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SHORT COMMUNICATION

Therapeutic Duplicates in a Cohort of Hospitalized Elderly Patients: Results from the REPOSI Study

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Abstract

Background Explicit criteria for potentially inappropriate prescriptions in the elderly are recommended to avoid prescriptions of duplicate drug classes and to optimize monotherapy within a single drug class before a new agent is considered. Duplicate drug class prescription (or therapeutic duplicates) puts the patient at increased risk of adverse drug reactions with no additional therapeutic benefits. To our knowledge, the prevalence of elderly inpatients receiving therapeutic duplicates has never been studied.

Objectives Our objective was to assess the prevalence of therapeutic duplicates at admission, discharge, and 3-month follow-up of hospitalized elderly patients.

Methods This cross-sectional prospective study was conducted in 97 Italian internal medicine and geriatric wards. Therapeutic duplicates were defined as at least two drugs of the same therapeutic class prescribed simultaneously to a patient. A patient's drug therapy at admission relates to prescriptions from general practitioners, whereas prescriptions at discharge are those from hospital internists or geriatricians.

Results The study sample comprised 5821 admitted and 4983 discharged patients. In all, 143 therapeutic duplicates were found at admission and 170 at discharge. The prevalence of patients exposed to at least one therapeutic duplicate rose significantly from hospital admission (2.5 %) to discharge (3.4 %; $p = 0.0032$). Psychotropic drugs and drugs for peptic ulcer or gastroesophageal reflux disease were the most frequently involved. A total of 86.8 % of patients discharged with at least one therapeutic duplicate were still receiving them at 3-month follow-up.

Conclusions Hospitalization and drugs prescribed by internists and geriatricians are both factors associated with a small but definite increase in overall therapeutic duplicates in elderly patients admitted to internal medicine and geriatric wards. More attention should be paid to the indications for each drug prescribed, because therapeutic duplicates are not supported by evidence and increase both the risk of adverse drug reactions and costs. Identification of unnecessary therapeutic duplicates is essential for the optimization of polypharmacy.

REPOSI stands for Registry of Polytherapies SIMI (Società Italiana di Medicina Interna).

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Key Points

Hospital discharge is associated with a small but definite increase in the overall number of therapeutic duplicates.

Psychotropic drugs and drugs for peptic ulcer or gastroesophageal reflux disease were the most frequently involved; in most cases, duplicates were maintained at 3-month follow-up.

More attention must be given to the indications for each drug, because duplication is not supported by evidence and increases both the risk of adverse drug events and costs.

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1 Introduction

Polypharmacy is very common among older adults and is often needed to improve symptoms, disease-related problems, and quality of life [1–3]. However, it may also be a major risk factor for inappropriate prescribing, poor adherence to therapies, adverse drug events (ADEs), potentially severe drug–drug interactions (DDIs), and other adverse health outcomes [4–8]. Inappropriate prescribing is highly prevalent in older people and has become a global healthcare concern because of its association with negative health outcomes, including ADEs, hospitalization, and resource utilization [9].

In relation to older people, inappropriate medications can be defined as "medications or medication classes that should generally be avoided in persons 65 years or older because they are either ineffective or they pose unnecessarily high risk for older persons and a safer alternative is available" [10]. Explicit criteria for potentially inappropriate medications (PIMs) have been developed to identify and reduce the use of drugs that involve a substantial risk of adverse side effects in elderly patients [11]. One recommendation included in some explicit criteria (e.g., START [Screening Tool to Alert doctors to Right, i.e. appropriate, indicated Treatment] STOPP [Screening Tool of Older People's potentially inappropriate Prescriptions] criteria [12], Rancourt et al. [13], Laroche et al. [14], NORGEP criteria [15], and the PRISCUS list [16]) is to avoid any duplicate drug class prescription and optimize monotherapy within a single drug class before considering a new agent.

Duplicate drug class prescription (or therapeutic duplicates) puts the patient at increased risk of adverse drug reactions with no additional therapeutic benefits, and the risk of receiving duplicate therapy increases as patients receive more drugs from multiple healthcare institutions [17]. Therefore, the elderly are at increased risk of therapeutic duplicates because they often need many medications.

