



Potential drug interactions with antibacterials in long-term care facilities analyzed by two interaction checkers

Matej Štuhec^{1,2,3} · Ines Potočin¹ · Dora Stepan⁴ · Lea Ušaj⁴ · Marija Petek Šter⁵ · Bojana Beović^{4,6}

Received: 6 August 2018 / Accepted: 28 May 2019 / Published online: 6 June 2019
© Springer Nature Switzerland AG 2019

Abstract

Background Residents in long-term care facilities take many medications concomitantly, including antibacterials, which increases the risk of drug–drug interactions. **Objectives** The aims of the study were to investigate the prevalence of severe potential interactions between antibacterials and other medications in Slovenian long-term care facilities and to compare the performance of two different drug–drug interaction checkers in these settings. **Setting** Residents in long-term care facilities in Slovenia. **Method** A point-prevalence study was conducted from April 2016 to June 2016. Residents' characteristics, antibacterial treatment, and concomitant medications were obtained from their medical charts. Potential drug–drug interactions were determined using Lexicomp Online™ 3.0.2 and the online Drugs.com Drug Interactions Checker. The study only included potential drug–drug interactions categorized as type MA (major interactions) by the Drugs.com checker and as type X (should be avoided) by Lexicomp Online™. The study calculated the differences in the number of type X and MA potential drug–drug interactions between different antibacterial classes and between the two drug–drug interactions checkers. **Main outcome measure** Number of medications per patient, number of potential drug–drug interactions with antibacterial, and differences between two drug–drug interactions checkers. **Results** Eighty (68.4%) of Slovenian general long-term care facilities with 13,032 residents responded to the invitation. 317 (2.4%) of the residents received antibacterial treatment and 212 residents were included in the analysis. On average, they received 10.9 medications (SD=3.9). Antibacterials were involved in 24.1% type MA potential drug–drug interactions and 26.4% type X potential drug–drug interactions. A significant difference in the total number of potential drug–drug interaction between the two checkers was found for all antibacterials, co-trimoxazole and fluoroquinolones ($p < 0.005$). Type X and MA potential drug–drug interactions were more common with fluoroquinolones than with beta-lactams or co-trimoxazole ($p < 0.005$). **Conclusion** Potential interactions between antibacterials, especially fluoroquinolones and other drugs, were common in long-term care facility residents treated with antibacterials. Differences in the number of potential drug–drug interactions between the two checkers indicate that if available the use of several sources of information is recommended in clinical practice. The results call for a collaborative approach to address the risks of drug–drug interactions.

Keywords Antibacterials · Drug–drug interactions · Interactions checkers · Elderly · Long-term care · Slovenia

Some results of this paper were presented as a poster presentations at the European Congress of Psychiatry (EPA) in Florence (2017) and at European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) in Vienna (2017).

✉ Bojana Beović
bojana.beovic@kclj.si

¹ Faculty of Pharmacy, University of Ljubljana, Ljubljana, Slovenia

² Department for Clinical Pharmacy, Psychiatric Hospital Ormoz, Ormoz, Slovenia

³ Department of Pharmacology, Faculty of Medicine Maribor, University of Maribor, Maribor, Slovenia

⁴ Department of Infectious Diseases, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

⁵ Department of Family Medicine, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

⁶ Department of Infectious Diseases, University Medical Centre Ljubljana, Japljeva 2, 1525 Ljubljana, Slovenia

Impacts on practice

- Elderly patients are often treated with many concomitant medications. Prudent drug selection assisted by a clinical pharmacist is needed to reduce irrational polypharmacy and minimize the risk of drug–drug interactions.
- Most frequent potential antibacterial–drug interactions can be found in patients who receive fluoroquinolone antibiotics and psychotropic drugs. The interactions may be avoided, by replacement of fluoroquinolones with safer antibacterials.
- The Lexicomp and Drugs.com interactions checkers can give different results. If available, the use of several sources of information is recommended in clinical practice.

Introduction

Many residents in long-term care facilities (LTCFs) are treated with several concomitant medications that increase the probability of severe drug–drug interactions (DDIs) and treatment failure. A Canadian observational study reports that the mean number of medications per LTCF resident was 16.7 [1]. In a Belgian study including 1226 LTCF residents (mean age = 83.9), the mean number of medications per person was 9.0 (SD = 3.6, range 0–23, median = 9.0), and inappropriate prescribing was observed in many cases [2]. Mortality and morbidity are increased in patients experiencing DDIs and inappropriate prescribing [3–5].

