Prescription of proton pump inhibitors in older adults with complex polytherapy

Clara Cena,¹ Sara Traina,¹ Beatrice Parola,¹ Mario Bo,² Riccardo Fagiano,² Carlotta Siviero¹

¹Dipartimento di Scienza e Tecnologia del Farmaco, Università degli Studi di Torino, Torino, Italy
²Azienda Ospedaliero Universitaria Città della Salute e della Scienza di Torino, Torino, Italy

Correspondence to
 Professor Clara Cena,
 Dipartimento di Scienza e Tecnologia del Farmaco,
 Università degli Studi di Torino,
 Turin, Italy; clara.cena@unito.it

Received 26 July 2018
 Revised 28 January 2019
 Accepted 12 February 2019
 Published Online First
 16 March 2019

EAHP Statement 6: Education and Research.

ABSTRACT

Objectives Prescription of proton pump inhibitors (PPIs) may be a source of potentially clinically relevant drug–drug interactions (DDIs) and related complications for elderly patients with complex polytherapy at discharge from hospital. The aim of the study was to identify, through the analysis of hospital discharge records, the co-administrations (PPIs + one or more drugs potentially generating DDIs) hypothetically leading to severe consequences according to the literature and online databases. Subsequently, alternatives to PPIs were evaluated for the treatment of gastric acidity and ulcers.

Methods The medical records of 1288 patients, discharged from a geriatric ward at the Città della Salute e della Scienza Hospital in Turin from January 2012 to December 2013, were collected in an Excel database for analysis of DDIs using the literature and online sources such as Micromedex.

Results Six hundred and sixty-three of the 1288 clinical folders had a PPI prescription. A list of 18 drugs considered potentially hazardous and able to trigger a DDI when co-administrated with PPIs was drafted; the frequencies of the co-prescriptions of each PPI with one of the listed drugs were esomeprazole 65.38%, lansoprazole 52.87%, omeprazole 48.19% and pantoprazole 37.11%. An analysis of these co-prescriptions, according to Micromedex classification, gave a percentage of major interactions of 11.01% over 663 clinical folders including a PPI.

Conclusions This study provides a collection of potentially hazardous drug associations and helpful suggestions to improve the quality of prescriptions for elderly patients and strengthens the case for synergic work between doctors and pharmacists in the wards.

INTRODUCTION

There has been a significant rise in proton pump inhibitor (PPI) prescriptions in recent years. PPI usage has been especially high in a number of European countries as well as others.^{1 2} In addition to the economic burden of PPIs, there is also a health issue to consider connected to the inappropriate prescription of PPIs.³ For these reasons, this topic has been gaining the attention of the NHS managements.

PPIs are often prescribed to people who already receive other medications and, although considered safe, several concerns have been raised about their safety in long-term use.⁴ Potential adverse effects of long-term PPI use have been identified and include an increased risk of infections, specifically pneumonia, *Clostridium difficile* infections,^{5 6} hypomagnesaemia^{7 8} and, most recently,

bone fractures.⁹ Drug–drug interactions (DDIs) can occur: it is known that PPIs can increase the absorption of weak acid drugs such as aspirin, and omeprazole and lansoprazole are inhibitors of the cytochrome P450 isoenzyme system, specifically of the CYP2C19 and CYP2D6 isoforms, respectively. A deeper knowledge of genetic variations in drug metabolism—with particular focus on the cytochrome P450 isoenzyme system—may help to predict drug response and drug outcomes.¹⁰

Ko *et al*¹¹ have investigated the inhibitory effects of omeprazole and lansoprazole on human CYP isoforms using human liver microsomal preparations, which showed that omeprazole and lansoprazole had in vitro inhibitory effects on CYP2C19, CYP3A4, CYP2C9 and CYP2D6. These same isoforms are also accountable for the metabolism of other drugs. In fact, omeprazole has been reported to inhibit the metabolism of drugs such as diazepam, phenytoin and clarithromycin.^{12–14}

Previous studies have also shown that among PPI prescriptions, highly prevalent in older patients discharged from internal medicine and geriatric wards, 43.4% of prescriptions were inappropriate according to the AIFA (Agenzia Italiana del Farmaco, the Italian Medicines Agency) rules. Older patients discharged from geriatric wards were associated with increased appropriateness of PPI prescriptions, possibly suggesting that greater attention is paid to age-specific therapeutic recommendations in this setting. At least one potential major DDI, often involving citalopram and clopidogrel (48% and 46% of cases, respectively), was observed in 9% of patients, while at least one potential moderate DDI was found in 36% of patients. Cases presenting two or three moderate DDIs were found in 6.3% and 1.1% of patients, respectively.^{15 16}

The main purpose of the present study is to identify the most dangerous co-prescriptions to which PPIs are added (and the related outcomes of risk). Complex drug interaction schemes have been analysed, using the literature and recognised databases, in order to detect the presence of DDIs. A number of alternative anti-acid treatments have also been suggested.