A nationwide Austrian cohort study found that unintended overlapping prescription of two identical substances with the same route of administration by two different prescribers to the same patient occurred in about 13–15 % of patients treated with antihypertensives, lipid-lowering, or hypoglycemic medication [18]. Although potentially common in clinical practice, therapeutic duplicates are an under-studied problem in healthcare delivery and in the medical error literature.

The prevalence of patients receiving therapeutic duplicates has never been studied among elderly inpatients. We examined the Italian Society of Internal Medicine [SIMI] Registry of Polytherapies (REPOSI), a network of internal medicine and geriatric wards created to investigate the prevalence and correlates of polymorbidity and polypharmacy in elderly hospital patients, to assess the prevalence of exposure to therapeutic duplicates at admission, discharge, and 3-month follow-up.

2 Methods

2.1 Data Collection

The REPOSI is a collaborative and independent initiative of the SIMI, the IRCCS[1] Istituto di Ricerche Farmacologiche Mario Negri, and the IRCCS Ca' Granda Maggiore Policlinico Hospital Foundation. The registry was set up in 2008 from a network of internal medicine and geriatric wards to collect information on hospitalized elderly patients with multimorbidities receiving multiple drugs. The first run of data collection was between January and December 2008; the second, third, fourth, and ongoing runs were between January and December 2010, 2012, 2014, and 2016, respectively. To ensure an unselected population of elderly patients admitted to internal medicine and geriatric wards, the first ten patients admitted to the wards participating in the study during 4-week periods 3 months apart were consecutively recruited if they were aged $\geq$65 years. Participation was voluntary, and all patients gave signed informed consent. Data collection complied fully with Italian law on personal data protection, and the ethical committees of each ward participating in the REPOSI approved the study.

The attending physicians completed a standardized web-based case report form showing sociodemographic details, diagnosis, and drug treatment at admission, during hospital stay, and at discharge. From the second REPOSI runs, we collected additional information and conducted a short-term follow-up to improve the quality of data: main laboratory parameters, comorbidity according to the Cumulative Illness Rating Scale (CIRS), basic activities of daily living, cognitive impairment, depression, and clinical events during hospital stay. At 3 months after discharge, patients were followed-up with a telephone interview to collect information on new diagnoses, hospital re-admissions, drug regimens, adverse events, and basic activities of daily living.

To establish the prevalence of patients receiving therapeutic duplicates, we considered all patients recruited in REPOSI; at discharge, we excluded only those who had died in hospital or had been transferred to another ward while in hospital. Of the 4983 inpatients discharged, 3401 were eligible for the 3-month follow-up, and data were available for

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2412 (70.9 %). Follow-up data were not available for 2571 patients for various reasons: lack of follow-up in the first run of data collection (year 2008; $n = 1158$); lack of follow-up data for the ongoing run (year 2016; $n = 424$); death before hospital discharge; refusal of the 3-month telephone interview; discharge in critical condition (life expectancy <3 months), or logistic reasons (see the literature search and study selection flowchart in Figure S1 in the Electronic Supplementary Material [ESM]).

2.2 Duplicate Medications

Therapeutic duplicates were defined as at least two drugs of the same therapeutic class simultaneously prescribed to the same patient. To identify duplicates, we considered the third level of the Anatomical Therapeutic Chemical (ATC) code [19]; in certain circumstances, we considered the fourth level of the ATC code to exclude combinations supported by clinical evidence or suggested by clinical guidelines (e.g., an alpha-adrenoreceptor antagonist plus testosterone-5-alpha reductase inhibitor for benign prostatic hypertrophy or double antiplatelet therapy for myocardial infarction). A patient's drug therapy at admission reflects prescriptions from general practitioners, whereas those at discharge relate to prescriptions from hospital internists or geriatric physicians.

2.3 Drug–Drug Interactions

DDIs were evaluated using INTERcheck, a computerized prescription support system that classifies potential DDIs according to their clinical relevance: contraindicated (D, drug combinations should be avoided); major (C, drug combinations requiring close monitoring for potentially serious clinical consequences, such as severe adverse effects or lack of clinical efficacy); moderate (B, drug combinations requiring dose adjustment and/or drug concentration monitoring); minor (A, drug combinations with no known clinical relevance) [20].