The annual prevalence of antibacterials use in long-term care facilities (LTCFs) ranges from 47 to 79%. [6]. Some authors claim that inappropriate antibacterials prescriptions account for 25–75% of all antibacterials prescriptions in LTCFs [7, 8]. The extensive use of antibacterials does not only result in a higher risk for adverse drug reactions, but also promotes antimicrobial resistance and *Clostridium difficile* infection [9, 10]. In addition, antibacterial use may increase the risk of potential drug–drug reactions (pDDIs). A recent study by the authors on antibacterial use in psychiatric hospitals found important pDDIs between antibacterials and other medications in almost a quarter of patients treated with antibacterials. The most frequent pDDIs included co-trimoxazole and quetiapine, followed by pDDIs with ciprofloxacin [11]. Potential DDIs including antibacterials were also reported in a systematic review of 17 papers on potentially harmful DDIs in the elderly. Antibacterials, especially co-trimoxazole, macrolides, and

ciprofloxacin were involved in more than half of the combinations with DDI potential [12]. Different DDIs checkers, such as Lexicomp Online™, Drugs.com Drug Interactions Checker, and the Stockley's Interactions Checker, are used in clinical practice. Different DDIs checkers may identify different pDDIs and the results may also vary with different versions of a single DDIs checker. Thus additional information on the performance of the checkers in various settings is needed.

Drug prescribing patterns including pDDIs in LTCFs have been investigated in several studies, but there are no data on pDDIs between antibacterials and other medications in LTCFs [1, 2].

Aim of the study

The aims of this study were to investigate the prevalence of severe pDDIs between antibacterials and other medications in Slovenian LTCFs and to compare the performance of two different DDIs checkers in this setting.

Ethics approval

This study was approved by the National Medical Ethics Committee of the Republic of Slovenia (n. 0120–568/2015–4, KME 32/12/15).

Method

In 2016, Slovenia had 129 LTCFs, 12 of them specialized and 117 general, tending to approximately 18,458 residents [13]. For our point-prevalence study, we used an adapted version of the protocol developed by the European Centre for Disease Prevention and Control (ECDC) for the Point prevalence survey of healthcare-associated infections and antimicrobial use in European long-term care facilities [14]. The study was conducted from April 2016 to June 2016 in all general Slovenian LTCFs. The inclusion criteria for the study participants was that they received at least one dose of antibacterials on the day of the point-prevalence survey (PPS) and that they agreed to the survey by signing an informed consent form. In each LTCF, two researchers (DS and LU) collected the data on the residents' age, sex, medical conditions, and antibacterial treatment using an electronic case report form. The data was collected from the residents' medical records and the medication lists were printed from the LTCFs' computer systems. The medication lists were sent

to the investigators in an anonymized form using the same patient ID as in the electronic survey form. All study participants' medications were included in this study, except medications for dermal use and eye drops (including as-needed medications). Treatment with a single medication with two different substances was considered as two different medications. The paper only presents findings on pDDIs as other results including indications for antibacterial treatment have recently been described elsewhere [15].

Two different freely available DDIs checkers were used to identify pDDIs: the Lexicomp Online™ (version 3.0.2) and the online Drugs.com Drug Interactions Checker [16, 17]. Lexicomp categorizes pDDIs into five groups according to clinical significance: (A) *No known interaction.*; (B) *Specified agents may interact, but with little to no evidence for clinical concern.*; (C) *Specified agents may interact in a clinically significant manner. Monitoring therapy is suggested.*; (D) *The two medications may interact in a clinically significant manner (moderate severity), modification of therapy is suggested.*; (X) *Contraindicated combination (should be avoided).* Only type X pDDIs were included in the final analysis. Drugs.com Drug Interactions Checker categorizes pDDIs into three groups: minor interactions (minimal clinical importance), moderate interactions (medium clinical significance, to be used under special conditions), and major interactions (type MA, clinically very important, the benefit does not outweigh the risk) [16, 17]. Only type MA pDDIs were included in the analysis. The pDDIs were checked by a pharmaceutical student (IP) under the supervision of a clinical pharmacist (MS). The analysis was performed in the period from August 20, 2017 to September 30, 2017.

