Age and Ageing 2023; **52:** 1–5
https://doi.org/10.1093/ageing/afac278

SHORT REPORT

Drug–drug interactions in nursing home residents: analysis from the COME-ON trial

Simon Lion[1,†], Perrine Evrard[1,†], Veerle Foulon[2], Anne Spinewine[1,3]

[1]Clinical Pharmacy Research Group, Louvain Drug Research Institute, UCLouvain, Brussels, Belgium
[2]Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium
[3]Pharmacy Department, UCLouvain, CHU UCL Namur, Yvoir, Belgium

Address correspondence to: Anne Spinewine, Avenue E. Mounier 72/B1.72.02, Brussels 1200, Belgium.
Email: anne.spinewine@uclouvain.be
[†]These authors contributed equally.

Abstract

Background: as a result of the high prevalence of polypharmacy in nursing homes (NHs), nursing home residents (NHRs) are exposed to numerous drug–drug interactions (DDIs) that can lead to adverse drug effects, and increased morbidity and mortality.
Objectives: to evaluate (i) the prevalence of DDIs among NHRs and its evolution over time, and (ii) factors associated with a favourable evolution.
Design: posthoc analysis of the COME-ON study, a cluster-randomised controlled trial aiming at reducing potentially inappropriate prescriptions in NHs, through the implementation of a complex intervention.
Setting and subjects: 901 NHRs from 54 Belgian NHs.
Methods: DDIs were identified using a validated list of 66 potentially clinically relevant DDIs in older adults. We defined a favourable evolution at 15 months as the resolution of at least one DDI present at baseline, without the introduction of any new DDI. Factors associated with a favourable evolution were analysed using multivariable logistic regression.
Results: at baseline, 475 NHRs (52.7%) were exposed to at least 1 DDI and 225 NHRs (25.0%) to more than one DDI. Most common DDI was 'Concomitant use of at least three central nervous system active drugs'. At 15 months, we observed a 6.3% absolute decrease in DDI prevalence in intervention group, and a 1.0% absolute increase in control group. The intervention, older age and private NH ownership were significantly associated with a favourable DDI evolution.
Conclusion: a high prevalence of DDI in Belgian NHs was observed, but the COME-ON intervention was associated with a favourable evolution over time.

Keywords: drug–drug interactions, nursing homes, older adults, polypharmacy, older people

Key Points

- At baseline, 52.7% of nursing home residents were exposed to at least one drug–drug interaction (DDI), and 25.0% to more than one DDI.
- Over a 15-month period, we observed a 6.3% absolute decrease in DDI prevalence in intervention group, and a 1.0% absolute increase in control group.
- Being in the intervention arm, older age and a private nursing home ownership were associated with a favourable evolution over time.

Introduction

Polypharmacy is highly prevalent in the nursing home (NH) setting, with 91 and 65% of nursing home residents (NHRs) taking >5 and 10 medications respectively [1]. Polypharmacy is associated with an increased risk of drug–drug interactions (DDIs) [2]. DDIs occur when two or more drugs interact on a pharmacokinetic and/or a pharmacodynamic level, with the risk of increasing the toxicity or reducing the effect of one or more of the involved drugs. This is a particular concern in NHRs, a frail population with increased sensitivity to adverse drug reactions. For example, the concomitant intake of hyperkalaemia inducing drugs led to a 20-fold increase in the risk of hospitalisation among older people with heart failure [3]; likewise, part of the observed excess risk of death associated with the use of antipsychotic medications in NHRs with cognitive impairment was found to be attributable to antipsychotic DDIs [4].

DDI prevalence in NHRs ranges between 38 and 88% for DDIs of any severity, and between 10 and 40% for potentially moderate to severe DDIs [5–7]. These data come from a limited number of studies, mainly retrospective and cross-sectional, which used commercial DDI databases to identify potential DDI. Evolution of DDIs over time and factors associated with reduction of DDIs remain largely unknown in the NH setting.