METHODS

Setting

Medical records were collected from the Geriatric and Metabolic Bone Diseases ward of the Città della Salute e della Scienza Hospital of Turin via the consultation of the clinical discharge folders of patients admitted in the period 2012–2013.

© European Association of Hospital Pharmacists 2020. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Cena C, Traina S, Parola B, *et al*.
Eur J Hosp Pharm
 2020;**27**:341–345.

Only the clinical records of patients aged 65 years and over were selected as part of this research, while oncological and haematological patients were excluded due to the pre-existing and constant medical supervision inherent to these therapies. A standardised electronic form was created and included the following data: date of discharge; age and gender; principal diagnosis at admission; medical history; and therapy at discharge.

All personal data were replaced by a univocal numerical code and the work was carried out on an anonymous database, in compliance with the Italian Privacy Law (Decree 196, 30/06/2003, as amended). Informed consent was not required as this was an observational and retrospective study (Decree 196/03, art. 110, as amended).

Study design

Clinical records in which a PPI was prescribed were then analysed in order to find any interactions. The most clinically hazardous DDIs were identified and 18 drugs were selected for further examination.

The Micromedex database (IBM Watson Health, Greenwood Village, Colorado, USA. Available at: <https://www.micromedexsolutions.com/> Accessed May, 2018) was then consulted in order to analyse the DDIs found; this online resource classifies potential DDIs according to two parameters. The first is clinical relevance and consists of potential clinical outcomes in terms of type and quality. Relevance is ranked as contraindicated, major, moderate, minor and unknown. The second parameter is the availability of pharmacological documentation and is subdivided into excellent, good, fair and unknown bibliography.

Specifically, prescriptions were separated into four groups using Microsoft Office Excel 2016 charts, identifying co-prescriptions of each PPI, as a means to detect differences and to have a clearer view of the therapies.

PPI interactions were linked to interfering metabolic pathways, except in the cases of digoxin and levothyroxine. In fact, their absorption may be influenced by the higher pH caused by PPI functioning.

Besides the mentioned action of PPIs, the analysis of interactions was extended to the drugs reported in the 663 clinical records (such as atypical antipsychotics¹⁷), since it was evident that PPIs were not the only drugs concurring to a possible DDI. Such cases are discussed in the Multiple Interactions section in the Discussion below.

RESULTS

Observations

From a total of 1288 clinical folders, 663 showed the presence of a PPI prescription and were thus examined. Table 1 reports the prevalence of prescription of the four main PPIs. Omeprazole was the most prescribed (376 patients), accounting for 29.19% of the total patient prescriptions. Table 2 shows the prevalence of prescriptions according to age and gender.

Table 1 Number of proton pump inhibitor (PPI) prescriptions collected at discharge

PPI	2012 (n=588)	2013 (n=700)	Total (n=1288)
Omeprazole	169	207	376
Lansoprazole	81	55	136
Pantoprazole	62	68	130
Esomeprazole	10	11	21

Table 2 Proton pump inhibitor (PPI) prescriptions by age and gender

	Men			Women		
	2012	2013	Frequency (%)	2012	2013	Frequency (%)
No of patients	208	306	514	380	394	774
Age (mean)	82.3	82.7	82.5	82.3	82.7	82.5
Omeprazole	59	97	156 (30.3)	110	110	220 (28.4)
Lansoprazole	30	22	52 (10.1)	51	33	84 (10.8)
Pantoprazole	23	36	59 (11.5)	39	32	71 (9.2)
Esomeprazole	2	3	5 (1.0)	8	8	16 (2.1)

Key findings

Figure 1 shows the prevalence of single (only one drug) and multiple (one or more interacting drugs) interactions of each PPI with drugs that were concomitantly prescribed at discharge. PPIs were often co-administered with more than two potentially interacting drugs; the graph highlights the frequency with which each PPI interacts with only one drug and compares this situation with the co-existence of one or more interacting drugs in the same therapy.