Baseline characteristics of residents were described as the mean \pm standard deviation (SD) or the median. The Kolmogorov–Smirnov and Shapiro–Wilk test were used to test for normality. A correlation between age and the number of prescribed medications was tested with a Spearman coefficient of correlation. A correlation between the number of prescribed medications per resident and the occurrence of both type X (Lexicomp) and MA (Drugs.com) pDDIs was also tested with a Spearman coefficient of correlation. The difference in the total number of type X and MA pDDIs was examined with a Mann–Whitney U test (independent samples). The difference in the number of type X and MA pDDIs for each antibacterial group was examined with a Wilcoxon signed-rank test (two related samples). The differences in the total number of type X and MA pDDIs between more than 2 different antibacterial groups were examined with a Kruskal–Wallis test. The statistical significance threshold was set at $p < 0.005$.

The analyses were carried out with the Statistical Package for Social Science 22.0 for Windows® (SPSS). Written

informed consent was obtained from all residents included in the study.

Results

Demographic data

Eighty (68.4%) of Slovenian general LTCFs with 13,032 residents (70.6% of the total population in general LTCFs in the country), responded to the invitation to participate in the study. On the day of the PPS, 317 (2.4%) residents were receiving antibacterials. Indications for antibacterial use and other patient and LTCF characteristics have been described in a recent paper [15]. Informed consent and a complete data collection for the analysis of pDDIs were available for 212 residents, who constituted the study population. Women outnumbered men (155 or 73.1% and 57 or 26.9%, respectively). The mean age of the residents included in the study was 84.9 (median = 85). Women were older than men (mean = 86.1 and 81.9; median = 87 and 82, respectively).

The study participants were treated with 2338 different medications, as part of regular therapy or as-needed therapy. On average, the 212 residents received 11.0 medications (median 11, maximum 33, and minimum 2) on the day of the PPS. Women were prescribed a greater number of medications, but the difference was not significant ($p = 0.429$). No correlation was found between age and the number of prescribed medications per patient ($P = 0.403$).

Antibacterial data

The most commonly prescribed antibacterial in the study was amoxicillin with clavulanic acid (88 prescriptions; 39.3% of all prescribed antibacterials), followed by ciprofloxacin (37 prescriptions; 16.5%), and co-trimoxazole (22 prescriptions; 9.8%).

Potential drug–drug interactions data from two different DDIs checkers

A positive correlation between the total number of prescribed medications per resident and the occurrence of pDDIs was found for type X DDIs (Lexicomp) and MA pDDIs (Drugs.com) (Lexicomp: $k = 0.267$; $P < 0.005$; Drugs.com: $k = 0.339$; $P < 0.005$).

The analysis with Lexicomp Online™ detected 110 type X pDDIs (48 unique combinations). At least one pDDI was detected in 66 residents (31.1%). The maximum number of different type X pDDIs per patient was six.

29 type X pDDIs with antibacterials were detected with the Lexicomp checker, which is 26.4% of all type X pDDIs in this study (0.14 type X pDDIs per participant). The most

common antibacterial that interacted was ciprofloxacin, involved in 18 type X pDDIs (62.1% of all type X pDDIs with antibacterials, and 16.3% of all detected type X pDDIs), followed by moxifloxacin (Tables 1 and 2).

264 type MA pDDIs were detected with the Drugs.com checker and 134 of them were unique. In 123 residents (58.0%), Drugs.com detected at least one type MA pDDI. The maximum number of different pDDIs per resident was eight. The most common medication included in type MA pDDIs was tramadol with 95 pDDIs (36.0% of all type MA pDDIs). Antibacterials were involved in 64 cases (24.1% of all type MA pDDIs). The most common antibacterial-related

pDDI was between ciprofloxacin and tramadol. The results are summarized in Tables 1 and 2.

Significant differences in the frequency of type MA and X pDDIs were found between the antibiotic groups. Type X and MA pDDIs were detected in 36% (13 cases) and 62% (23 cases) of fluoroquinolone prescriptions, respectively. The comparison of individual antibacterial groups revealed that significantly more type X pDDIs were observed with fluoroquinolones than with beta-lactams or co-trimoxazole, while only the difference between fluoroquinolones and beta-lactams was statistically significant for type MA pDDIs (Table 2).