Approaches to reduce DDIs in older adults include education of physicians, computerised decision support, medication review and collaborative approaches involving pharmacists [8]. Data from randomised controlled trials (RCTs) about medication review in NHs indicate that DDIs are part of the drug-related problems addressed during the medication review process, yet the occurrence of DDI was not part of the outcome measures [9, 10]. This is an important research gap, as DDIs have been identified as core outcomes to measure in medication optimisation trials, including in the NH setting [11, 12].

The COME-ON study was a cluster RCT evaluating the effect of a complex intervention on potentially inappropriate prescriptions (PIPs) in NHs [13]. Its positive impact on PIPs [14] and benzodiazepine receptor agonists [15] has been reported, yet the effect on DDIs had not been evaluated. Consequently, we aimed to evaluate (i) the prevalence of DDIs at baseline and their evolution over time—both in the overall sample and in each trial arm; and (ii) factors associated with DDI reduction over time.

Methods

The COME-ON study

The protocol and results of the COME-ON study, including 1,804 NHRs in 54 Belgian NHs, were described elsewhere [13, 14]. Briefly, the intervention encompassed e-learning and training for health care providers (HCPs), multidisciplinary local concertation and interdisciplinary case conferences (ICCs). Although the intervention did not focus specifically on DDIs, these were approached in the e-learning, and could be discussed in ICCs. In particular, many pharmacists considered it an important contribution to medication review to check for DDI. In addition, pharmacists could also use their software to support the identification of DDIs. Participating HCPs collected nursing home resident (NHR)-specific data at three study points: baseline, month 8 and month 15 (end of study). The ethical committee at UZ/KULeuven approved the COME-ON study, and it has been registered at http://www.isrctn.com/ (trial registration number: ISRCTN66138978).

Eligibility criteria

For the present work, we included participants with complete data at both baseline and end of study.

Identification of DDIs

DDIs were identified using a detection algorithm in R software based on a list of 66 potentially clinically significant DDIs in older people validated by a group of international experts [16]. Compounded medications had no Anatomical Therapeutic Chemical (ATC) codes in the trial database and were therefore not considered. Evolution from baseline to end of study was evaluated for each NHR and considered favourable if at least one DDI present at baseline was not present anymore at the end of the study (i.e. when one of the interacting drugs had been discontinued), without a new DDI being introduced.

Factors associated with favourable evolution

We evaluated potential factors associated with favourable DDI evolution, among NHRs with at least one DDI at baseline, using logistic regression. The list of 31 factors analysed was selected from literature review and discussions between the authors (Appendix 1). All variables associated with the outcome in univariate analysis with $P < 0.15$ were candidates for the multivariable model. A stepwise selection based on the Akaike information criterion was then applied to select the final multivariable model and variables with a variance inflation factor above five were excluded.

Statistical analysis

All analyses were performed using R software version 4.0.3 (R Foundation for statistical computing, Vienna, Austria).

Results

A total of 901 NHRs were included. Median age was 86 (interquartile range, IQR: 81–89). The median number of drugs taken was 8 (IQR: 6–10). Baseline data are provided in Appendix 2.

DDI prevalence and evolution over time

At baseline, 475 (52.7%) NHRs (25.0%) were exposed to at least 1 DDI (Table 1). The most common DDIs

