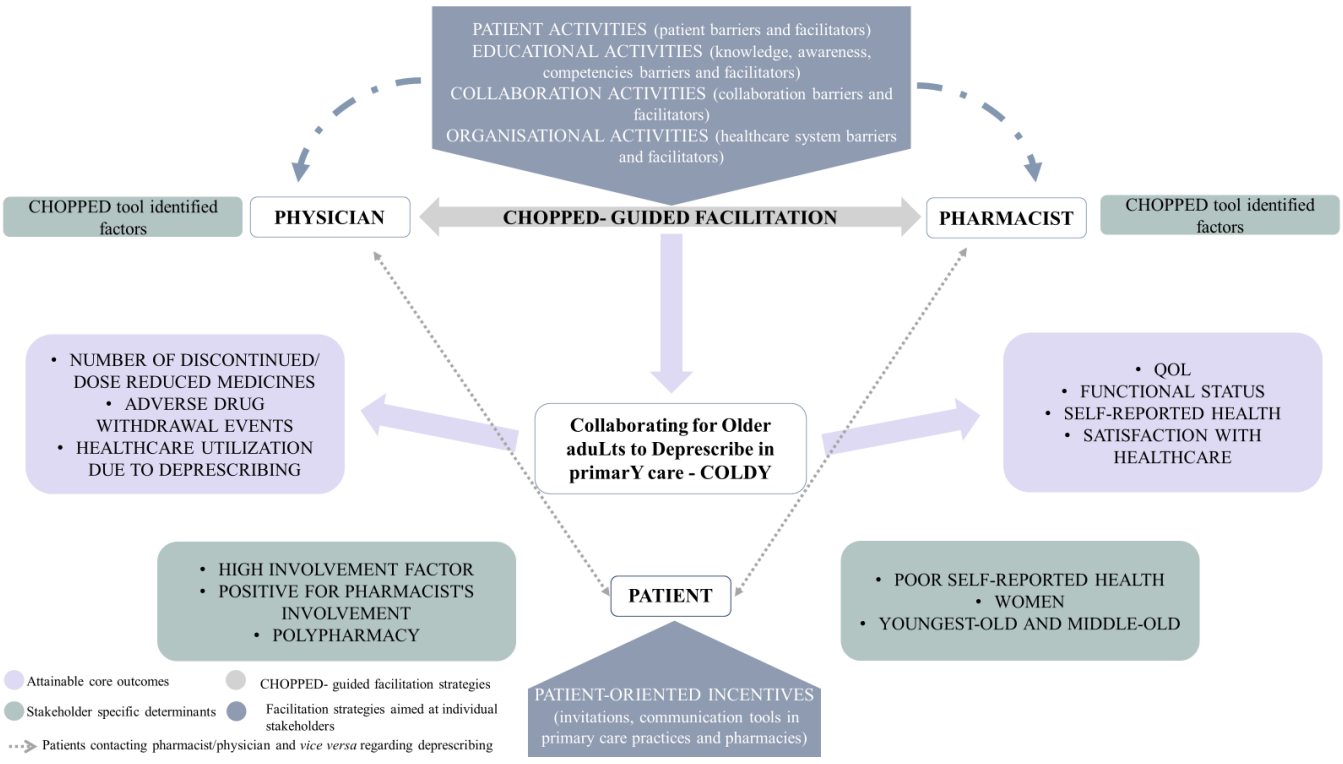

Figure 3 Implementation strategy based on research findings

During the second phase of research Croatian patients reported they would welcome telephone calls, as well as web-based communication as methods of follow-up. Reaching out to seniors' organizations to participate in design and choice of deprescribing communication tools can be a good starting point to involve the target population and adjust the tool to appropriate health literacy levels.

Moreover, tailored strategies can be directed towards those population groups which were identified as priority deprescribing candidates in this research, such as women or patients exposed to polypharmacy. Patient-oriented communication should also help in the identification of those patients who are open to a discussion about deprescribing, for example those with high involvement factor, or positive opinion on pharmacists' involvement (*i.e.,* rephrased questions from the rPATD questionnaire can be used as a part of a brochure). Successful patient-oriented strategies should lead to patients' increased comfort in contacting healthcare providers to initiate shared-decision making regarding deprescribing.