Table 1 Frequencies and percentages of pDDIs with antibiotics in the study

Name of DDI	Frequency of MA pDDI Drugs.com	Percentage of pDDI (%) Drugs.com	Frequency of X pDDI Lexicomp	Percentage of pDDI (%) Lexicomp
Amoxicillin-methotrexate	1	1.6	0	0
Azithromycin-amiodarone	1	1.6	1	3.4
Azithromycin-escitalopram	1	1.6	1	3.4
Azithromycin-haloperidol	2	3.1	0	0
Azithromycin-quetiapine	0	0	1	3.4
Ciprofloxacin-amiodarone	1	1.6	1	3.4
Ciprofloxacin-domperidone	0	0	1	3.4
Ciprofloxacin-duloxetine	2	3.1	2	6.9
Ciprofloxacin-escitalopram	1	1.6	1	3.4
Ciprofloxacin-haloperidol	6	9.4	0	0
Ciprofloxacin-ivabradine	0	0	1	3.4
Ciprofloxacin-oxycodone	2	3.1	0	0
Ciprofloxacin-tramadol	14	21.9	0	0
Ciprofloxacin-sotalol	0	0	1	3.4
Ciprofloxacin-quetiapine	0	0	11	37.9
Ciprofloxacin-warfarin	6	9.4	0	0
Levofloxacin-tramadol	2	3.1	0	0
Levofloxacin-quetiapine	0	0	1	3.4
Moxifloxacin-sertraline	1	1.6	0	0
Moxifloxacin-escitalopram	3	4.7	3	10.3
Moxifloxacin-methylprednisolone	1	1.6	0	0
Moxifloxacin-mirtazapine	1	1.6	0	0
Moxifloxacin-quetiapine	4	6.3	4	13.8
Moxifloxacin-risperidone	2	3.1	0	0
Moxifloxacin-tramadol	2	3.1	0	0
Moxifloxacin-warfarin	1	1.6	0	0
Norfloxacin-tramadol	2	3.1	0	0
Trimethoprim-perindopril	4	6.3	0	0
Trimethoprim-potassium chloride	2	3.1	0	0
Trimethoprim-ramipril	1	1.6	0	0
Trimethoprim-valsartan	1	1.6	0	0
Total	64	100.0	29	100.0

^aMA, major drug interaction in Drugs.com online drug interaction checker

^aX, “should be avoided” interaction in Lexicomp Online interaction checker

^bpDDI, potential drug–drug interaction

Table 2 The number of X and MA pDDIs between antibiotics and other concomitant medications in LTCF residents and eventual statistical differences between both programs and between different antibiotic groups

Prescribed antibiotic	N antibiotic prescriptions	N of antibiotic prescriptions with X ^a pDDI ^c (%)	N of antibiotic prescriptions with MA ^b pDDI ^c (%)	The difference between the X ^a and MA ^b pDDIs ^c (X DDI/MA pDDI)
Fluoroquinolones	47	17 (36.0)	29 (61.7)	$P < 0.005$
Beta-lactam antibiotics	123	1 (0.8)	1 (0.8)	NS ($P = 0.317$)
Macrolides	4	2 (50.0)	3 (75)	NS ($P = 0.157$)
Co-trimoxazole	19	0	9 (36.4)	$P < 0.005$
Others	19	5 (26.3)	4 (21.1)	NS ($P = 0.317$)
Total	212	25 (11.8)	46 (21.7)	$P < 0.005$
Between groups difference (all groups)		$P < 0.005$	$P < 0.005$	
Between groups difference		(1 vs. 2) $P < 0.005$	(1 vs. 2) $P < 0.005$	
		(1 vs. 4) $P < 0.005$	(1 vs. 4) $P = 0.062$	
		(2 vs. 4) $P = 0.694$	(2 vs. 4) $P < 0.005$	

