

Strategies for Improving Polypharmacy in the Elderly Population in Europe – Evidence from ADVANTAGE Joint Action

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ABSTRACT - Polypharmacy in polymorbid elderly as well as frailty represent substantial health care problems that should be addressed. Our aim was to define the current situation regarding tools, guidelines and policies in the field of polypharmacy in the elderly in Europe. Therefore, we conducted a systemic search of articles, published from 2002 to 2017 in peer-reviewed scientific journals, as well as international standards, guidelines and research studies performed in the European Union. Grey literature documents identified opportunistically were reviewed as well. The total number of all search results was 28,796; after exclusions, 25 articles remained for the analysis. Several approaches to reduce polypharmacy have been studied, however, each has limitations which are mostly specific to the region and context of their origin. It was concluded that promotion of appropriate polypharmacy is very complex. Considerable efforts have been made, however, programmes which attempt tackling polypharmacy in seniors with polymorbidity must be patient-centered, multidisciplinary and must take into consideration the context of healthcare system in which they are delivered.

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KLJUČNE BESEDE: polifarmacija, starostniki, krhkost, predpisovanje, smernice

POVZETEK - Polifarmacija pri multimorbidnih starejših in krhkost predstavljata pomemben zdravstveni problem, ki ga je treba reševati. Naš cilj je bil opredeliti trenutno stanje glede uporabe orodij, smernic in politik na področju polifarmacije pri starostnikih v Evropi. Zato smo sistemsko iskali članke, objavljene med letoma 2002 in 2017, v strokovnih in znanstvenih revijah, kot tudi mednarodne standarde, smernice in raziskovalne študije, ki se izvajajo v Evropski uniji. Pregledali smo tudi sive dokumente, ki smo jih iskali oportunistično. Skupno število vseh rezultatov iskanja je bilo 28796, po upoštevanju izključitvenih kriterijev je za analizo ostalo 25 člankov. Proučenih je bilo več pristopov za zmanjšanje polifarmacije, vendar ima vsaka omejitve, ki so večinoma specifične za regijo in kontekst njihovega izvora. Ugotovljeno je bilo, da je spodbujanje ustrezne polifarmacije zelo kompleksno. Vsekakor je bilo vložena že veliko truda, vendar morajo biti programi, ki poskušajo rešiti problem polifarmacije pri starejših z multimorbidnostjo, osredotočeni na bolnika, multidisciplinarni in morajo upoštevati kontekst sistema zdravstvenega varstva, v katerem se jih izvaja.

1 Introduction

The expression polypharmacy indicates concurrent use of multiple medication items by one individual (Duerden, Avery & Payne, 2013). It has been estimated that more than 50% of persons aged 65 years or older receive five or more drugs concomitantly (Marengoni et al., 2011; Palmer, Marengoni, Russo, Mammarella & Onder, 2016). In fact, older people often have co-occurring multiple chronic and acute diseases, which progressively and steadily increase in prevalence with age, and the treatment of these diseases usually requires multiple drugs (Palmer et al., 2016). Drug

use in older population might raise several concerns related to an increased risk of drug-drug and drug-disease interactions, poor adherence to treatment, and increased risk of adverse drug reaction (ADR) or event (ADE). These contribute to hospitalizations and high avoidable costs of medical care (Dumbreck et al., 2015; Marengoni et al., 2014). Therefore, polypharmacy represents a substantial burden for individuals and for healthcare systems.

The World Health Organisation describes frailty as a “progressive age-related decline in physiological systems that results in decreased reserves of intrinsic capacity, which confers extreme vulnerability to stressors and increases the risk of a range of adverse health outcomes.” As negative health outcomes, such as disability, hospitalisation, institutionalisation and mortality, are associated with increased resource use, the prevention, assessment and treatment of frailty are considered an essential step to improving the efficiency of healthcare systems (Onder & Marengoni, 2016). Successful prevention of frailty requires knowledge about the risk factors as well as better definitions of risk groups and evidence-based interventions that can be offered earlier and tailored to an individual’s needs (Clegg, Young, Iliffe, Rikkert & Rockwood, 2013).