In prior deprescribing research there has been limited consideration of implementation factors, especially with regard to the personnel and resources, and the feasibility of incorporating deprescribing into routine care (138). The CHOPPED tool can be used as a part of an implementation study, in two instances. At the very beginning of implementation (CHOPPED guided facilitation of implementation), and at potential fidelity or sustainability points of failure, to identify barriers and facilitators, and explore whether or not, and how they change with implementation in both the research and healthcare context (139). CHOPPED-guided facilitation can be used for healthcare providers oriented discrete strategies (Figure 3). After applying CHOPPED, crucial shared and profession-specific determinants are identified, on which a strategy can be developed. Research shows clinical champions can assist with faster initiation of the application of novel intervention, as well as increase clinicians' self-efficacy (140,141). Potential leaders and champions should be selected from those who possess a strong willingness to deprescribe, low barriers to deprescribing, with achievable and opportunity-seizing facilitators. For this research setting, this would involve selecting physicans and pharmacists who stated, in the case-vignette study, they would like to participate in a deprescribing trial, and who satisfy above mentioned criteria.

Educational activities can be used to tackle lack of knowledge or awareness, and competencies barriers. To overcome time constraints, and upkeep healthcare providers interest and motivation, it can be suggested to implement the intervention on a small scale first, such as

choosing one day a week or a month when deprescribing activities would take place (142). Small-group, or pharmacist-physician paired educational activities using real-life case vignettes prepared by the trainees, can tackle educational gaps, shared patient barriers, and collaborative needs. Patient representatives can be included in educational activities to give insight into the most appropriate approach a healthcare provider needs to take when initiating a conversation on deprescribing.

Important outcome measures in deprescribing research are starting to crystallize, in form of recommended core outcome sets (86,143). During educational activities as a part of implementation strategy, healthcare providers should discuss the choice of attainable outcome measures, which can easily be collected during and after the intervention, without negatively impacting the provision of deprescribing or other forms of care (*i.e.* do not affect the healthcare providers' decision not to suggest deprescribing) (Figure 3). The attainable outcome measures set should include patient-related, medication-related, and resource-related outcomes (86,144).

Firstly, patient-related outcomes should include both patient-reported experience measures (PREMs) and patient-reported outcome measures (PROMs) (145), such as self-reported health and/or health-related quality of life, presence of adverse drug withdrawal events during and after deprescribing, effect on functional status and symptom control, or in case of unsuitable measuring tools, lack of deterioration in health status. Patients' satisfaction with provided healthcare and healthcare providers, during and after deprescribing should also be monitored and appropriately captured. Patient-reported and patient-important outcomes should become central, and adequate tools and measures are needed to prove deprescribing impact and effectiveness. Current scales for health-related quality of life, or medication-related quality of life are unsuitable for most patients' groups who are considered deprescribing candidates (146). Research and evidence are needed to address which tool would be most sufficient to examine the potential effects and benefits of deprescribing on specific aspects of patients' quality of life.

Secondly, number of discontinued medications, number of medications with reduced dosage, change in number of prescribed and dispensed prescriptions (number of returned unused medications to the pharmacy), change in number of used replacement over-the-counter medications, or medication free time can be considered as medication-related outcomes. While these measures might not fully reflect the clinical impact deprescribing can have on the patient (the downstream of medication-related outcomes), they are still considered as key indicators of successful deprescribing (144).

Lastly, to help with future policy making, resource-related outcomes should be captured as well. These should include easily measured healthcare utilization such as hospitalisations, emergency-department, or primary care physician visits due to worsening of health related to deprescribing, as well as, cost evaluations and reimbursement models, and measures of impact on healthcare providers workflow.

As a result of CHOPPED-guided facilitation of implementation, a clear collaboration should be established between the primary care physician and community pharmacist, in order to integrate and sustain a proposed collaborative deprescribing intervention, named "**C**ollaborating for **O**lder adu**L**ts to **D**eprescribe in primar**Y** care" (COLDY) (Figure 4). The intervention should be seamlessly integrated or framed in routine care, and not require or cause disruption in everyday practice.