Table 1. Prevalence and characteristics of DDIs at baseline and end of study

	Total sample		Control group		Intervention group	
	N = 901		*N* = 396		*N* = 505	
	Baseline	End	Baseline	End	Baseline	End
Overall number of DDIs per resident						
Median (P25; P75)	1 (0; 1)	0 (0; 1)	0 (0; 1)	0 (0; 1)	1 (0; 2)	0 (0; 1)
Range (Min–Max)	0–8	0–9	0–6	0–6	0–8	0–9
Residents with ≥1 DDI, *n* (%)	475 (52,7)	447 (49,6)	193 (48,7)	197 (49,7)	282 (55,8)	250 (49,5)
1 DDI	250 (27,7)	244 (27,1)	111 (28,0)	114 (28,8)	139 (27,5)	130 (25,7)
2 DDI	113 (12,5)	91 (10,1)	35 (8,8)	30 (7,6)	78 (15,4)	61 (12,1)
3 DDI	59 (6,5)	66 (7,3)	29 (7,3)	33 (8,3)	30 (5,9)	33 (6,5)
≥ 4 DDI	53 (5,9)	46 (5,1)	18 (4,5)	20 (5,1)	35 (6,9)	26 (5,1)
Residents with ≥1 pharmacodynamic DDI, *n* (%)	458 (50.8)	430 (47.7)	184 (46.5)	188 (47.5)	274 (54.3)	242 (47.9)
Residents with ≥1 pharmacokinetic DDI, *n* (%)	52 (5.8)	45 (5.0)	23 (5.8)	22 (5.6)	29 (5.7)	23 (4.6)
Residents with ≥1 mixt DDI (pharmacodynamic + pharmacokinetic), *n* (%)	4 (0.4)	1 (0.1)	1 (0.25)	1 (0.25)	3 (0.6)	0 (0)
Residents with ≥1 DDI with unknown mechanism, *n*(%)	1 (0.1)	1 (0.1)	0 (0)	1 (0.25)	1 (0.2)	0 (0)
Prevalence of individual DDIs, for the 10 most prevalent DDIs at baseline						
	Total sample		**Control group**		**Intervention group**	
	***N* = 901**		***N* = 396**		***N* = 505**	
DDIs, n of residents (%)	**Baseline *n* (%)**	**End *n* (%)**	**Baseline *n* (%)**	**End *n* (%)**	**Baseline *n* (%)**	**End *n* (%)**
Concomitant use of ≥3 CNS drugs	294 (32,6)	290 (32,2)	116 (29,3)	123 (31,1)	178 (35,2)	167 (33,1)
Oral NSAID + SSRI or SNRI	116 (12,9)	102 (11,3)	49 (12,4)	48 (12,1)	67 (13,3)	54 (10,7)
SSRI + loop or thiazide diuretic	85 (9,4)	77 (8,5)	32 (8,1)	29 (7,3)	53 (10,5)	48 (9,5)
SSRI + another serotoninergic drug	81 (9,0)	81 (9,0)	31 (7,8)	32 (8,1)	50 (9,9)	49 (9,7)
Concomitant use of ≥2 potassium-conserving drugs	51 (5,7)	41 (4,6)	21 (5,3)	20 (5,1)	30 (5,9)	21 (4,2)
Concomitant use of ≥2 drugs that reduce potassium	44 (4,9)	51 (5,7)	15 (3,8)	23 (5,8)	29 (5,7)	28 (5,5)
Acetylcholinesterase inhibitor + drug that reduces heart rate	42 (4,7)	28 (3,1)	13 (3,3)	13 (3,3)	29 (5,7)	15 (3,0)
Simvastatin + amlodipine	26 (2,9)	19 (2,1)	12 (3,0)	12 (3,0)	14 (2,8)	7 (1,4)
Diuretic + oral NSAID	20 (2,2)	16 (1,8)	9 (2,3)	8 (2,0)	11 (2,2)	8 (1,6)
Antiplatelet drug (including aspirin) + oral NSAID	19 (2,1)	13 (1,4)	7 (1,8)	7 (1,8)	12 (2,4)	6 (1,2)

CNS, central nervous system; DDI, drug–drug interaction; NHR, nursing home resident; NSAID, non-steroidal anti-inflammatory drug; SNRI, serotonin and noradrenaline reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor.

were 'Concomitant use of at least three central nervous system active drugs' (*n* = 294; 32.6%), 'Oral non-steroidal anti-inflammatory drug plus selective serotonin reuptake inhibitor or serotonin and noradrenaline reuptake inhibitor' (*n* = 116; 12.9%) and 'Selective serotonin reuptake inhibitor plus loop or thiazide diuretic' (*n* = 85; 9.4%). Prevalence data for the complete list of 66 DDIs is available in Appendix 3.