Numerous specific medications (for example, diuretics, proton pump inhibitors, anticholinergic drugs) have been shown to be associated with frailty and risk factors for frailty. There is also evidence that polypharmacy itself may be involved in the development of frailty (Bronskill et al., 2012; Gnjjidic et al., 2012; Gokce Kutsal et al., 2009). Polypharmacy was shown to be associated with more than a twofold increased incidence of developing frailty over two years in men (Gnjjidic et al., 2012). Some authors suggested that high-risk prescribing may have directly aggravated the clinical features of frailty. Thus, a reduction of polypharmacy is advised for both the prevention and management of frailty (Morley et al., 2013). The pharmacological treatment of older adults might differ based on their frailty status and, in particular, the benefits of a given pharmacological treatment might be reduced in the presence of frailty (Palmer et al., 2016). Compared with non-frail patients without polypharmacy, frail elderly patients with polypharmacy belong to a high-risk group and should receive urgent geriatric assessment and treatment (Rosted, Schultz & Sanders, 2016).

Although there is a growing recognition of the importance of appropriate prescribing and management of polypharmacy in older people, there is considerable variation in the approach. ADVANTAGE is a Joint Action (JA), co-financed by Member States (MSs) and the European Commission, involving 22 MSs and 33 organisations working together to prevent and manage frailty in Europe. One of the tasks of the project was to consider the evidence and actions required to address polypharmacy. This paper describes the process and findings of a narrative literature review on managing polypharmacy in older people.

2 Method

We conducted a narrative review of peer reviewed literature published in the period from 2002 to 2017. The search was conducted in the PubMed, Cochrane, Embase, Cinahl and UpToDate databases. Several combinations of selected search words in the English language and their synonyms were prepared and used with Boolean operators AND or OR: Multimедication *() OR Multimедication Frail *() OR Poly medicine *() OR Polymedicine Older person *() OR Polypharmacy *() OR Polypharmacy Geriatric *() OR Polypragmasy Aged *() OR Polytherapy Elderly *() OR Multiple medication Disability *() OR Polypragmasy *() OR Polytherapy *() OR Multiple medication Frail *() OR Polypragmasy Function *() OR Multimедication Vulnerable *() OR Polypharmacy Functional decline *(); searching in title, key words and in abstracts. The exclusion criteria were: editorials, letters, interviews, posters and no access to full text.

We also reviewed relevant international documents, government reports, professional guidelines, standards and research studies performed in the European Union (EU) which comprehensively investigate and describe management of polypharmacy. Grey literature was identified opportunistically by members of the ADVANTAGE JA.

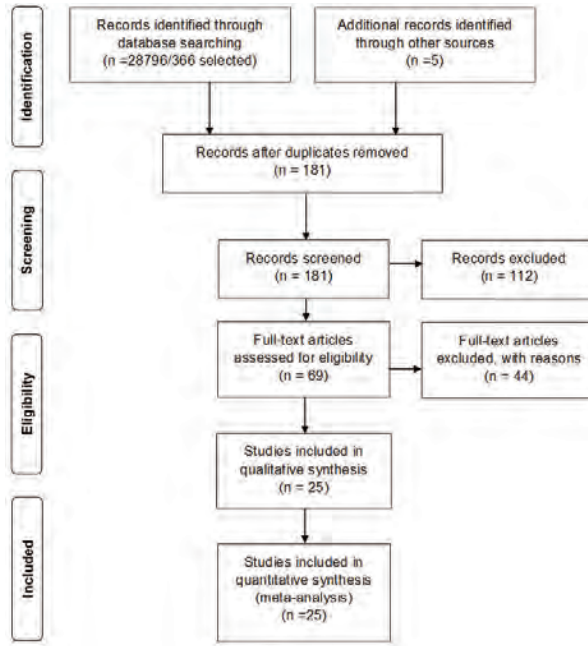
3 Results

The total number of all search results was 28,796. After excluding duplicates and taking into account inclusion criteria, 25 articles/sources remained for the analysis. The process is displayed in the search table (Table 1) and in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) diagram (Moher et al., 2015), as shown in Figure 1.