10.2.1. Deprescribing intervention based on research findings

During usual practice both primary care physicians and community pharmacists can screen and identify potential deprescribing candidates. Patients should be screened for inclusion if they are 65 years of age or older, exposed to polypharmacy, prescribed and taking one or more medications from the list of potential target medications, such as those recognised in the third and fourth phase of this doctoral research, and express high medication or treatment burden and involvement which can be assessed through selected questions from the questionnaire used in the second phase of research. Patients, who identify with the invitation to participate in deprescribing through patient-oriented strategies, would be able to contact either healthcare provider to discuss potential inclusion in the intervention (self-referral), which supports shared decision-making as part of deprescribing important to patients (147) .

If appropriate, physicians and pharmacists can agree on a set of preselected patients (identified during educational activities) they can target during their next visit to the pharmacy or physician's practice. A list of potential target medication groups (BZN, NSAID, OPI, AHTN, PPI) with curated deprescribing resources, for both healthcare providers and patients, should be available to help guide the intervention, with healthcare providers' discretion to deprescribe other identified potentially inappropriate medication, such as anticholinergics or antipsychotics.

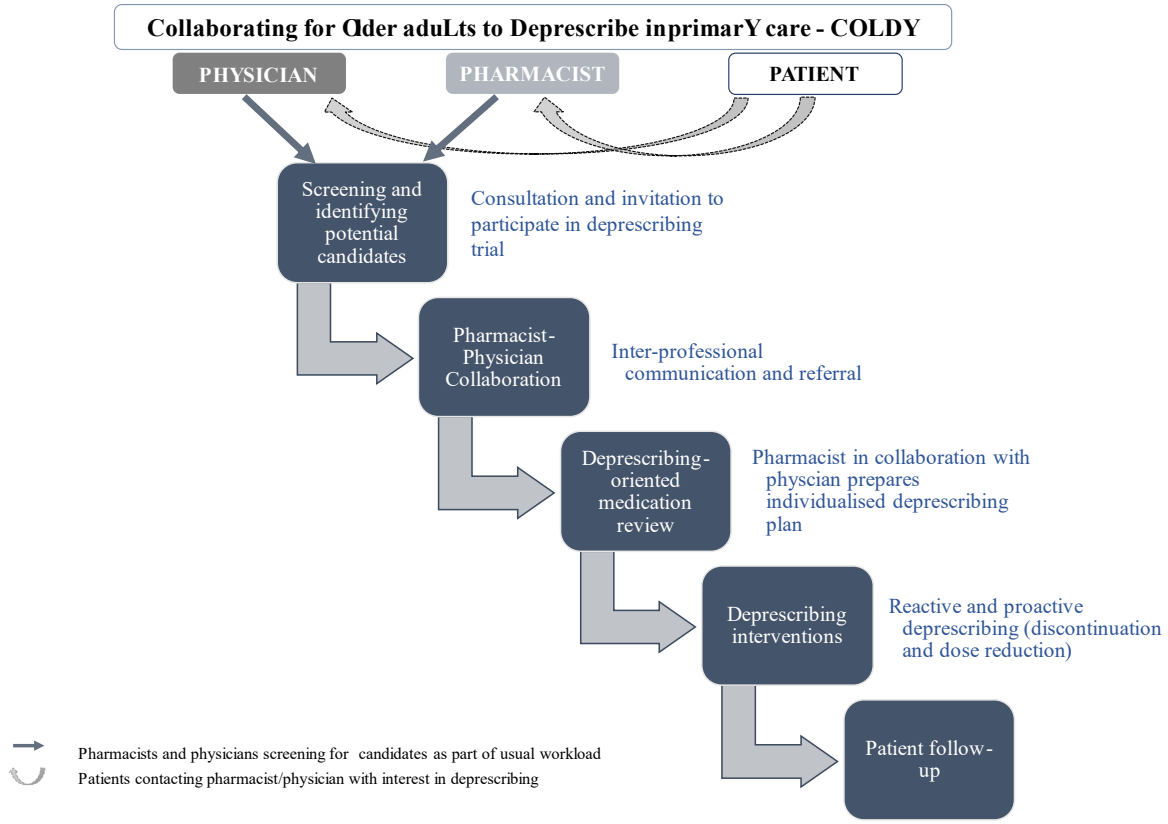

*Figure 4 Proposed collaborative deprescribing intervention (**C**ollaborating for **O**lder adu**L**ts to **D**eprescribe in primar**Y** care-COLDY)*