The frequency of single interactions between one of the listed drugs and esomeprazole was 65.38%, while for lansoprazole it was 52.87%, for omeprazole it was 48.19% and for pantoprazole 37.11%. These percentages mean that around 50% of the records, presenting at least one interaction, included two or more drugs that might lead to a risk of interaction and probable adverse effects.

The work is focused on a number of complex cases in which it can be expected that a PPI prescription (or deprescription) might alter the bioavailability of the other drugs unpredictably. The intake of PPIs may lead to reduced metabolism of other drugs, such as their potential inhibitory action on CYP450, causing increased concentrations in plasma and lower drug elimination. Higher than expected plasma concentrations of the other drugs taken may generate a risk of toxicity. Despite high percentages of co-prescriptions, most DDIs do not develop into clinical issues. According to the Micromedex database, which is constantly updated with the most recent evidence, attention should be focused on a relatively small number of cases (figure 2).

DISCUSSION

This retrospective study aimed to evaluate the prevalence and severity of potential DDIs that may be linked to a PPI prescription in older medical patients discharged from hospital. The collection of our data highlights the known risks of associating various drugs to a PPI, which may lead to worsening of the patient's condition.

Single interactions

Citalopram and escitalopram are metabolised by CYP2C19, which is inhibited by PPIs (omeprazole and lansoprazole). This process leads to high (es)citalopram plasma concentration levels, which possibly prolong the QT interval and can lead to serious damage to heart function.¹⁷ According to Gjestad *et al.*,¹⁸ the effect of co-medication with PPIs and selective serotonin reuptake inhibitors (SSRIs) on the serum concentration was previously thought to be more pronounced for omeprazole and esomeprazole than for lansoprazole and pantoprazole, while escitalopram was considered to be affected more than citalopram and sertraline. However, the most recent version of the Micromedex database states that all four drugs had major interactions

Figure 1 Frequency of drug–drug interactions (DDIs) with the four proton pump inhibitors (PPIs) considered in 2012–2013. Single interaction: interactions that occurred when the PPI was associated with the drug indicated below the bar chart only. Multiple interactions: interactions that occurred when the PPI was added to a polytherapy with more than one of the 18 drugs shown below the bar charts.

with (es)citalopram, apart from the association of pantoprazole with escitalopram.

Omeprazole–clopidogrel was the association with the most pronounced evidence of interaction.^{19–21} Clopidogrel was also found to interact with lansoprazole and esomeprazole, while pantoprazole was not found to have any interaction, according to the Micromedex database. Consequently, the risk of thrombosis would be increased for patients on polytherapy as clopidogrel would not be activated. Notably, pantoprazole did not appear to interact with clopidogrel whereas all the other PPIs did; in fact, pantoprazole is known to weakly inhibit CYP2C19.^{22,23} The non-interaction of pantoprazole could be a potential solution in cases where an antiplatelet agent and a PPI are strictly needed and could be explained by its slightly different mechanism of action. Seventy-eight drug charts included warfarin over the 2-year period considered. Warfarin is metabolised by CYP2C9 and by CYP3A4: the plasma concentration of the anticoagulant would not decrease as expected, meaning that the INR may be higher and that there may be a higher risk of bleeding in the patient.

The administration of digoxin or levothyroxine together with PPIs may cause the absorption of the first two to decrease, because of the change in gastric pH induced by PPIs. Digoxin has a narrow therapeutic index and the change in pH may bring about variability in its serum level and typical adverse effects

may occur. The association between levothyroxine and PPIs, and specifically the plasmatic dose of the thyroidal hormone, may require careful monitoring.

Multiple interactions

Adding a PPI to a therapeutic treatment can be complicated, since interactions with drugs included in the polytherapy may occur. It was decided that only major and moderate interactions detected using Micromedex would be analysed, to focus on the cases in which unpredictable outcomes may be generated by the multiple association of interacting drugs (figure 3).

Citalopram and escitalopram showed major risks of interaction when combined with haloperidol, but the addition of a PPI to this combination would also lead to a probable QT interval prolongation.²⁴

One patient showed an association between citalopram and metoprolol (major risk) in addition to haloperidol and omeprazole; the risk of an adverse drug reaction increases as the unpredictable concentration of drugs may eventually be a cause of rehospitalisation.