At the end of study, the percentage of NHRs with at least one DDI decreased to 49.6%, with contrasting results by intervention arm (−6.3% in the intervention group, versus +1.0% in the control group). Among the 10 most prevalent DDIs at baseline, a lower prevalence at end of study was observed for all DDIs in the intervention group and for four DDIs in the control group (Table 1).

Factors associated with favourable evolution

Among the 475 NHRs with at least one DDI at baseline, 136 (28.6%) had a favourable evolution over time. In the multivariate analysis, three factors were found to be associated with a statistically significant favourable evolution: study arm, age and ownership status of the NH (Table 2). No significant association was found with comorbidities or medications taken.

Discussion

In this secondary analysis of the COME-ON trial, we found that more than half of NHRs had at least one DDI at baseline, and that being in the intervention arm was associated with a significant favourable evolution over time. To the best of our knowledge, this is the first controlled trial in the NH setting to report DDI prevalence and evolution over time, as well as factors associated with reduction in DDIs.

The prevalence of DDIs in our study is similar to the prevalence found in the European OPERAM (Optimising Therapy to prevent avoidable hospital admissions in the multimorbid elderly) trial that included older adults with multimorbidity and polypharmacy admitted to hospital (52.7 and 53.6%, respectively) [17]. In both studies, most DDIs were pharmacodynamic in nature. However, the prevalence of DDIs involving psychotropic drugs was much higher in the present study. The overuse of psychotropic drugs remains a substantial concern in NHs [18–20]. Given the association of psychotropic DDIs with increased morbidity and mortality [4], this must be a priority target for the future.

Data from the intervention group showed a 6.3% absolute decrease in prevalence over time, and being in the intervention arm was significantly associated with a favourable

Table 2. Factors associated with a favourable evolution among NHRs with at least one DDI at baseline, in the final multivariable logistic regression model ($N = 475$)

Variable	Univariate model		Multivariable model	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Study arm				
Intervention versus control	1.97 (1.30;3.05)	0.002*	2.28 (1.45;3.64)	<0.001*
Patient's baseline characteristics				
Age				
65–84	1		1	
≥85	1.75 (1.16;2.66)	0.008*	1.74 (1.14;2.69)	0.012*
Medications at baseline				
Number of medications				
0–9	1		1	
≥10	1.37 (0.92;2.06)	0.125	1.43 (0.94;2.19)	0.097
Comorbidities at baseline				
Falls in the past 3 months	1.49 (0.93;2.35)	0.091	1.49 (0.91;2.42)	0.105
Depression	0.72 (0.48; 1.08)	0.111	0.70 (0.46;1.06)	0.091
NH characteristics				
Ownership status				
Public	1		1	
Private non for profit	1.55 (0.98;2.50)	0.065	1.62 (1.01;2.67)	0.051*
Private for profit	1.92 (0.81;4.38)	0.128	2.86 (1.14; 7.07)	0.023*

CI, confidence interval; CIRS-G, cumulative illness rating scale—geriatric; DDI, drug–drug interaction; NH, nursing home; NHR, nursing home interaction; OR, odds ratio. *: statistically significant ($P < 0.05$) The complete results from analysis are available in Appendix 5.

evolution. This is an important finding, for a trial in which DDIs were not the main focus of the intervention. There remains much opportunity for further improvement. One important opportunity to further reduce DDIs is to enhance deprescribing of medications for which there is no (or no longer) valid indication. Better addressing barriers to deprescribing at the patient and professional levels is needed. There have been a few reports on DDIs from uncontrolled intervention studies in NHs showing no to substantial effect [21–23]. For example, Pasina *et al*. found that education of prescribers and computerised decision support reduced the prevalence of potentially severe psychotropic DDIs from 53.3 to 32.0%, but validity of the findings is limited by the uncontrolled pilot nature of the study [22].