For identified patients, who wish to participate, a pharmacist should perform a deprescribing-oriented medication review based on thoroughly collected medication history, comprehensive geriatric assessment, and through the collaboration with the physician, as research shows pharmacists' involvement in deprescribing interventions not only leads to better health and economic outcomes, but has a positive effect on deprescribing implementation and establishment of a multidisciplinary approach to the patient (148–150). The comprehensive geriatric assessment should be grounded on information from the physician's data (electronic health record) and expertise, and/or when missing patient's input (collected by either healthcare provider using structured scales and measures). After reviewing the data, pharmacist suggests a detailed individualised deprescribing plan, including both reactive and proactive deprescribing to the physician. A programme theory resulting from a realist review and synthesis, supports COLDY-like collaborative multidisciplinary approach to deprescribing for older adults in primary care, and highlights the importance of pharmacists' integration in medication review as well as involvement of other specialist physicans, such as geriatricians in the process of care (149). Evidence is emerging on the benefits of pharmacist-physician collaboration during comprehensive geriatric assessment (151). Pharmacists can be well placed,

as member of the multidisciplinary team, to help prevent inappropriate prescribing and support deprescribing in the management of geriatric syndromes worsened by medications (152). Following physician's approval, either healthcare provider discusses the deprescribing intervention with the patient and creates a follow-up plan. Collaboration should be maintained throughout the follow-up to ensure success of the intervention and patient safety. Reasonable time intervals of continuous follow-up should be established in order to provide adequate patient support regarding ADWEs, as well as to capture necessary outcomes (22).

Not least, healthcare system changes and adaptation are needed to sustain the newly introduced approach and to adequately capture system-related outcomes (resource, cost, or utilization). For Croatian healthcare system, currently available electronic infrastructure can be utilised, with minimum adjustments. Both primary care physicians and community pharmacists use the same central health information system, regardless of local workflow software. E-prescription, e-medical record, and e-referrals can be used to collect data for providers, researchers, and policy makers, and facilitate seamless collaboration between healthcare providers, patient follow-up, and transfer and consolidation of the novel approach into its other components.

Implementation outcomes, acceptability, appropriateness, fidelity, and feasibility need to be measured to ensure the strategy and the intervention are robust, yet flexible enough for the healthcare system in question. These outcomes can be captured using data collected from healthcare providers' feedback on the provided activities during and after the intervention. Three implementation outcomes can be measured using Acceptability of Intervention Measure (AIM), Intervention Appropriateness Measure (IAM), and Feasibility of Intervention Measure (FIM) scales (153). Simple 5-point Likert scaled questions, psychometrically balanced, are appropriate for a fast and easy data collection. Fidelity can be measured through healthcare providers' self-report checklist of intervention steps. Descriptions of deviation in intervention can be collected through open-ended questions. Analysis of answers will give insight into potential adaptations of both implementation and intervention. When it comes to sustainability as an outcome, the Provider Report on Sustainment Scale can be used (154).

It is pertinent to apply CHOPPED, CHOPPED-guided implementational strategy and intervention in other more developed healthcare settings. Using a comprehensive tool will allow for a uniform methodology to be applied to this aspect of deprescribing, yielding standardised results for comparison. This, in return, can streamline the process of selecting a well-established strategy for implementers, researchers, and healthcare providers, to conquer obstacles and

leverage facilitators leading to a successful implementation, adoption and sustainment of deprescribing.

10.3. Strengths and limitations

While this multi-phased mixed-methods oriented research allowed for comprehensive approach to the topic of deprescribing, its strengths and weaknesses should be stated.

The included systematic review is one of the first to focus on the pharmacist, as the leader and provider of deprescribing, rather than to focus on specific populations or medications. Due to heterogeneity of included studies, meta-analysis of impact on reported outcomes was not possible. Regardless, it brings a clear summary of type of interventions and outcomes in deprescribing interventions led by a community-based pharmacist.