2.4 Statistical Analysis

The patients' sociodemographic characteristics were described using univariate analysis. We used JMP Pro 12 (SAS Institute Inc., Cary, NC, USA) to conduct analyses. p values <0.05 were considered statistically significant.

3 Results

The study sample included 5821 patients admitted to and 4983 discharged from 97 internal medicine and geriatric wards. A total of 143 and 170 therapeutic duplicates were found at admission and at discharge, respectively. The prevalence of patients exposed to at least one therapeutic duplicate rose significantly from hospital admission (2.5 %) to discharge (3.4 %; $p = 0.0032$). Furthermore, the same therapeutic duplicate was maintained in hospital (from admission to discharge) for 64 patients and at the same dosage for 60 (93.8 %) patients.

Table 1 shows the most frequent therapeutic duplicates. Four patients at admission and seven at discharge were exposed to more than one duplicate drug. Four received duplicates with three drugs: three patients at admission were being treated with three antidepressants, benzodiazepines, or drugs for peptic ulcer or gastroesophageal reflux disease (GERD) and one received three antidepressants at discharge.

At least one of the duplicate drugs was involved in potentially severe DDIs in 59 (41.3 %) patients at admission and 65 (38.2 %) patients at discharge. Table 2 shows the most frequent potentially severe DDIs.

Of the 170 patients discharged with at least one therapeutic duplicate, follow-up was available for 92 and information about drug therapy for 76 (16 patients died after discharge). The therapeutic duplicate was continued for 66 patients (86.8 %) and at the same dosage in all cases. Follow-up was available for 50 of the patients discharged with newly created therapeutic duplicates ($n = 108$, 63.5 %); information about drug therapy was available for 41 (nine patients died after discharge), and the duplication was continued for 32 (Table 3). Most of the newly created therapeutic duplicates were prescribed for the same indication, e.g., proton pump inhibitor (PPI) and other drugs for gastritis or GERD in 92.5 % ($n = 37$) of cases; antipsychotics for neuropsychiatric symptoms in patients with dementia and antidepressants for depression in all cases; hypnotic sedatives for anxiety in 50 % of cases (in three, the indications were different: anxiety and insomnia); and long-acting nitrates for ischemic cardiomyopathy or coronary heart disease in all cases.

4 Discussion

In the present study, hospital discharge was associated with a small but definite increase in overall number of therapeutic duplicates, which in most cases were maintained at 3-month follow-up, raising concerns about avoidable harm to elderly patients. Prescribers must pay close attention to the indications for each drug used, because therapeutic duplicates put the patient at increased risk of ADEs with no additional therapeutic benefits and increases the costs for the National Health System. Our findings suggest that therapeutic duplication is of special concern among elderly hospital patients, because in this setting confirmation of the

Table 1 Main characteristics of patients in REPOSI and most frequent therapeutic duplicates

Characteristic	At admission (n = 5821)	At discharge (n = 4983)
Age, years	79.2 ± 7.5	79.1 ± 7.5
Women (%)	51.6	52.2
Drugs	5.1 ± 3.1	6.0 ± 3.3
CIRS[a]		
Diagnosis	5.8 ± 3.0	6.5 ± 3.2
Severity index	1.7 ± 0.3	1.7 ± 0.3
Comorbidity index	3.0 ± 1.9	3.1 ± 2.0
Short blessed test[b]	9.1 ± 8.0	
Barthel index[c]	78.0 ± 29.3	72.8 ± 32.5
Patients with therapeutic duplicates	143	170
Psychotropic drugs	57 (39.9)	56 (32.9)
Antidepressant	31	27
SSRI + TCA	3	2
SSRI + other antidepressant[d]	19	17
TCA + other antidepressant	4	2
Combination of other antidepressants	5	6
Hypnotic sedatives	11	12
Antipsychotic	16	20
Atypical + typical	13	13
Typical + typical	3	7
Gastrointestinal drugs	35 (24.5)	59 (34.7)
Drug for peptic ulcer and GERD	31	52
PPI + PPI	1	5
PPI + anti H_2	6	4
PPI + antacid	11	16
PPI + sucralfate	12	26
PPI + misoprostol	0	1
Anti H_2 + antacid	1	0
Laxatives	3	5
Prokinetic	1	2
Cardiovascular drugs	37 (25.8)	36 (21.2)
Long-acting nitrates[e]	14	14
High-ceiling diuretics	5	5
Other cardiac therapy[f]	2	1
ACE inhibitors	2	1
Calcium channel blockers	5	4
Beta blockers	5	7
ARBs	0	2
Potassium-sparing diuretics	2	2
Capillary-stabilizing agents	1	0
Statins	1	0
Others	15 (10.5)	22 (12.9)
NSAIDs	6	0
Bisphosphonates	1	0
Cholecalciferol	0	2
Calcium carbonate	0	1
Systemic corticosteroids	0	7
Alpha antagonists for BPH	2	1
Testosterone 5 alpha reductase inhibitors	1	1
Low-molecular weight heparin	1	0