The therapies of three patients included clopidogrel, duloxetine and omeprazole, a combination that could cause a serious risk of bleeding. Moreover, they found that the addition of an SSRI to dual antiplatelet therapy (aspirin and clopidogrel) increased the risk by 57% compared with dual antiplatelet therapy alone. Clinicians should therefore prescribe SSRI antidepressants to these patients with caution, even more so when an anti-acid treatment is needed and a PPI is chosen.

The major cross-interaction between haloperidol and quetiapine may result in an increased risk of QT interval prolongation. Micromedex did not flag any interaction between either of these drugs and the PPIs, but it may be assumed that, as they are all metabolised by liver cytochromes, the combination and addition of drugs that have the same metabolism pathway should not be recommended as they cause predictable adverse drug reactions.

The association of clopidogrel with (es)citalopram is also considered a threatening interaction. In fact, drugs that are substrates of CYP1A2, CYP2D6 and CYP3A4 were found to interact with citalopram, independently from the presence of PPIs. According to the literature, a combination of the antiplatelet agent, SSRI plus lansoprazole (1) or pantoprazole (4)

	Omeprazole	Lansoprazole	Pantoprazole	Esomeprazole
Citalopram				
Clopidogrel				
Diazepam				
Digoxin				
Doxofylline				
Duloxetine				
Escitalopram				
Fluconazole				
Haloperidol				
Levothyroxine				
Metoprolol				
Olanzapine				
Propranolol				
Quetiapine				
Risperidone				
Verapamil				
Warfarin				
Zolpidem				

Figure 2 Interactions detected using the Micromedex database. Level of risk: major risks shown in brown-red, moderate risks as chequered pattern, minor risks in grey stripes and no interaction indicated in white.

Figure 3 Polytherapy patterns found in a geriatric ward that present a major risk interaction. The numbers at the top indicate the number of cases while the colours indicate the interactions found among all the drugs (black), among non-PPI drugs and multiple interactions of various risk among all the drugs including PPIs (white).

may cause disorders of plasma drug concentrations that are difficult to manage, especially in older people. The prescription of an additional antiplatelet therapy (eg, clopidogrel plus warfarin) would obviously amplify the anticoagulant effects. Similarly, the inclusion of a PPI may not facilitate the situation. Five cases are reported in our data, four with pantoprazole and one with lansoprazole.

Various interactions can be found to occur between warfarin and other drugs independently of the presence of PPIs. Associations with (es)citalopram (considered major, three cases), duloxetine (moderate, one case reported) or quetiapine (moderate, one case) might cause an increase in the risk of bleeding for the patient. In addition, the inhibition of CYP isoforms brought about by PPIs may lead to an overextended high dose of both the antidepressants and warfarin.

The association of levothyroxine with clopidogrel and a PPI was classified as a major interaction whereas the association with citalopram was classified as moderate and with warfarin minimum only. The result would nevertheless be a decrease in levothyroxine efficacy, which would lead to an increased hormone dose requirement. Moreover, levothyroxine may also represent a difficult pattern of treatment due to variability of the various available pharmaceutical formulations (tablets, capsules, injections).

The total number of high-risk cases reported were 47 single interaction drug–PPI cases (see figure 1) plus 26 cases in which a more complex pattern of interactions resulted from multiple drug associations (see figure 3), according to the Micromedex database. The percentage of major interactions in the total number of patients considered (663 with a PPI prescription) was 11.01%.

In conclusion, even if the number of major interactions was limited, 73 older people were at risk of rehospitalisation, organ failure or a worsening of their condition, possibly because of the interactions reported. As reported by the Beers criteria,²⁵ treatment with PPIs should not extend beyond a period of 8 weeks, except in high-risk patients. Relative high-risk conditions include: use of oral corticosteroids or chronic non-steroidal anti-inflammatory drugs, erosive oesophagitis and a demonstrated need for maintenance due to the failure of H₂-blocker action. All professionals should therefore be aware of the relevance of cyclic therapy revision.