Apart from intervention arm, private ownership of the NH and older age were significantly associated with a favourable evolution in DDIs. We previously reported a similar association between NH ownership and benzodiazepines receptor agonists deprescribing, which might be due to a difference in organisational culture [15]. The positive effect of age might be indirectly related with more attention towards medication overuse with increasing age or with more deprescribing of preventive medications. Our results also suggest a trend towards better evolution in NHRs taking a higher number of drugs. This is good news, given that the risk of DDIs increases with the number of drugs taken.

Our study has several limitations. First, we identified 'potential' DDIs and not 'actual' DDIs (i.e. DDIs resulting in adverse drug events or treatment failure). Many of these DDIs might have been appropriate at patient level, if adequate management measures are taken. Likewise, some DDIs might have been resolved at the patient level while keeping both drugs prescribed (e.g. by applying dose reductions or increasing monitoring), although a signal for DDI was retained in the sample. Nevertheless, we detected DDIs using a list of 66 DDIs validated for use in older adults by an international panel, and the presence of such DDI remains a strong signal that should alert the prescriber. Second, DDIs were measured on a subgroup of NHRs with complete data at baseline and end of study. The characteristics of included and excluded NHRs are overall similar, except that there were more NHRs from the control arm among excluded NHRs (Appendix 4). Caution in interpretation is however required, as missing data were more frequent in the group of excluded NHRs. Third, we excluded compounded drugs. As these mainly included calcium and riboflavin, which are drugs not listed in the 66 DDIs, this is not an important source of bias.

Conclusion

The prevalence of DDIs among Belgian NHRs is very high, and a complex intervention to optimise the use of drugs in this population was associated with decreased occurrence of DDIs. Additional efforts are required to curb psychotropic DDIs, and to document adverse consequences of potential DDIs.

Supplementary Data: Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

Declaration of Conflicts of Interest: None.

Declaration of Sources of Funding: The COME-ON project was supported by the National Institute for Health

and Disability Insurance (Belgium). The funding body had a limited role in the design of the COME-ON study, but it had no role in data collection, implementation, analysis or the decision to publish the results.

Data Availability Statement: Part of the data generated or analyzed during this study is included in this article and its supplementary information files or is available from the corresponding author on reasonable request. The full datasets generated or analyzed during the current study are not publically available because consent to make data publically available was not part of the consent by participants.