Table 1 continued

Characteristic	At admission (n = 5821)	At discharge (n = 4983)
Anti-parathyroid agents	2	2
Thyroid hormones	1	3
Antihistamine drugs	1	1
Iron supplements	0	1
Antibiotics (same drug)	0	3

Data are presented as n or n (%) or mean ± standard deviation unless otherwise indicated

ACE angiotensin-converting enzyme, *anti* H_2 H_2-receptor antagonist, *ARB* angiotensin II receptor antagonist, *BPH* benign prostatic hypertrophy, *CIRS* Cumulative Illness Rating Scale, *GERD* gastroesophageal reflux disease, *NSAID* non-steroidal anti-inflammatory drug, *PPI* proton pump inhibitor, *REPOSI* Italian Society of Internal Medicine Registry of Polytherapies, *SSRI* selective serotonin reuptake inhibitor, *TCA* tricyclic antidepressant

[a] Data available for 4489 at admission and 3825 at discharge

[b] Data available for 3998 only during the hospitalization

[c] Data available for 3002 at admission and 2015 at discharge

[d] Including trazodone, mianserin, mirtazapine, venlafaxine, duloxetine

[e] Nitroglycerin and isosorbide mononitrate

[f] Ranolazine and ivabradine

Table 2 Most frequent potentially severe drug–drug interactions involving at least one of the therapeutic duplicate drugs

Drug class combination	Potential adverse events	Patients	
		At admission (n = 143)	At discharge (n = 170)
Drugs associated with QT prolongation [37]	Increased risk of QT prolongation and torsades de pointes	40 (28.0)	50 (29.4)
SSRI or SNRI + trazodone	Increased risk of serotonin syndrome	16 (11.2)	15 (8.8)
SSRI + diuretics	Hyponatremia	12 (8.4)	9 (5.3)
SSRI + acetylsalicylic acid	Increased risk of intracranial hemorrhage	5 (3.5)	6 (3.5)
Digoxin + PPI or torasemide	Increased risk of digoxin toxicity	3 (2.1)	5 (2.9)
SSRI + anticoagulants	Increased risk of bleeding	2 (1.4)	5 (2.9)

Data are presented as n (%)

PPI proton pump inhibitor, *SSRI* selective serotonin reuptake inhibitor, *SNRI* serotonin–norepinephrine reuptake inhibitor

duplicate prescription comes from expert hospital internists or geriatricians.

One of the most frequent therapeutic duplicates found in our study was psychotropic drugs: in three patients (two at admission and one at discharge), three different antidepressants or benzodiazepines were prescribed, although no evidence supports their effectiveness. The use of three or more psychotropic drugs should be avoided in the elderly because of their increased risk of falls and fractures, according to the recent update of the Beers criteria [21]. The evidence for combining antidepressants is scant and limited to short-term studies with small samples in adults with major depression [22], and the best evidence is for the combination of a selective serotonin reuptake inhibitor (SSRI) with either mirtazapine or mianserin [23, 24]. However, no studies have evaluated the efficacy of combining antidepressants in elderly patients, especially those with chronic multi-morbidity. Consequently, the efficacy and safety profile of this approach is actually unknown, as is the associated risk of DDIs. This is particularly concerning because many potentially serious DDIs are overlooked in guidelines, as found in a recent analysis of the National Institute for Health and Care Excellence guidelines for depression [25].