The second phase of research brought one of the first studies exploring patients' preference towards pharmacists' involvement in deprescribing, and proving positive opinion on pharmacists' involvement is a predictive factor of increased willingness to have medicines deprescribed. This is also one of the first studies to include younger adults when using the rPATD questionnaire. Younger adults, while showing less interest in deprescribing, but a positive attitude towards it, are likely to benefit from an early introduction to the concept of deprescribing overall, as it is more likely medications will be added to their pharmacotherapy. In addition, this was one of the first studies to examine patients' preference on deprescribing specific medication. Limitations include collecting limited sociodemographic data which could be potential predictors of willingness to deprescribe, and including community-dwelling participants able to visit the pharmacy. For these reasons results cannot be generalised to other community-dwelling populations. Regardless, sample size adequately presented the population in question including spatial distribution throughout Croatia, and questionnaire response rate of 82% additionally support the design of the questionnaire and low selective nonresponse bias.

One of the main restrictions of the CHOPPED tool is its validation on one sample of primary healthcare providers and use in one language. The straightforward and promising tool needs revaluation and validation in other languages to verify its highest potential. Nonetheless, methodical, and comprehensive preparatory work led to a development of a psychometrically sound tool, which can be used and reused as needed, in its entirety or partially. Development of two profession-specific version can be viewed as a strength, as each version can further be adapted for use in different healthcare professionals, such as nurses (155–157). Lack of confirmation of concurrent validity could be viewed as a limitation, but there were no other

scales or gold standards for comparison at the time of development and validation. This opens an opportunity for CHOPPED tool to become the standard of practice. When discussing the use of CHOPPED tool in a cross-sectional study the following limitations arose, nonresponse bias and inability to determine true response rate due to use of online survey as a method of data collection. Likewise, could be said for the case vignette study. Notwithstanding, the samples sufficiently represented Croatian primary care healthcare providers regarding important characteristics (gender, educational attainment, practice location) minimising the potential selection bias. Moreover, these were one of the first studies, in form of an extensive formative evaluation (158), exploring deprescribing barriers and facilitators involving such a high number of both prescribing and non-prescribing healthcare providers, bringing an insight into genuine real-world problems healthcare providers face daily.

Exploration of the deprescribing potential, assessed on a sample of community-dwelling older adults, was one of the first studies combining pharmacist's geriatric assessment and deprescribing-oriented medication review. Two limitations should be addressed, sample selection and choice of medication groups. The Croatian cohort of the EuroAgeism H2020 ESR7 project was used, as only this portion of data was available to the research team. Nevertheless, sample sufficiently represented the population of interest regarding characteristics such as use of PIMs, or frailty prevalence. Additionally, the importance of presented findings is emphasized by lack of data on deprescribing potential in community-dwelling older adults from Central and Eastern Europe. True deprescribing potential is underestimated as only four medication groups were chosen for analysis. While pharmacist's geriatric assessment gathers ample data on patients' health status, there was not enough clinically relevant data to appropriately assess deprescribing potential of other commonly used medications such as cardiometabolic medications. Irrespective, the four chosen medication groups are most commonly used medications, and were recognised as deprescribing targets, not only in the case vignette phase of this research, but in other research as well (125,159).

Lastly, it could be stated that this research's limitation is lack of an interventional study. This multi-phased research explored deprescribing for the first time in a setting unfamiliar with the approach, and venturing into an interventional trial could be viewed as wasteful, thoughtless, unprepared, and scientifically unfounded yielding unreliable or heavily biased results. In contrast, the above presented research examined all the important aspects and stakeholders of deprescribing, collecting the necessary pre implementation evidence (acceptability of a

healthcare intervention) required for future timely, sensible, and sustainable implementation into practice.

11. CONCLUSIONS

The following conclusions are drawn from this four-phased research on the potential and opportunities, challenges and need for deprescribing in the primary care setting of a healthcare system unfamiliar with the deprescribing:

- Patients, primary care physicians, and community-based pharmacists are open to the concept and approach of deprescribing. Patients' comfortability with pharmacists' involvement can be used to support pharmacist-led deprescribing initiatives while reducing primary care physicans' workload.
- Patient determinants need to be counted for when considering deprescribing. Selected group of patients, such as those exposed to polypharmacy with negative opinion on medication appropriateness and poor self-reported health, should be targeted as priority candidates. Shared decision-making should be honoured at every stage of the deprescribing conversation.
- To aid in the facilitation of deprescribing implementation into everyday practice a comprehensive, yet profession-sensitive validated tool should be used to identify obstacles and enablers.
- Profession-specific barriers and facilitators should be balanced against shared ones to utilise best agents for deprescribing. Pharmacists' uncertainty in suggesting deprescribing, but high knowledge and awareness of deprescribing benefits, with physicians' confidence in deprescribing should be offset against common collaboration or patient barriers.
- A large number of older adults are candidates for proactive and reactive deprescribing of benzodiazepines, opioid analgesics, and nonsteroidal anti-inflammatory medications, indicating a prompt action to reduce the use of commonly prescribed potentially inappropriate medications is needed.
- Extensive formative evaluation emerged from the results of all four phases of research elucidating the necessary pillars which can be used to facilitate an effective design and implementation of a deprescribing intervention
- A multifaceted, multistakeholder-oriented implementation strategy was elucidated from the results of this research, and can be used to engage healthcare providers in collaborative patient care with the goal of promoting deprescribing to enhance patient safety and optimise pharmacotherapy.

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13. LIST OF ABBREVATIONS

ADeN	Australian Deprescribing Network
ADWE	adverse drug withdrawal effects
AHTN	antihypertensive medication/ antihypertensives
AI	artificial intelligence
AIM	Acceptability of Intervention Measure
BZN	benzodiazepine/benzodiazepines
CaDeN	Canadian Medication Appropriateness and Deprescribing Network
CEASE	Clinical Features, Effectiveness, Ask, Stop, Explain
CFIR	Consolidated Framework for Implementation Research
CHOPPED	Comprehensive Healthcare providers' OPinions, Preferences, and attitudEs towards Deprescribing
COLDY	Collaborating for Older aduLts to Deprescribe in primarY care
COST	European cooperation in science and technology
EDeN	English Deprescribing Network
EPIS	Exploration, Preparation, Implementation, Sustainment
ERASE	Evaluate, Resolved conditions, Ageing normally, Select targets, Eliminate
ERIC	Expert Recommendations for Implementing Change
FIM	Feasibility of Intervention Measure
IAM	Intervention Appropriateness Measure
i-PARIHS	integrated Promoting Action on Research Implementation in Health Services
MAI	medication appropriateness index
NERD	Network of European Researchers in Deprescribing
NSAID	non-steroidal anti-inflammatory drug/non-steroidal anti-inflammatory drugs
OPI	opioid analgesic/opioid analgesics
PIMs	potentially inappropriate medicines
PPI	proton pump inhibitor/proton pump inhibitors
PREMs	patient-reported experience measures
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta Analysis
PROMs	patient-reported outcome measures
PROSPERO	International prospective register of systematic reviews
rPATD	Revised Patients Attitude Towards Deprescribing
USDeN	US Deprescribing Research Network

14. BIOGRAPHY

Iva Bužančić was born in Zagreb, Croatia, on 26th of June 1988. She completed her formal education, graduating with the degree of Master of Pharmacy in 2011 at the Faculty of Pharmacy and Biochemistry, University of Zagreb. During 2011 and 2012 she completed her preregistration period and became a registered pharmacist in 2013. She has been working as a community pharmacist in Gradska ljekarna Zagreb since 2013. In 2018 she completed her postgraduate specialist studies, acquiring the academic title University Master of Clinical pharmacy. In 2019/2020 she enrolled in the postgraduate doctoral programme "Pharmaceutical-Biochemical Sciences" at the Faculty of Pharmacy and Biochemistry, University of Zagreb.

Iva is an active member of the Croatian Chamber of Pharmacists, mentor to pharmacy students during Professional Training for Pharmacists, and participates as an external associate on the course Pharmaceutical care at the Centre for Applied Pharmacy, Faculty of Pharmacy and Biochemistry, University of Zagreb. She co-authored eight peer-reviewed papers, and participated with oral communications and posters at several international and Croatian scientific conferences.