Macrolides were not compared because small sample size; n = 4

^aX “should be avoided” interaction in Lexicomp Online interaction checker

^bMA major drug interaction in Drugs.com online drug interaction checker

^cpDDI potential drug–drug interactions

Discussion

Our study found that antibacterials were involved in 29 (26.4%) out of 110 type X pDDIs and 64 (24.2%) out of 264 type MA pDDIs. The Lexicomp Online analysis showed that one half of residents prescribed fluoroquinolones was at risk for severe type X DDIs, and the risk appeared even higher using the Drugs.com criteria. Macrolides were only prescribed to four residents, but were involved in three type X pDDIs and type MA pDDIs. Co-trimoxazole was involved in type MA pDDIs in one-third of its prescriptions. Beta-lactams and other antibacterials appeared to be much safer than fluoroquinolones and co-trimoxazole. In 24 out of 29 cases of potentially critical combinations, antibacterials were combined with psychotropic drugs. Frequent pDDIs involving antibacterials and psychotropic drugs were found in our previous analysis of antibacterial prescribing patterns in psychiatric wards [11]. A Norwegian study reported that antibacterials were not involved in pDDIs and a previous extensive Scandinavian study in the elderly did not find antibacterials among the 10 most common drug combinations that need dose adjustment, or in the 10 most common combinations that should be avoided because of potential adverse events, which might be related to the fact that Norway for years have had a very strict policy on antibiotics [18, 19].

On the day of the PPS, the study participants received 11.0 medications on average. Polypharmacy has been observed in other studies in LTCF residents. In recent studies

from different parts of the world, the number of medications ranged from four to 16 per LTCF resident [8, 20]. Our study corroborates several studies showing that polypharmacy increases the risk of DDIs [20]. The prevalence of type MA and X pDDIs (X as defined by Lexicomp and MA by the Drugs.com Drug Interactions Checker) in our study was 110 and 264 per 212 residents, respectively. Other studies have shown significant DDIs in geriatric patients, yet specific data on the situation in LTCFs is scarce. A Brazilian study using the Micromedex database found 256 potential interactions in 132 LTCF residents [20]. In a Norwegian study, 15 (1.2%) out of 1241 residents received drug combinations classified as “should not be combined” by the Norwegian Drug database and 592 (47.7%) combinations classified as “take precautions” [20]. Increased risk of mortality and morbidity related to DDIs [3–5] calls for the reduction of irrational polypharmacy in the elderly.

A very important finding of this study is that pDDIs checkers differ significantly in their ability to detect severe pDDIs which can have an impact on the clinical usefulness of different pDDIs checkers. The checkers differed in the total number of identified medications and diverged on some pDDIs, most notably for combinations involving co-trimoxazole or a fluoroquinolone. The differences could be explained by the different data sources used by the DDIs checkers. Although they are both US databases, they include a different degree of non-US approved medicines and foreign studies [16, 17]. The checkers also differ in the definition

and grading of DDIs. In our study, the pDDI between tramadol and co-trimoxazole was not detected by Lexicomp but it would have been if type D and C DDIs had been included. This study should be replicated for all pDDI classes not included in this study for greater representativeness. The difference in the sensitivity of different checkers has been reported in a study on observed adverse DDIs, which found Complete Drug Interaction (0.76) the most sensitive, followed by Lexicomp Online (0.50), and the Drug Interaction Checker (0.40) [21]. In addition to the differences between the two databases, the differences between various versions of a single DDIs checker should be considered, since both DDIs checkers are being updated regularly.

The results of this study have many practical implications. A high number of pDDIs including fluoroquinolones can be avoided by replacing them with other safer drugs for respiratory infections, such as penicillins and cephalosporins, in accordance with national guidelines and resistance rates. Nitrofurantoin, fosfomycin, and beta-lactams can be used in some cases for lower urinary tract infections [22, 23]. Recently, the European Medicines Agency (EMA) has recommended restrictions on the use of fluoroquinolone and quinolone antibacterials following a review of disabling and potentially long-lasting side effects mostly affecting the locomotor and nervous systems that were reported with these medicines, another reason to restrict fluoroquinolones [24].

Because antibacterial treatments are usually short and the patients already use medications for chronic diseases when the antibacterial is added, we suggest to select an antibacterial with a favourable interaction profile, and switching the medications for chronic diseases only if needed. Some pDDIs found in this study could have been avoided by using various tools and approaches appropriate for elderly patients (e.g. START/STOPP and Priscus list) [25–28]. The majority of antibiotics in Slovenia are prescribed by GPs [15], which means that further interventions in this field are needed, such as the inclusion of clinical pharmacists in the pharmacotherapy of LTCF residents, the wider use of computerized physician order entries, quick interaction checkers, and the development of LTCF-specific guidelines [27].