Drugs for peptic ulcer or GERD were the most frequent therapeutic duplicates found at discharge. Despite the different mechanisms of action, the combination of a PPI with an H_2-receptor antagonist (anti-H_2), antacid, or sucralfate is

Table 3 Therapeutic duplications newly created at discharge and maintained at 3-month follow-up

Therapeutic duplication	Newly created at discharge (n = 108)	3-month follow-up (n = 32)
PPI and other drugs for acid-related disorders	40 (37.0)	13 (40.6)
Antipsychotic	11 (10.2)	3 (9.4)
Antidepressant	8 (7.4)	1 (3.1)
Long-acting nitrates	8 (7.4)	4 (12.5)
Systemic corticosteroids	7 (6.5)	2 (6.2)
Hypnotic sedatives	6 (5.5)	2 (6.2)
Beta blockers	5 (4.6)	4 (12.5)
Calcium channel blockers	3 (2.7)	0
Antibiotics (same drug)	3 (2.7)	0
Alpha-adrenoreceptor antagonists for BPH	1 (0.9)	1 (3.1)
Other	18 (16.6)	3 (9.4)

Data are presented as n (%)

BPH benign prostatic hypertrophy, *PPI* proton pump inhibitor

not supported by evidence. Although PPIs are associated with serious ADEs [26], overuse is widespread in primary and secondary care, and a previous REPOSI study found that 62.4 % of patients at admission and 63.2 % at discharge were inappropriately treated with PPIs [27]. The appropriateness of acid-suppressant therapy should also be carefully assessed before such therapy is commenced. This study confirmed inappropriate prescribing in five patients who were discharged with two PPIs.

Careful review of drug therapy may be useful to avoid unnecessary dispensing leading to therapeutic duplicates. In 63.5 % of patients with therapeutic duplicates at discharge (reflecting prescriptions by hospital internists or geriatricians), these duplicates were newly created at discharge, and drugs were mainly prescribed for the same indication. It is possible that, in particular circumstances, therapeutic duplicates may have been used 'as needed'; however, a large percentage of patients continued to receive therapeutic duplicates at follow-up and the dosage tended to remain as initially prescribed. This suggests that drug therapy is not being reviewed or optimized. Reducing inappropriate prescriptions is an important patient-centered intervention to reduce the incidence of drug-related adverse events [28]. Unnecessary therapeutic duplicates must be identified to optimize drug therapy. Medication reconciliation, a process to avoid inadvertent inconsistencies within a patient's drug regimen that can occur during transitions between different care settings, could also be useful to prevent medical errors and drug-related problems [29]. Electronic health systems that monitor prescribing and provide alerts for inappropriate prescriptions help to reduce therapeutic duplication, improving patient safety and rational prescribing [29] as found for overused PPIs in both outpatient [30] and inpatient [31] settings. A multicenter study in nursing homes in Italy combined an educational intervention and use of the computerized prescription support system INTERcheck. This combination significantly reduced both the number of patients receiving potentially inappropriate psychotropic drugs and psychotropic duplicates and the number of patients exposed to potentially severe DDIs [32]. Prescriptions resulting in potentially serious DDIs were also significantly reduced after integration of the DDI database SFINX into electronic health records in primary care in Sweden [33]. However, the efficacy of electronic health systems is debated [34], and physicians must still be vigilant when prescribing and pay more attention to the indication for each drug [35].

Because the decision to stop unnecessary medication is an important step toward drug optimization and de-prescribing, it should be considered a positive patient-centered intervention that calls for shared decision making and close monitoring of effects. For these reasons, advising patients about potentially serious adverse reactions of long-term use of a duplicate or an unnecessary drug (e.g., community-acquired pneumonia, *Clostridium difficile* diarrhea, osteoporosis, hip fractures, or severe hypomagnesemia in patients receiving PPIs) and close monitoring of rebound symptoms (such as hypersecretion of gastric acid and dyspepsia) may be an essential step in successful de-prescribing.

To our knowledge, this is the first observational study to examine the prevalence of therapeutic duplication at admission and discharge in a large sample of hospitalized elderly patients, thus reflecting therapeutic duplicates prescribed by general practitioners (at admission) and by hospital internists or geriatric physicians (at discharge). Our findings confirm the results of a previous study in a sample of 384 hospitalized frail elderly, which found that therapeutic duplication was one of the main reasons for unnecessary drug use at hospital discharge [36].