LIST OF PUBLICATIONS:

1. **Bužančić I**, Držaić M, Kummer I, et al. Deprescribing potential of commonly used medications among community-dwelling older adults: insights from a pharmacist's geriatric assessment. Sci Rep 14, 6235 (2024). https://doi.org/10.1038/s41598-024-56780-1
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BASIC DOCUMENTION CARD

University of Zagreb
Faculty of Pharmacy and Biochemistry

Iva Bužančić
Doctoral Thesis

FORMATIVE EVALUATION OF THE NEEDS, OPPORTUNITIES, AND BARRIERS IN THE IMPLEMENTATION OF DEPRESCRIBING IN PRIMARY HEALTHCARE

SUMMARY

Deprescribing is the planned and supervised process of dose reduction or tapering, and stopping of medication, which might be causing harm, or is no longer of benefit to the patient, with the goal of managing polypharmacy and improving outcomes. This research aimed to explore the need for, and the barriers and facilitators of deprescribing in primary care in a healthcare system where it has not been researched, implemented, or provided. Four phases of research were carried out. The systematic review performed in the first phase of this research shows community-based pharmacists can successfully lead deprescribing interventions and are valuable partners in deprescribing. Second phase of research unveils the finding that the majority of adults 40 years and older (84%) would be willing to deprescribe one or more medications, with older adults (65 years and older) being more willing to have medications deprescribed than younger adults ($\chi 2$ (1) = 4.06; p = 0.044). Furthermore, majority of participating adults (71%) would feel comfortable with pharmacist's involvement in deprescribing, and 69% believes pharmacists have competencies to suggest deprescribing to physicians. Positive opinion on pharmacists' involvement was assessed as a predictive factor for positive attitude towards deprescribing (aOR = 2.351, 95% CI = 1.176 – 4.699; p = 0.016). Comprehensive Healthcare providers' OPinions, Preferences, and attitudEs towards Deprescribing (CHOPPED) questionnaire was developed in the third phase of research, to aid in exploration of healthcare providers' determinants important for implementing and providing deprescribing regardless of their familiarization with deprescribing. Using the CHOPPED questionnaire, it was found that the majority of healthcare providers (87%) would suggest deprescribing to a patient if appropriate. For pharmacists, the most important facilitators were extrinsic factors (collaboration facilitators and healthcare facilitators factors), while for physicians intrinsic (knowledge and awareness) and patient-related factors were more prominent. Moreover, a case vignette study elucidated pharmacists can identify potential deprescribing targets and suggest deprescribing rationales which physicians would accept. Collaborative deprescribing targets should be medicines both healthcare providers share most agreement on, such as nonsteroidal anti-inflammatories (NSAID), opioids (OPI) or diuretics. In a cross-sectional stud conducted in community pharmacies across Croatia, which enrolled 388 patients older than 65 years, 55.2% of participants were identified as potential candidates for deprescribing of one or more medications; 31.1% of proton pump inhibitors (PPI) users, 74.8% of NSAID, 75.0% of OPI, and 96.1% of benzodiazepine (BZN) users met at least one deprescribing criterion. Several predictive factors were identified for increased need for deprescribing, including identifying as a woman (aOR = 2.58; 95% CI =1.59 - 4.18; p < 0.001), poor self-reported health (aOR = 5.14; 95% CI = 1.73-15.25; p < 0.001), and polypharmacy (aOR = 1.29; 95% CI = 1.17 - 1.44; p < 0.001). Formative evaluation, as a result of this doctoral research, can lead to an implementation strategy facilitated by CHOPPED questionnaire and interventional protocol (Collaborating for Older aduLts to Deprescribe in primarY care" (COLDY)), proposed in this doctoral thesis, which can help engage healthcare providers in collaborative patient care with the goal of promoting deprescribing to enhance patient safety and optimise pharmacotherapy.

The thesis is deposited in the Central library of the Faculty of Pharmacy and Biochemistry, University of Zagreb.
Thesis includes: 135 pages, 9 figures, 21 tables, and 157 references. Original is in English language.
Key words: deprescribing; primary healthcare; physician; pharmacist; patient; older adults; comprehensive geriatric assessment; tool development; formative evaluation; pre implementation research
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TEMELJNA DOKUMENTCIJSKA KARTICA

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FORMATIVNA PROCJENA POTREBA, MOGUĆNOSTI I PREPREKA U PROVEDBI DEPRESKRIPCIJE TERAPIJE U PRIMARNOJ ZDRAVSTVENOJ ZAŠTITI