This study has several important limitations. The most important one is the lack of information on the duration of antibacterial and other treatments because of the point-prevalence design of the study. The pDDIs were also examined 1 year after data collection, which can impact the results because of checker updates. The study only used two DDIs checkers commonly used in Slovenia and produced divergent results from them, so future studies could include additional checkers, such as the Stockley's Interactions Checker. The study only included potential and not observed DDIs [16] and did not examine the consequences of observed DDIs in the study period (e.g. hospitalizations and important harms).

The study also did not control for appropriate medication dosing, which can have an impact on dose-dependent aspects of DDIs (e.g. QT prolongation). Though prospective studies in clinical settings are needed to address these limitations, this study is the first to our knowledge that elucidates the problem of pDDIs in LTCF residents treated with antibacterials.

Conclusion

Antibacterial treatment is a critical event in LTCF residents because of the risk of clinically important pDDIs. Observing national guidelines and resistance rates, the risk of severe pDDIs in LTCFs can be reduced by replacing fluoroquinolones with beta-lactam antibacterials as well as prudent prescribing, especially of psychotropic drugs. DDIs checkers differ significantly in their ability to detect severe pDDIs, which suggests that more than one checker should be used in clinical practice. Future measures to reduce antibacterial-related DDIs could include antimicrobial stewardship interventions, the inclusion of clinical pharmacists in the pharmacotherapy of LTCF residents, wider use of computerized physician order entries, quick interaction checkers, and the development of LTCF-specific national guidelines.

Funding None.

Conflicts of interest The authors declare that they have no conflict of interest.

References

1. Andrew MK, Purcell CA, Marshall EG. Polypharmacy and use of potentially inappropriate medications in long-term care facilities: does coordinated primary care make a difference? *Int J Pharm Pract.* 2017;1:11. <https://doi.org/10.1111/ijpp.12397>.
2. Janssens B, Petrovic M, Jacquet W. Medication use and its potential impact on the oral health status of LTCF residents in Flanders (Belgium). *J Am Med Dir Assoc.* 2017;18:809.e1–8.
3. Hajjar ER, Cafiero AC, Hanlon JT. Polypharmacy in elderly patients. *Am J Geriatr Pharmacother.* 2007;5:345–51.
4. Gallagher PF, Barry PJ, Ryan C, Hartigan I, O'Mahony D. Inappropriate prescribing in an acutely ill population of elderly patients as determined by Beers' Criteria. *Age Ageing.* 2008;37:96–101.
5. Dechanont S, Maphanta S, Butthum B, Kongkaew C. Hospital admissions/visits associated with drug–drug interactions: a systematic review and meta-analysis. *Pharmacoepidemiol Drug Saf.* 2014;23:489–97.
6. Buil LW, van Steen JT, van der Veenhuizen RB, Achterberg WP, Schellevis FG, Essink RT, et al. Antibiotic use and resistance in long term care facilities. *J Am Med Dir Assoc.* 2012;13:568.e1–13.
7. Fleming A, Browne J, Byrne S. The effect of interventions to reduce potentially inappropriate antibiotic prescribing in