Limitations include the lack of information about clinical outcome and adherence to drug therapy after discharge. A prospective design, including longer follow-up and collection of drug-related problems, would better quantify the clinical relevance of therapeutic duplicates. Our small sample of patients with therapeutic duplicates and follow-up data limited our ability to assess relationships with clinical outcome. A further limitation concerns the lack of data about *pro re nata* prescriptions and exacerbations or withdrawal symptoms after an attempt to discontinue a medicine (e.g., SSRIs and benzodiazepines on a long-term basis should be tapered slowly over several weeks or months to avoid withdrawal symptoms);

however, the lack of dosage changes in hospital and the large percentage of patients continuing to receive therapeutic duplicates at follow-up suggests that de-prescribing was not evaluated.

5 Conclusion

There tends to be a small but definite increase in overall therapeutic duplicates in elderly patients admitted to internal medicine and geriatric wards. Psychotropic drugs and drugs for peptic ulcer or GERD are the most frequently involved. More attention must be paid to the indications for each drug, because duplication is not supported by evidence and increases both the risk of ADEs and costs. Unnecessary therapeutic duplicates must be identified to optimize polypharmacy.

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Compliance with Ethical Standards

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Conflict of interest Luca Pasina, Sarah Astuto, Laura Cortesi, Mauro Tettamanti, Carlotta Franchi, Alessandra Marengoni, Pier Mannuccio Mannucci and Alessandro Nobili have no conflicts of interest relevant to the content of this article.

References

1. Fried TR, O'Leary J, Towle V, et al. Health outcomes associated with polypharmacy in community-dwelling older adults: a systematic review. J Am Geriatr Soc. 2014;62:2261–72.
2. Spinewine A, Schmader KE, Barber N, et al. Appropriate prescribing in elderly people: how well can it be measured and optimised? Lancet. 2007;370(9582):173–84.
3. Hajjar ER, Cafiero AC, Hanlon JT. Polypharmacy in elderly patients. Am J Geriatr Pharmacother. 2007;5:345–51.
4. Hilmer SN, Gnjidic D. The effects of polypharmacy in older adults. Clin Pharmacol Ther. 2009;85:86–98.
5. Steinman MA, Landefeld CS, Rosenthal GE, et al. Polypharmacy and prescribing quality in older people. J Am Geriatr Soc. 2006;54:1516–23.
6. Koh Y, Kutty FBM, Li SC. Drug-related problems in hospitalized patients on polypharmacy: the influence of age and gender. Ther Clin Risk Manag. 2005;1:39–48.
7. Lund BC, Carnahan RM, Egge JA, et al. Inappropriate prescribing predicts adverse drug events in older adults. Ann Pharmacother. 2010;44(6):957–63.
8. Nobili A, Garattini S, Mannucci PM. Multiple diseases and polypharmacy in the elderly: challenges for the internist of the third millennium. J Comorbidity. 2011;1:28–44.
9. O'Connor MN, Gallagher P, O'Mahony D. Inappropriate prescribing: criteria, detection and prevention. Drugs Aging. 2012;29(6):437–52.
10. Beers MH, Ouslander JG, Rollingher I, et al. Explicit criteria for determining inappropriate medication use in nursing home residents. Arch Intern Med. 1991;151:1825–32.
11. Chang CB, Chan DC. Comparison of published explicit criteria for potentially inappropriate medications in older adults. Drugs Aging. 2010;27(12):947–57.
12. O'Mahony D, O'Sullivan D, Byrne S, et al. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Ageing. 2015;44(2):213–8.
13. Rancourt C, Moisan J, Baillargeon L, et al. Potentially inappropriate prescriptions for older patients in long-term care. BMC Geriatr. 2004;15(4):9.
14. Laroche ML, Charmes JP, Merle L. Potentially inappropriate medications in the elderly: a French consensus panel list. Eur J Clin Pharmacol. 2007;63(8):725–31.
15. Rognstad S, Brekke M, Fetveit A, et al. The Norwegian General Practice (NORGEP) criteria for assessing potentially inappropriate prescriptions to elderly patients: a modified Delphi study. Scand J Prim Health Care. 2009;27(3):153–9.
16. Holt S, Schmiedl S, Thurmann PA. Potentially inappropriate medications in the elderly: the PRISCUS list. Dtsch Arztebl Int. 2010;107(31–32):543–51.
17. Steinman MA, Landefeld CS, Rosenthal GE, et al. Polypharmacy and prescribing quality in older people. J Am Geriatr Soc. 2006;54(10):1516–23.
18. Heinze G, Jandeck LM, Hronsky M, et al. Prevalence and determinants of unintended double medication of antihypertensive, lipid-lowering, and hypoglycemic drugs in Austria: a nationwide cohort study. Pharmacoepidemiol Drug Saf. 2016;25(1):90–9. doi:10.1002/pds.3898.
19. WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2016. Available at: http://www.whocc.no/atc_ddd_index/. Accessed 9 Aug 2016.
20. Ghibelli S, Marengoni A, Djade CD, et al. Prevention of inappropriate prescribing in hospitalized older patients using a computerized prescription support system (INTERcheck®). Drugs Aging. 2013;30(10):821–8.
21. By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 updated beers criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2015;63(11):2227–46.
22. Dodd S, Horgan D, Malhi GS, et al. To combine or not to combine? A literature review of antidepressant combination therapy. J Affect Disord. 2005;89(1–3):1–11.
23. Feetam C. Are two antidepressants always better than one? Prog Neurol Psychiatry. 2012;16:5–8.
24. National Institute for Health and Care Exellence. Depression in adults: recognition and management. 2013. Available from: https://www.nice.org.uk/guidance/cg90/chapter/1-Guidance. Accessed 9 August 2016.
25. Dumbreck S, Flynn A, Nairn M, et al. Drug–disease and drug–drug interactions: systematic examination of recommendations in 12 UK national clinical guidelines. BMJ. 2015;11(350):h949.
26. Benmassaoud A, McDonald EG, Lee TC. Potential harms of proton pump inhibitor therapy: rare adverse effects of commonly used drugs. CMAJ. 2016;188(9):657–62. doi:10.1503/cmaj.150570.
27. Pasina L, Nobili A, Tettamanti M, et al. Prevalence and appropriateness of drug prescriptions for peptic ulcer and gastro-esophageal reflux disease in a cohort of hospitalized elderly. Eur J Intern Med. 2011;22(2):205–10.
28. Scott IA, Hilmer SN, Reeve E, et al. Reducing inappropriate polypharmacy: the process of deprescribing. JAMA Intern Med. 2015;175(5):827–34.