SAŽETAK

Depreskripcija terapije je planirani proces smanjivanja doze ili potpunog ukidanja lijeka iz farmakoterapije, za koji je rizik korištenja veći od potencijalne koristi ili za kojim više nema potrebe odnosno dokazane učinkovitosti. Ovo istraživanje za cilj je imalo istražiti potrebe, prepreke i poticatelje depreskripcije u primarnoj zdravstvenoj zaštiti u zdravstvenom sustavu u kojem dosada nije istraživana, implementirana ili provođena. Istraživanje je provedeno u četiri faze. Sustavni pregled proveden u prvoj prvi fazi istraživanja pokazuje da javni ljekarnici mogu uspješno predvoditi depreskripcijske intervencije te da su vrijedni suučesnici u depreskripciji. Druga faza istraživanja otkriva da bi većina osoba 40 godina i starijih (84%) pristala na depreskripciju jednog ili više lijekova. Osobe starije životne dobi (starije od 65 godina života) sklonije su prihvatiti depreskripciju terapije u usporedbi s mlađim odraslim osobama ($\chi 2$ (1) = 4.06; p = 0.044). Nadalje, većina ispitanika (71%) osjećala bi se ugodno ako bi ljekarnik bio uključen u proces depreskripcije, a 69% njih dodatno smatra da ljekarnik ima dovoljno kompetencija predložiti depreskripciju. Pozitivno mišljenje o uključenosti ljekarnika u proces depreskripcije terapije utvrđeno je kao prediktivni čimbenik spremnosti na depreskripciju (aOR = 2,351, 95% CI = 1,176 – 4,699; p = 0,016). Sveobuhvatni CHOPPED upitnik (engl. *Comprehensive Healthcare providers' OPinions, Preferences, and attitudEs towards Deprescribing*) razvijen u trećoj fazi istraživanja omogućuje ispitivanje čimbenika depreskripcije među zdravstvenim radnicima koji su važni za implementaciju i provođenje depreskripcije. Većina zdravstvenih radnika (87%) predložila bi depreskripciju terapije pacijentu. Za ljekarnike najvažniji poticatelji depreskripcije su ekstrinzični čimbenici (čimbenik poticatelja suradnje i čimbenik poticatelja zdravstvenog sustava), dok su za liječnike primarne zdravstvene zaštite najvažniji intrinzični čimbenici (znanje, osviještenost) te čimbenici povezani s pacijentom. Rezultati studije prikaza slučaja pokazuju da ljekarnici imaju potrebne kompetencije prepoznati potencijalno neprikladne lijekova a liječnici su spremni prihvatiti ljekarnikov depreskripcijski prijedlog (diuretici, nesteroidni protuupalni lijekovi, opioidni analgetici i benzodiazepini). U posljednjoj fazi istraživanja, koje je uključila 388 osoba starije životne dobi, otkriveno je da je više od polovice ispitanika (55,2%) kandidat za depreskripciju jednog ili više lijekova, od toga 31,1% korisnika inhibitora protonske crpke, 74,8% korisnika nesteroidnih protuupalnih lijekova, 75% korisnika opioidnih analgetika, te 96% korisnika benzodiazepina. Ženski spol (aOR = 2,58; 95% CI =1,59 – 4,18; p < 0,001), politerapija (aOR = 1,29; 95% CI = 1,17 – 1,44; p < 0,001) i loša samoprocjena zdravlja (aOR = 5,14; 95% CI = 1,73-15,25; p < 0,001) prediktivni su čimbenici za povećanu potrebu za depreskripcijom terapije. Formativna procjena, kao rezultat četiriju faza ovog doktorskog istraživanja, omogućuje kreiranje implementacijske strategije potpomognute CHOPPED upitnikom, kao i intervencijskog protokola za kolaborativni pristup depreskripciji terapije osoba starije životne dobi u primarnoj zdravstvenoj zaštiti (engl. *Collaborating for Older aduLts to Deprescribe in primarY care (COLDY)*) koje će omogućiti će provođenje depreskripcijske s ciljem optimizacije farmakoterapije i poboljšanja ishoda.

Rad je pohranjen u Središnjoj knjižnici Sveučilišta u Zagrebu Farmaceutsko-biokemijskog fakulteta.

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Ključne riječi: depreskripcija terapije; primarna zdravstvena zaštita; liječnik; ljekarnik; pacijent; osobe starije životne dobi; sveobuhvatna gerijatrijska procjena; razvoj alata; formativna procjena; pre implementacijsko istraživanje
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