This observational study is based on a detailed collection of data, which was made available thanks to the cooperation of the Geriatric and Metabolic Bone Diseases ward of Città della Salute e della Scienza Hospital of Turin. The major limitation of the

present study is its single-centre setting, which does not thereby allow for the generalisation of the current results. Moreover, the lack of a unified database of patient prescriptions in Italy means that this work was carried out on reviewed prescriptions at the time of discharge. Consequently, it was not possible to extend the study and to evaluate the appropriateness of PPI prescriptions on the territory (by general practitioners).

CONCLUSION

The analysis of the prescriptions collected from the Geriatric and Metabolic Bone Diseases ward of the Città della Salute e della Scienza Hospital of Turin showed that 11.01% of the patients investigated displayed major DDIs. The percentage was in line with results obtained in other papers.^{26 27} However, previous studies of the same group consistently compare the prescription appropriateness of this geriatric ward favourably with the internal Medical unit in the same hospital.^{15 16}

One possible strategy to deal with contraindicated or major DDI conditions is not using the specific drugs that interact with PPIs. However, there are great differences within the PPI drug class that must be considered. For instance, choosing omeprazole instead of lansoprazole or switching the prescription to pantoprazole could have a significant effect on metabolism. It may be useful to consider changing in favour of H₂-antihistamines such

What this paper adds

What is already known on this subject

- ▶ Proton pump inhibitors (PPIs), although considered safe, raise several concerns about their safety in long-term use.
- ▶ PPIs are persistently administered to elderly complex patients, even without appropriate indications, creating solid bases for drug–drug interactions, implications and adverse effects.
- ▶ It is widely known that PPI prescriptions should be reduced to essential cases.

What this study adds

- ▶ This study focuses on the clinical folders of 1288 older patients, where over half of them had a PPI prescription, confirming the general trends.
- ▶ Selecting 18 recurring drugs prescribed among the total prescriptions, the study reports the complex situations found, displaying several interacting medications, and the heightened risks related to the addition of a PPI specifically.

as ranitidine, which showed fewer interactions according to the Micromedex database.

Ranitidine does not inhibit the cytochrome (because of the lack of an imidazolyl cycle) and may be safely associated with escitalopram, citalopram, clopidogrel and levothyroxine. Association with warfarin showed a moderate interaction, so ranitidine may not necessarily ameliorate the situation.

In conclusion, interventions and contributions of clinical pharmacists should be considered as they can offer advice and support when making difficult decisions.^{28 29}

Acknowledgements We are grateful to Professor Giovanni Carlo Isaia for allowing us to use the data gathered in the Geriatric and Metabolic Bone Diseases ward of Città della Salute e della Scienza Hospital of Turin for this observational study.

Contributors All authors contributed equally to the study design.

Funding This work was supported by Università degli Studi di Torino (Ric.Loc. 2016 to 2017).

Competing interests None declared.

Patient consent for publication This was a retrospective study conducted on anonymous data.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