Table 1: Search table

	<i>Key word</i>	<i>No. of hits</i>	<i>Chosen hits</i>	<i>Repeated chosen hits</i>	<i>Final selection</i>
PubMed	Multimedication	18	0	0	0
	Multimedication Frail	1	0	0	0
	Poly medicine	17976	112	38	5
	Polymedicine Older person	6	0	0	
	Polypharmacy	6698	64	64	4
	Polypharmacy Geriatric	1101	56	56	4
	Polypragmasy Aged	22	0	0	0
	Polytherapy Elderly	516	33	33	2
	Multiple medication Disability	667	18	18	1
	Polypragmasy	57	0	0	0
	Polytherapy	1452	61	28	2
	Cochrane	Multiple medication Frail	10	0	0
Polypragmasy Aged		3	0	0	0
Polypragmasy Function		0	0	0	0
Embase	Polymedicine Older person	10	0	0	0
	Multimedication Vulnerable	95	6	6	1
UpToDate	Polypharmacy Geriatric	91	12	12	1
	Polypharmacy Functional decline	62	4	1	0
Cinahl	Multimedication Frail	0	0	0	0
	Multimedication	2	0	0	0
	Polymedicine Older person	1	0	0	0
	Polymedicine	3	0	0	0
Other sources		5			5
		28796	366		25

Figure 1: Flowchart of search strategy and literature selection process



3.1 Quality assessment of the review

Results of the quality assessment of narrative literature review is shown in Table 2.

Table 2: Results of the quality assessment of narrative literature review

Criteria	Yes	No	Other
1. Is the review based on a focused question that is adequately formulated and described?	X		
2. Were eligibility criteria for included and excluded studies predefined and specified?	X		
3. Did the literature search strategy use a comprehensive, systematic approach?	X		
4. Were titles, abstracts, and full-text articles dually and independently reviewed for inclusion and exclusion to minimize bias?	X		
5. Was the quality of each included study rated independently by two or more reviewers using a standard method to appraise its internal validity?	X		
6. Were the included studies listed along with important characteristics and results of each study?	X		
7. Was publication bias assessed?	X		
8. Was heterogeneity assessed? (This question applies only to meta-analyses.)			X

3.2 Results of the review

Both polypharmacy and inappropriate prescribing are acknowledged as increasingly complex issues in a multimorbid ageing population and represent a problem that should be solved (Cooper et al., 2015; Farrell et al., 2015; Maher et al., 2014). Several approaches have been proposed; different guidelines and lists have been prepared and some have been evaluated (All Wales Medicines Strategy Group, 2014; Blozik et al., 2010; Garfinkel & Mangin, 2010; Garfinkel et al., 2007; Guiding principles for the care of older adults with multimorbidity: an approach for clinicians, 2012; Holt et al., 2010; Patterson et al., 2014; Scottish Government Model of Care Polypharmacy Working Group, 2015; Williams et al., 2004).

In an extensive systematic literature review described by Kaufmann et al. (2014), different tools to assess inappropriate prescribing were identified. The tools vary in methodological aspects and lack validation in clinical settings. Many of the described tools might serve as useful aids to improve prescribing, however, each tool has its limitations, strengths and weaknesses, and most are specific to a certain region and context in which they were developed. The tools were categorised as explicit, implicit or combined. Implicit criteria focus on clinician interpretation and are time-consuming, while explicit criteria are designed to be easily and effectively interpreted. They provide details of medicine categories and associated prescribing indicators to enhance reliable treatment evaluation. Authors reported that none of the described tools covered all aspects of inappropriate prescribing and they proposed further research in this area (Kaufmann et al., 2014).