References

1. Jokanovic N, Tan EC, Dooley MJ, Kirkpatrick CM, Bell JS. Prevalence and factors associated with polypharmacy in long-term care facilities: a systematic review. J Am Med Dir Assoc 2015; 16: 535.e1–12.
2. Salazar JA, Poon I, Nair M. Clinical consequences of polypharmacy in elderly: expect the unexpected, think the unthinkable. Expert Opin Drug Saf 2007; 6: 695–704.
3. Juurlink DN, Mamdani M, Kopp A, Laupacis A, Redelmeier DA. Drug-drug interactions among elderly patients hospitalized for drug toxicity. JAMA 2003; 289: 1652–8.
4. Liperoti R, Sganga F, Landi F *et al.* Antipsychotic drug interactions and mortality among nursing home residents with cognitive impairment. J Clin Psychiatry 2017; 78: e76–82.
5. Bories M, Bouzille G, Cuggia M, Le Corre P. Drug-drug interactions in elderly patients with potentially inappropriate medications in primary care, nursing home and hospital settings: a systematic review and a preliminary study. Pharmaceutics 2021; 13: 266–89.
6. Iniesta-Navalon C, Gascon-Canovas JJ, Gama Z *et al.* Potential and clinical relevant drug-drug interactions among elderly from nursing homes: a multicentre study in Murcia, Spain. Cien Saude Colet 2019; 24: 1895–902.
7. Pasina L, Novella A, Cortesi L, Nobili A, Tettamanti M, Ianes A. Drug prescriptions in nursing home residents: an Italian multicenter observational study. Eur J Clin Pharmacol 2020; 76: 1011–9.
8. Mallet L, Spinewine A, Huang A. The challenge of managing drug interactions in elderly people. Lancet 2007; 370: 185–91.
9. Alldred DP, Kennedy MC, Hughes C, Chen TF, Miller P, Cochrane effective practice and organisation of care group. Interventions to optimise prescribing for older people in care homes. Cochrane Database Syst Rev 2016; 2: CD009095. https://doi.org/10.1002/14651858.CD009095.pub3.
10. Spinewine A, Evrard P, Hughes C. Interventions to optimize medication use in nursing homes: a narrative review. Eur Geriatr Med 2021; 12: 551–67.
11. Beuscart JB, Knol W, Cullinan S *et al.* International core outcome set for clinical trials of medication review in multimorbid older patients with polypharmacy. BMC Med 2018; 16: 21. https://doi.org/10.1186/s12916-018-1007-9.
12. Millar AN, Daffu-O'Reilly A, Hughes CM *et al.* Development of a core outcome set for effectiveness trials aimed at optimising prescribing in older adults in care homes. Trials 2017; 18: 175. https://doi.org/10.1186/s13063-017-1915-6.
13. Anrys P, Strauven G, Boland B *et al.* Collaborative approach to optimise MEdication use for older people in nursing homes (COME-ON): study protocol of a cluster controlled trial. Implement Sci 2015; 11: 35. https://doi.org/10.1186/s13012-016-0394-6.
14. Strauven G, Anrys P, Vandael E *et al.* Cluster-controlled trial of an intervention to improve prescribing in nursing homes study. J Am Med Dir Assoc 2019; 20: 1404–11.
15. Evrard P, Henrard S, Foulon V, Spinewine A. Benzodiazepine use and deprescribing in Belgian nursing homes: results from the COME-ON study. J Am Geriatr Soc 2020; 68: 2768–77.
16. Anrys P, Petit AE, Thevelin S *et al.* An international consensus list of potentially clinically significant drug-drug interactions in older people. J Am Med Dir Assoc 2021; 22: 2121–2133.e24.
17. Zerah L, Henrard S, Wilting I *et al.* Prevalence of drug-drug interactions in older people before and after hospital admission: analysis from the OPERAM trial. BMC Geriatr 2021; 21: 571. https://doi.org/10.1186/s12877-021-02532-z.
18. Jester DJ, Molinari V, Zgibor JC, Volicer L. Prevalence of psychotropic polypharmacy in nursing home residents with dementia: a meta-analysis. Int Psychogeriatr 2021; 33: 1083–98.
19. Ruths S, Straand J, Nygaard HA. Psychotropic drug use in nursing homes–diagnostic indications and variations between institutions. Eur J Clin Pharmacol 2001; 57: 523–8.
20. Schulze J, van den Bussche H, Glaeske G, Kaduszkiewicz H, Wiese B, Hoffmann F. Impact of safety warnings on antipsychotic prescriptions in dementia: nothing has changed but the years and the substances. Eur Neuropsychopharmacol 2013; 23: 1034–42.
21. Mahlknecht A, Krisch L, Nestler N *et al.* Impact of training and structured medication review on medication appropriateness and patient-related outcomes in nursing homes: results from the interventional study InTherAKT. BMC Geriatr 2019; 19: 257. https://doi.org/10.1186/s12877-019-1263-3.
22. 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: 143–9.
23. Stuhec M, Bratovic N, Mrhar A. Impact of clinical pharmacist's interventions on pharmacotherapy management in elderly patients on polypharmacy with mental health problems including quality of life: a prospective non-randomized study. Sci Rep 2019; 9: 16856. https://doi.org/10.1038/s41598-019-53057-w.

Received 22 April 2022; editorial decision 18 September 2022