REFERENCES

- 1 Lanas A. We are using too many PPIs, and we need to stop: a European perspective. *Am J Gastroenterol* 2016;111:1085–6.
- 2 Nishtala PS, Soo L. Proton pump inhibitors utilisation in older people in New Zealand from 2005 to 2013. *Intern Med J* 2015;45:624–9.
- 3 van Vliet EPM, Otten HJAM, Rudolphus A, et al. Inappropriate prescription of proton pump inhibitors on two pulmonary medicine wards. *Eur J Gastroenterol Hepatol* 2008;20:608–12.
- 4 Garnett WR. Considerations for long-term use of proton-pump inhibitors. *Am J Health Syst Pharm* 1998;55:2268–79.
- 5 Kwok CS, Arthur AK, Anibueze CI, et al. Risk of *Clostridium difficile* infection with acid suppressing drugs and antibiotics: meta-analysis. *Am J Gastroenterol* 2012;107:1011–9.
- 6 Linsky A, Gupta K, Lawler EV, et al. Proton pump inhibitors and risk for recurrent *Clostridium difficile* infection. *Arch Intern Med* 2010;170:772–8.
- 7 Hess MW, Hoenderop JGJ, Bindels RJM, et al. Systematic review: Hypomagnesaemia induced by proton pump inhibition. *Aliment Pharmacol Ther* 2012;36:405–13.
- 8 Pastorino A, Greppi F, Bergamo D, et al. Proton pump inhibitors and hypomagnesemia in polymorbid elderly adults. *J Am Geriatr Soc* 2015;63:179–80.
- 9 Metz DC. Examining the potential relationship between proton pump inhibitor use and the risk of bone fracture. *Gastroenterol Hepatol* 2011;7:831–3.
- 10 Brewer L, Williams D. Drug interactions that matter. *Medicine* 2012;40:371–5.
- 11 Ko JW, Sukhova N, Thacker D, et al. Evaluation of omeprazole and lansoprazole as inhibitors of cytochrome P450 isoforms. *Drug Metab Dispos* 1997;25:853–60.
- 12 Andersson T, Andrén K, Cederberg C, et al. Effect of omeprazole and cimetidine on plasma diazepam levels. *Eur J Clin Pharmacol* 1990;39:51–4.
- 13 Prichard PJ, Walt RP, Kitchingman GK, et al. Oral phenytoin pharmacokinetics during omeprazole therapy. *Br J Clin Pharmacol* 1987;24:543–5.
- 14 Gustavson LE, Kaiser JF, Edmonds AL, et al. Effect of omeprazole on concentrations of clarithromycin in plasma and gastric tissue at steady state. *Antimicrob Agents Chemother* 1995;39:2078–83.
- 15 Bo M, Quaranta V, Fonte G, et al. Prevalence, predictors and clinical impact of potentially inappropriate prescriptions in hospital-discharged older patients: a prospective study. *Geriatr Gerontol Int* 2018;18:561–8.
- 16 Fagiano R, Falcone Y, Fonte G, et al. Indications, appropriateness and drug interactions of proton pump inhibitors prescribed at hospital discharge in older medical patients. *Geriatr Gerontol Int* 2017;17:1238–40.
- 17 Ojero-Senard A, Benevent J, Bondon-Guitton E, et al. A comparative study of QT prolongation with serotonin reuptake inhibitors. *Psychopharmacology* 2017;234:3075–81.
- 18 Gjestad C, Westin AA, Skogvoll E, et al. Effect of proton pump inhibitors on the serum concentrations of the selective serotonin reuptake inhibitors citalopram, escitalopram, and sertraline. *Ther Drug Monit* 2015;37:90–7.
- 19 Tragni E, Casula M, Pieri V, et al. Prevalence of the prescription of potentially interacting drugs. *PLoS One* 2013;8:e78827.
- 20 Kwok CS, Loke YK. Meta-analysis: the effects of proton pump inhibitors on cardiovascular events and mortality in patients receiving clopidogrel. *Aliment Pharmacol Ther* 2010;31:810–23.
- 21 Goodman SG, Clare R, Pieper KS, et al. Association of proton pump inhibitor use on cardiovascular outcomes with clopidogrel and ticagrelor: insights from the platelet inhibition and patient outcomes trial. *Circulation* 2012;125:978–86.
- 22 Juurlink DN, Gomes T, Ko DT, et al. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. *CMAJ* 2009;180:713–8.
- 23 Choi YJ, Kim N, Jang I-J, et al. Pantoprazole does not reduce the antiplatelet effect of clopidogrel: a randomized controlled trial in Korea. *Gut Liver* 2017;11:504–11.
- 24 Meyer JM, Leckband SG. Loss of enzyme induction: ups and downs of a hidden drug-drug interaction. *Current Psychiatry* 2009;8:47–53.
- 25 American Geriatrics Society. Updated Beers criteria for potentially inappropriate medication use in older adults. *JAGS* 2015;63:2227–46.
- 26 Askari M, Eslami S, Louws M, et al. Frequency and nature of drug-drug interactions in the intensive care unit. *Pharmacoepidemiol Drug Saf* 2013;22:430–7.
- 27 Smithburger PL, Kane-Gill SL, Seybert AL, et al. Drug-drug interactions in the medical intensive care unit: an assessment of frequency, severity and the medications involved. *Int J Pharm Pract* 2012;20:402–8.
- 28 Cornu P, Steurbaut S, Soštarić S, et al. Performance of a clinical decision support system and of clinical pharmacists in preventing drug-drug interactions on a geriatric ward. *Int J Clin Pharm* 2014;36:519–25.
- 29 Leger DY, Moreau S, Signol N, et al. Polypharmacy, potentially inappropriate medications and drug-drug interactions in geriatric patients with hematologic malignancy: observational single-center study of 122 patients. *J Geriatr Oncol* 2018;9:60–7.