- long-term care facilities: a systematic review of randomised controlled trials. *Drugs Aging*. 2013;30:401–8.
8. Stuart RL, Wilson J, Bellaard-Smith E, Brown R, Wright L, Vandergraaf S, et al. Antibiotic use and misuse in residential aged care facilities. *Intern Med J*. 2012;42:1145–9.
 9. Drinka PJ, Crnich CJ, Nace DA. An antibiotic prescription induces resistance at the individual level more than the group level. *J Am Med Dir Assoc*. 2013;14:707–8.
 10. Malani AN, Brennan BM, Collins CD, Finks J, Pogue JM, Kaye KS. Antimicrobial stewardship practices in michigan long-term care facilities. *Infect Control Hosp Epidemiol*. 2016;37:236–7.
 11. Beovic B, Plesnicar BK, Potocan M, Zmitek A, Winkler V, Celan SS, et al. Antibiotic prescribing in psychiatric hospitals and interactions between antibiotics and psychotropic drugs: a prospective observational study. *Infect Control Hosp Epidemiol*. 2016;37:233–5.
 12. Hines LE, Murphy JE. Potentially harmful drug–drug interactions in the elderly: a review. *Am J Geriatr Pharmacother*. 2011;9:364–77.
 13. The Association of Social Institutions in Slovenia. (2016) Highlights from analyzes. <http://www.ssz-slo.si/wp-content/uploads/Poudarki-iz-komulativnega-statistike-iz-letnega-poročila-za-letno-2016.pdf>. Accessed 10 Oct 2017.
 14. European Centre for Disease Prevention and Control (ECDC) Point prevalence survey of healthcare-associated infections and antimicrobial use in European long-term care facilities. April–May 2013. Stockholm: ECDC. 2014. <https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/healthcare-associated-infections-point-prevalence-survey-long-term-care-facilities-2013.pdf>. Accessed 10 Oct 2017.
 15. Stepan D, Ušaj L, Petek Šter M, Smolinger Galun M, Smole H, Beović B. Antimicrobial prescribing in long-term care facilities: a nationwide point-prevalence study, Slovenia 2016. *Euro Surveill*. 2018;1:11. <https://doi.org/10.2807/1560-7917.ES.2018.23.46.1800100>.
 16. Lexicomp-Clinical Drug Information. 2018. <https://online.lexi.com/lco/action/home>. Accessed 10 Oct 2017.
 17. Drug Interactions Checker. 2018. https://www.drugs.com/drug_interactions.html. Accessed 10 Oct 2017.
 18. Søråas IA, Staurset HB, Slørdal L, Spigset O. Drug–drug interactions in nursing home patients. *Tidsskr Nor Laegeforen*. 2014;134:1041–6.
 19. Björkman IK, Fastbom J, Schmidt IK, Bernsten CB, Pharmaceutical Care of the Elderly in Europe Research (PEER) Group. Drug–drug interactions in the elderly. *Ann Pharmacother*. 2002;36:1675–81.
 20. Alves-Conceição V, Silva DTD, Santana VL, Santos EGD, Santos LMC, Lyra DP Jr. Evaluation of pharmacotherapy complexity in residents of long-term care facilities: a cross-sectional descriptive study. *BMC Pharmacol Toxicol*. 2017;18:59.
 21. Muhič N, Mrhar A, Brvar M. Comparative analysis of three drug–drug interaction screening systems against probable clinically relevant drug–drug interactions: a prospective cohort study. *Eur J Clin Pharmacol*. 2017;73:875–82.
 22. Bonkat G, Bartoletti RR, Bruyère F, Cai T, Geerlings SE, Köves B, et al. Urological infections. *Eur Assoc Urol*. 2019. <https://uroweb.org/guideline/urological-infections/#1>. Accessed 15 May 2019.
 23. Lim WS, Boudouin SV, George RC, Hill AT, Jamieson C, Le Jeune I, et al. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. *Thorax*. 2009;64(Suppl 3):iii1–55.
 24. European Medicines Agency. Disabling and potentially permanent side effects lead to suspension or restrictions of quinolone and fluoroquinolone antibiotics. European Medicines Agency. 2019. <https://www.ema.europa.eu/en/medicines/human/referrals/quinolone-fluoroquinolone-containing-medicinal-products>. Accessed 15 May 2019.
 25. Holt S, Schimedel S, Thürmann AP. Potentially inappropriate medications in the elderly: the PRISCUS list. *Dtsch Arztebl Int*. 2010;107:543–51.
 26. Gallagher P, Ryan C, Byrne S, Kennedy J, O’Mahony D. STOPP (screening tool of older person’s prescriptions) and START (screening tool to alert doctors to right treatment) consensus validation. *Int J Clin Pharmacol Ther*. 2008;46:72–83.
 27. Gorup EC, Šter MP. Number of medications or number of diseases: what influences underprescribing? *Eur J Clin Pharmacol*. 2017;73:1673–9.
 28. Gorup EC, Šter MP, Klančič D. Polypharmacy and inappropriate drug prescribing in elderly nursing home residents. *Zdrav vestn*. 2009;78:231–40.

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.