Different authors reviewed single tools used to manage inappropriate prescribing and reducing polypharmacy. The most widely used include Beers criteria, STOPP-START and Laroche criteria (Kaufmann et al., 2014). With the objective to examine healthcare outcomes associated with one of the most commonly used criteria, Beers' criteria of inappropriate medication use, some authors (Jano & Aparasu, 2007) reviewed 18 retrospective cohort studies involving patients of 65 years of age or older from diverse healthcare settings. In community settings, there was no evidence of association with mortality and healthcare use, and evidence regarding quality of life and costs was inconclusive. However, inappropriate medication use was associated with hospitalization measures in community elderly. In nursing homes, there was no evidence of association with mortality and the association with hospitalization measures was inconclusive. In hospitals, there was inconclusive evidence to make any generalizations. Across healthcare settings, inappropriate medication use was associated with adverse drug reactions and costs but not with other outcome measures (Jano & Aparasu, 2007).

Hamilton et al. (2011) assessed whether potentially inappropriate medications (PIMs) defined by the STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions) criteria were significantly associated with ADEs in elderly people with acute illness. They prospectively studied 600 patients aged 65 years or older who were admitted with acute illness to a university teaching hospital over a 4-month interval. Potentially inappropriate medicines were defined by both Beers and STOPP

criteria. Adverse drug events were defined by World Health Organization-Uppsala Monitoring Centre criteria and verified by a local expert consensus panel, which also assessed whether ADEs were causal or contributory to current hospitalization. They compared the proportions of patients taking Beers criteria PIMs and STOPP criteria PIMs with avoidable ADEs that were causal or contributory to admission. It was concluded that STOPP criteria PIMs, unlike Beers criteria PIMs, are significantly associated with avoidable ADEs in older people that cause or contribute to urgent hospitalization (Hamilton et al., 2011). STOPP criteria were evaluated also by other authors. Gallagher et al. (2008) compared the performance of STOPP to that of established Beers' criteria in detecting PIMs and related ADEs in older patients. STOPP criteria identified a significantly higher proportion of patients requiring hospitalization (Gallagher & O'Mahony, 2008). In a similar study, the same author confirmed that STOPP/START criteria is a valid, reliable and comprehensive screening tool (Gallagher & O'Mahony, 2008). On the basis of the results of the parallel-group randomized trial, Frankenthal concluded that the implementation of STOPP/START criteria reduced the number of medications, falls and costs in a geriatric facility. The author recommended the incorporation of the criteria in all similar settings (Frankenthal et al., 2014).

Other tools have been developed and/or evaluated. Comprehensive Geriatric Assessment (CGA) was identified by Sergi as a useful tool for optimizing polypharmacy and tailoring therapy for older patients with multiple morbidities (Sergi et al., 2011). The EU(7)-PIM list is a screening tool which was developed with participation of experts from seven European countries and it allows identification and comparison of PIM prescribing patterns for older people across European countries (Renom - Guiteras et al., 2015).

Some authors concluded that reference lists of medicines that suggest appropriate alternative medicines for prescribing in the elderly are very useful and suggested these should be updated and harmonised in the future (Možina & Voljč, 2017).

Within the pan-European initiative, Stimulating Innovation Management of Polypharmacy and Adherence in the Elderly-Simpathy (Stewart et al., 2017) summarised and extensively reviewed current policies and guidelines on polypharmacy management in older people. The project defined 'appropriate polypharmacy' according to the following criteria: when all medicines are prescribed for the purpose of achieving specific therapeutic objectives that have been agreed with the patient; therapeutic objectives are actually being achieved or there is a reasonable chance they will be achieved in the future; medicines have been optimised to minimise the risk of ADRs; and the patient is motivated and able to take all medicines as intended.