29. Kaushal R, Kern LM, Barron Y, et al. Electronic prescribing improves medication safety in community-based office practices. J Gen Intern Med. 2010;25(6):530–6.
30. Curtain C, Peterson GM, Tenni P, et al. Outcomes of a decision support prompt in community pharmacy-dispensing software to promote step-down of proton pump inhibitor therapy. Br J Clin Pharmacol. 2011;71(5):780–4.
31. Freedberg DE, Salmasian H, Abrams JA, et al. Orders for intravenous proton pump inhibitors after implementation of an electronic alert. JAMA Intern Med. 2015;175(3):452–4.
32. Pasina L, Marengoni A, Ghibelli S, et al. A multicomponent intervention to optimize psychotropic drug prescription in elderly nursing home residents: an Italian multicenter, prospective, pilot study. Drugs Aging. 2016;33(2):143–9.
33. Andersson ML, Böttiger Y, Lindh JD, et al. Impact of the drug–drug interaction database SFINX on prevalence of potentially serious drug–drug interactions in primary health care. Eur J Clin Pharmacol. 2013;69(3):565–71.
34. Marengoni A, Nobili A, Onder G. Best practices for drug prescribing in older adults: a call for action. Drugs Aging. 2015;32(11):887–90.
35. Electronic prescribing: the risk of errors and adverse effects. Prescrire Int. 2016;25(167):24–7.
36. Hajjar ER, Hanlon JT, Sloane RJ, et al. Unnecessary drug use in frail older people at hospital discharge. J Am Geriatr Soc. 2005;53(9):1518–23.
37. Risk Categories for Drugs that Prolong QT & induce Torsades de Pointes (TdP). Available from: https://www.crediblemeds.org. Accessed 9 Aug 2016.