4 Discussion

Chronic conditions in ageing population can lead to frailty via numerous pathways, including the onset of sarcopenia, or by causing disability or reduced physical functioning. Sarcopenia itself is associated with reduced physical functioning and the onset

of disability. All three pathways contribute both separately and together to an overall syndrome of frailty in the elderly. Therefore, the role of medicines on the development, management and treatment of frailty should take all three factors into account (Palmer et al., 2016). In addition to the discussion of how to treat frailty, the role that medicines may have on the development of frailty should also be taken into consideration (Palmer et al., 2016). Numerous specific medications have been shown to be associated with frailty and frailty-related factors. Inappropriate medicines prescribing as well as polypharmacy itself are pathways through which medicines can cause frailty (Bronskill et al., 2012; Gnjjidic et al., 2012; Gokce Kutsal et al., 2009). Therefore, in an ageing population with an increased prevalence of multimorbidity and a corresponding increase in inappropriate prescribing, polypharmacy and frailty are important challenges that must be addressed across primary care, community services, hospital and care home settings (Bronskill et al., 2012; Gnjjidic et al., 2012; Gokce Kutsal et al., 2009). Although several approaches have been proposed, the evidence of benefit regarding clinically relevant endpoints is scarce and current knowledge about optimal treatment with medicines in older patients with multiple chronic conditions is limited (Sönnichsen et al., 2010; Veninšek & Gabrovec, 2018). Numerous evidence-based guidelines for single conditions help drive the increase in polypharmacy, yet guidelines rarely advise on how to manage multimorbidity or frailty. Another important challenge in the area of polypharmacy is that of working alongside patients to empower them to make informed choices about the benefits and burden of treatments and medications. It is increasingly recognised that many people find their medication regimens an unpleasant chore and this can detract from their quality of life. If this is not managed well, medicines will not be taken as the prescriber intends, resulting in significant and costly waste, and of course a failure to realise the anticipated benefits of treatment (Duerden, Avery & Payne, 2013).

Maximizing medication safety is a key and increasingly important goal of high-quality healthcare (Lee et al, 2018). To be effective, safe and efficient, any programme that attempts to deal with prescribing in older adults with multimorbidity must be patient-centered, clinically robust, multidisciplinary as well as designed to fit into the healthcare system in which it is delivered. Challenges exist on different levels, including clinical, organisational and political, and all of these levels need to be addressed in preparing a comprehensive and effective programme for appropriate prescribing in frail elderly population (Stewart et al., 2017). There is a need for further research and guidance on managing multimorbidity and reducing inappropriate polypharmacy.

Improving appropriate prescribing and management of polypharmacy is a barometer for the transformational shift that healthcare systems are required to make to meet the challenges of an ageing population. This will require a significant shift in policy, education and delivery and poses a considerable challenge across Europe. Implementation plans must include a change management strategy and be coupled with rigorous and robust evaluation. Further research is required to examine policies, systems and processes designed to improve medicine management in relation to polypharmacy (Duerden, Avery & Payne, 2013).

The value of the present review lies in a comprehensive evaluation of the tools and strategies for improving polypharmacy in the elderly population that are available in the field of inappropriate prescribing in the elderly with multimorbidity or frailty.

5 Conclusion

Management of inappropriate polypharmacy and on the other hand the promotion of appropriate polypharmacy is very complex with multiple aspects of healthcare practice and delivery of care. Considerable efforts have been made to reduce polypharmacy and inappropriate prescribing in the elderly with multimorbidity or frailty. Nowadays, many different tools are available and a number of guidelines have been developed. However, evidence showing benefit on clinically relevant endpoints is scarce. There is an urgent need to implement more effective strategies. In the future, programmes that deal with prescribing in the elderly population must be patient-centered, multidisciplinary and clinically effective in order to be safe and efficient. The healthcare system in which the programmes are delivered must be taken into consideration and the approach adapted to the care setting. There is an urgent need to tackle inappropriate prescribing and promote appropriate polypharmacy. This will require clinicians across multiple healthcare disciplines, providers and funders in each country to agree on an evidence based approach and develop guidance that takes account of adults who require a more holistic approach. The time has come to reject the reliance on single disease state focused guidelines when treating patients with multimorbidity or frailty. It is crucial to address the proper specialisation of clinicians, train more clinicians with specific expertise in managing multimorbidity and clinical complexity, in addition to wider generalist skills.

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Strategije izboljšanja polifarmacije pri starajoči se populaciji v Evropi. Dokazi iz projekta skupnega ukrepanja ADVANTAGE

Izraz polifarmacija pomeni sočasno zdravljenje z več zdravili (Duerden, Avery in Payne, 2013). Ocenjeno je bilo, da več kot 50 % ljudi, starejših od 65 let, prejema pet ali več zdravil (Marengoni idr., 2011; Palmer, Marengoni, Russo, Mammarella in Onder, 2016). Starejši ljudje imajo pogosto več kroničnih in akutnih bolezni, katerih prevalenca narašča s starostjo in njihovo zdravljenje zahteva več različnih zdravil (Palmer idr., 2016).

Svetovna zdravstvena organizacija opredeljuje krhkost kot progresiven in s starostjo povezan fizični upad, ki vodi v zmanjšano rezervo, kar poveča ranljivost in tveganje za razvoj negativnih zdravstvenih izidov. Ker so negativni zdravstveni izidi, kot so odvisnost od drugih, hospitalizacija, institucionalizacija in smrtnost, povezani s povečanjem uporabe virov, sta preventiva in ocena krhkosti prepoznani kot esencialni korak k izboljšanju učinkovitosti zdravstvenih sistemov (Onder in Marengoni, 2016). Uspešna preventiva krhkosti zahteva znanje o dejavnih tveganja in tudi boljše poznavanje definicij ter z dokazi podprtih intervencij, prilagojenih posameznikovim potrebam (Clegg, Young, Iliffe, Rikkert in Rockwood, 2013).

Določena zdravila, npr. diuretiki, inhibitorji protonske črpalke ali antiholinergiki, so bila dokazano povezana s krhkostjo in dejavniki tveganja za razvoj krhkosti. Obstajajo tudi dokazi, da je polifarmacija povezana z ravojem krhkosti (Bronskill idr., 2012; Gnjudic idr., 2012; Gokce Kutsal idr., 2009). Polifarmacija je bila dokazano povezana z dvakratnim povečanjem incidence razvoja krhkosti v obdobju dveh let pri moških (Gnjudic idr., 2012). Kljub temu da narašča prepoznavanje pomembnosti primerne predpisovanja in upravljanja s polifarmacijo pri starejših, obstajajo pomembne variacije v pristopu. Projekt skupnega ukrepanja Evropske komisije Joint Action ADVANTAGE je projekt, ki so ga financirale Evropska komisija in države članice ter vključuje 22 držav članic in 33 povezanih organizacij z namenom dela na preventivi in upravljanju krhkosti v Evropi. Ena od nalog projekta je razmislek o dokazih in intervencijah, ki so potrebne za upravljanje polifarmacije. Ta prispevek obravnava proces in ugotovitve pregleda literature na temo upravljanja polifarmacije pri starejših ljudeh.

Narejen je bil pregled literature, objavljene v zadnjih 15 letih, od leta 2002 do leta 2017. Za iskanje literature so bile uporabljene naslednje podatkovne baze: PubMed, Cochrane, Embase, Cinahl in UpToDate date. Izključitveni kriteriji so bili: uredniški prispevki, pisma, intervjuji, posterji in omejen dostop do celotnega besedila. Prav tako so bili pregledani relevantni mednarodni dokumenti, vladna poročila, profesionalne smernice, strategije in raziskave, opravljene v Evropski uniji, ki celotno obravnavajo upravljanje polifarmacije. Sivo literaturo smo pridobili z oportunističnem iskanjem.

Najdeno je bilo skupno 28796 člankov. Po izločitvi duplikatov in ob upoštevanju vključitvenih in izključitvenih kriterijev je za analizo ostalo 25 virov.

Rezultati našega pregleda kažejo na to, da sta tako polifarmacija kot neprimerno predpisovanje zdravil prepoznana kot vse bolj kompleksno področje multimorbidne, starajoče se populacije. Gre vsekakor za problem, ki ga je treba rešiti (Cooper idr., 2015; Farrell idr., 2015; Maher idr., 2014). Predlaganih je bilo več rešitev, med njimi tudi različne smernice in navodila, nekatere celo evalvirane (All Wales Medicines Strategy Group, 2014; Blozik idr., 2010; Garfinkel in Mangin, 2010; Garfinkel idr., 2007; Guiding principles for the care of older adults with multimorbidity: an approach for clinicians, 2012; Holt idr., 2010; Patterson idr., 2014; Scottish Government Model of Care Polypharmacy Working Group, 2015; Williams idr., 2004).

V obsežnem sistematičnem pregledu literature, ki ga je opisal Kaufmann, so bila prepoznana različna orodja za oceno neprimernega predpisovanja. Orodja so si različna po metodoloških vidikih in pomanjkanju validacije v kliničnem okolju. Veliko opisanih orodij bi lahko služilo kot pomoč pri izboljšanju predpisovanja starejšim, a ima vsako orodje svoje omejitve, prednosti in slabosti, hkrati pa je večina specifična glede na področje in kontekst razvoja. Opisana orodja so bila eksplicitna, implicitna ali kombinirana. Implicitna orodja se osredotočajo na interpretacijo klinika in za uporabo zahtevajo veliko časa, medtem ko so eksplicitna orodja načrtovana za lahko in učinkovito interpretacijo. Oba pristopa zagotavljata večjo zanesljivost predpisovanja. Avtorji ugotavljajo, da nobeno opisano orodje ne pokriva vseh področij neprimernega predpisovanja, ter predlagajo nadaljne raziskovanje obravnavanega področja (Kaufmann idr., 2014).

Različni avtorji so pregledali posamezna orodja, ki se jih uporablja za preprečevanje neprimernega predpisovanja in zmanjševanje polifarmacije. Najpogosteje so uporabljeni Beersovi kriteriji, STOPP-START kriteriji in Laroche kriteriji (Kaufmann idr., 2014). Z namenom objektivne ocene Beersovih kriterijev za neprimerno predpisovanje zdravil so nekateri avtorji (Jano in Aparasu, 2007) pregledali 18 retrospektivnih kohortnih študij, ki so vključevale paciente, starejše od 65 let, iz različnih okolij. Med drugim je bila ugotovljena tudi povezava med neprimernim predpisovanjem zdravil in hospitalizacijo (Jano in Aparasu, 2007).

Hamilton je s soavtorji (Hamilton idr., 2011) ocenjeval, ali so neprimerna zdravila, definirana kot taka po STOPP-START kriterijih (Screening Tool of Older Persons' potentially inappropriate Prescriptions), pomembno povezana z neželenimi učinki zdravil pri starejši populaciji z akutno boleznijo. Prospektivna študija je zajemala 600 pacientov, starejših od 65 let, ki so bili sprejeti zaradi akutne bolezni v univerzitetno bolnišnico v obdobju štirih mesecev. Potencialno neprimerna zdravila so bila v raziskavah definirana tako po Beersovih kot tudi STOPP kriterijih. Neželene učinke zdravil je definirana Svetovna zdravstvena organizacija (World Health Organization-Uppsala Monitoring Centre criteria) in so jih potrdili na lokalnih panelih strokovnjaki, ki so prav tako ocenili, ali so bili neželeni učinki zdravil vzročno ali drugače povezani s trenutno hospitalizacijo. Primerjali so razmerje med pacienti, pri katerih so se upoštevali Beersovi in STOPP kriteriji za potencialno neprimerna zdravila s preprečljivimi neželenimi učinki, ki so bili vzročno ali drugače povezani s trenutno hospitalizacijo. Potrdili so, da so STOPP kriteriji v večji meri povezani z izogibom

neželenim stranskim učinkom zdravil pri starejših osebah, ki povzročajo ali doprine-sejo k urgentni hospitalizaciji (Hamilton idr., 2011). STOPP kriterije so evalvirali tudi drugi avtorji, kot npr. Gallagher s sodelavci (Gallagher idr., 2008). S pomočjo STOPP kriterijev so tudi identificirali značilno večji delež pacientov, ki potrebujejo hospitalizacijo (Gallagher in O'Mahony, 2008). V podobni študiji so isti avtorji potrdili, da so STOPP-START kriteriji veljavno, zanesljivo in celostno presejalno orodje (Gallagher in O'Mahony, 2008). Na podlagi rezultatov vzporedne skupine avtor Frankenthal zaključí, da je uporaba STOPP-START kriterijev zmanjšala porabo zdravil, padcev in stroškov v geriatrični oskrbi. Avtor priporoča vpeljavo orodja v podobna okolja (Frankenthal idr., 2014).

Razvita so bila tudi druga podobna orodja, od katerih so bila nekatera tudi evalvirana. Celovita geriatrična ocena (Comprehensive Geriatric Assessment - CGA) je bila identificirana kot koristno orodje za optimizacijo polifarmacije in prilagoditev terapije starejšim, multimorbidnim pacientom (Sergi idr., 2011). Orodje EU(7)-PIM list je presejalno orodje, ki je bilo razvito v sodelovanju s strokovnjaki iz sedmih EU držav in omogoča identifikacijo ter primerjavo vzorcev predpisovanja zdravil za starejše osebe v evropskih državah (Renom - Guiteras idr., 2015). Nekateri avtorji zaključujejo, da so referenčne liste alternativnih zdravil za predpisovanje starejšim osebam zelo koristne; predlagajo, da bi liste v prihodnje posodabljali in harmonizirali (Možina in Voljč, 2017).

V sklopu evropske pobude *Sympathy (Stimulating Innovation Management of Polypharmacy and Adherence in the Elderly)* so avtorji (Stewart idr., 2017) povzeli in analizirali trenutne politike ter smernice upravljanja polifarmacije pri starejših ljudeh. Projekt je definiral primerno polifarmacijo glede na sledeče kriterije: ko so vsa zdravila predpisana z namenom doseganja specifičnih terapevtskih ciljev in so v soglasju s pacientom; terapevtski cilji se že dosegajo, ali obstaja razumna verjetnost, da bodo doseženi v prihodnosti; zdravila so bila optimizirana tako, da minimizirajo možnost razvoja neželenih učinkov zdravil; in pacient je motiviran ter zmožen jemati zdravila, kot je načrtovano.

Kronične bolezni pri starostnikih lahko privedejo do krhkosti prek različnih mehanizmov, vključno z nastankom sarkopenije, nezmožnosti ali zmanjšane fizične sposobnosti. Ko govorimo o vlogi zdravil pri nastanku krhkosti, moramo vedno upoštevati vse našteje mehanizme. Ob tem moramo upoštevati še dejstvo, da zdravila sama lahko privedejo do krhkosti (Palmer idr., 2016).

Izboljšanje primernega predpisovanja in upravljanja s polifarmacijo je torej barometer za transformacijski preskok, ki ga potrebujejo zdravstveni sistemi pri soočanju s starajočo se populacijo. To bo zahtevalo pomembno spremembo v politikah, izobraževanju in zagotavljanju zdravstvenih storitev. Načrti implementacij morajo vključevati spremembo upravljalških strategij, hkrati z rigorozno in robustno evalvacijo (Duerden, Avery in Payne, 2013). Potrebno je nadaljnje razsikovalno delo, pregled politik, sistemov in procesov, ki bi izboljšali upravljanje z zdravili v razmerju do polifarmacije.

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