Medication changes implemented during medication reviews and factors related to overprescribing: post-hoc analyses of a randomized clinical trial in geriatric outpatients with polypharmacy

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November 18, 2022

Abstract

Aims: To describe the medication changes implemented during physician-led medication reviews that resulted in improved health-related quality of life; and to explore factors that could identify patients with overprescription.

Methods: Post-hoc analyses of data from a pragmatic, non-blinded, randomized clinical trial investigating a medication review intervention (NCT03911934) in 408 geriatric outpatients taking ≥9 medicines.

Results: The most frequent medicine change in the medication review group (n=196) was discontinuation (26% of the medicines) due to lack of indication (72% of the discontinuations). After 13 months, 82% of the discontinued medicines were persistently discontinued. The medicines most often discontinued in the medication review group compared with usual care included: metoclopramide (11/5=73% discontinued vs 1/12=8% in usual care), acetylsalicylic acid (20/48=42% vs 2/47=4%), simvastatin (18/48=38% vs 2/58=3%), zopiclone (23/59=39% vs 4/54=7%), quinine (9/14=64% vs 6/16=38%), citalopram (4/18=22% vs 0/20=0%), and tramadol (18/37=49% vs 8/30=27%). Factors associated with the number of overprescribed medicines included: number of prescribed medicines (8% increase per medicine), Drug Burden Index (15% increase per 1 increase), and patient motivation for medicine changes (26% less if not motivated). Prescriptions of metoclopramide, iron preparations, antidepressants other than SSRIs, NSAIDs, or drugs for urinary incontinence were associated with a higher number of overprescribed medicines.

Conclusion: Medication reviews can be used to persistently discontinue overprescribed medicines in older polypharmacy patients. Motivation for having their medicine changed, treatment with a higher number of medicines, and a higher bur-

den of sedative and anticholinergic drugs characterized patients most likely to benefit from physician-led medication reviews.

Title page

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Bullet point summary:

What is already known about this subject:

- Physician-led medication reviews improved health-related quality of life in geriatric outpatients with polypharmacy
- Medication reviews reduced the total number of medicines, but which medicines were reduced, why the medicines were reduced, and which patients had the most medicines reduced are not known

What this study adds:

- The most frequent change during medication reviews was discontinuation due to lack of indication
- The medicines most often discontinued may cause adverse effects in older patients, e.g. metoclopramide, zopiclone, citalopram, and tramadol
- Patient-related factors including number of medicines and motivation may identify patients most likely to benefit from medication reviews

Abstract

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Results: The most frequent medicine change in the medication review group (n=196) was discontinuation (26% of the medicines) due to lack of indication (72% of the discontinuations). After 13 months, 82% of the discontinued medicines were persistently discontinued. The medicines most often discontinued in the medication review group compared with usual care included: metoclopramide (11/5=73% discontinued vs 1/12=8% in usual care), acetylsalicylic acid (20/48=42% vs 2/47=4%), simvastatin (18/48=38% vs 2/58=3%), zopiclone (23/59=39% vs 4/54=7%), quinine (9/14=64% vs 6/16=38%), citalopram (4/18=22% vs 0/20=0%), and tramadol (18/37=49% vs 8/30=27%). Factors associated with the number of overprescribed medicines included: number of prescribed medicines (8% increase per medicine), Drug Burden Index (15% increase per 1 increase), and patient motivation for medicine changes (26% less if not motivated). Prescriptions of metoclopramide, iron preparations, antidepressants other than SSRIs, NSAIDs, or drugs for urinary incontinence were associated with a higher number of overprescribed medicines.

Conclusion: Medication reviews can be used to persistently discontinue overprescribed medicines in older polypharmacy patients. Motivation for having their medicine changed, treatment with a higher number of medicines, and a higher burden of sedative and anticholinergic drugs characterized patients most likely to benefit from physician-led medication reviews.

Introduction

Medication reviews are used as a tool to combat inappropriate polypharmacy and associated adverse effects.[1] In numerous trials, medication reviews have decreased the number of potentially inappropriate medicines and increased the prescribing appropriateness.[2]

We have previously reported on the clinical effects of medication reviews as a supplement to usual care in a geriatric outpatient clinic.[3] In a randomized clinical trial, medication reviews reduced the number of medicines after 4 months and led to relative increases in the patient's health-related quality of life (HRQoL) and reduced mortality. The combined beneficial effect on HRQoL and mortality support that the discontinued and dose-reduced medicines were in fact inappropriate and not merely *potentially* inappropriate. Thus, a detailed description of these medicines seem warranted as these medicines could be discontinued in a pragmatic clinical trial setting and thus are of clinical relevance for medication reviews in geriatric outpatients.

The purpose of this paper is twofold: 1) to provide a detailed description of the medication changes implemented during medication reviews to better understand the observed beneficial clinical effects and to guide future medication review interventions; and 2) to explore patient- and medication-related factors that may identify patients that will benefit most from medication reviews. To fulfill these purposes, the detailed descriptions include: 1) the actual changes to the medicine; 2) the persistence of the changes; 3) the medicines most often discontinued; 4) the reasons for discontinuing; 5) the medicines that most often were prescribed again after discontinuation; and 6) an exploratory analysis of factors that predicted the number of overprescribed medicines to help identify patients that may benefit the most from medication reviews.

Methods

All results in this paper are post-hoc analyses of data from a pragmatic, non-blinded, single-center, randomized clinical trial with follow-up 4 months and 13 months after the initial visit. For a detailed description of the trial see the primary publication.[3] Briefly, participants taking 9 or more different medicines were recruited from the geriatric outpatient clinic at Copenhagen University Hospital, Bispebjerg and Frederiksberg from June 2017 to December 2019. Participants were randomized to usual care or usual care plus a medication consultation including a medication review and increased cross-sectoral communication (termed the medication review group). The medication reviews were prepared and implemented by a physician from the Department of Clinical Pharmacology. Proposed changes to the medicine were discussed with the

patient's primary care physician and the treating geriatrician before an in-person consultation with the patient where the changes were implemented if the patient agreed to the changes. All included participants provided written, informed consent to the collection of data and the study was approved by the Danish Data Protection Agency (BFH-2017-031).

Baseline data

The following baseline data were collected: Age, sex, number of different medicines, Drug Burden Index[4] calculated using the Irish Drug Burden Index list[5] as an estimate of anticholinergic and sedative drug exposure, number of admissions the last 3 months, any falls the last 3 months (yes or no), weight, height, body mass index, nursing home resident (yes or no), home care (including frequency of visits), who dispensed the patient's medicine (the patient, relative, home nurse, nursing home or other), who referred the patient to the outpatient clinic (the patient's general practitioner, the geriatric department or another department), what was the patient referred to (geriatric assessment, follow up after admission or the falls clinic), diagnoses registered in the electronic health record, Charlson Comorbidity Index,[6] FRAIL scale,[7] and whether the patient was motivated for medicine changes (yes or no).

Medicine data

Detailed prescription data were obtained from the Shared Medicine Record[8] at baseline, immediately after the visit, and 4 and 13 months after the visit. The following medicines were excluded when tallying the number of different medicines during inclusion and were not registered during the trial: Topical treatments (such as eye drops, ear drops, and creams), antibiotics with limited treatment duration, multivitamins, and protein drinks. The data collected for each medicine included product name, dosage, and any changes to the medicine at the specified time points. When available, the reasons for the medicine changes were obtained from the physician's note in the electronic medical record.

Statistical methods

All medicines were aggregated per patient according to the fifth level codes (substance) in the Anatomical Therapeutic Chemical (ATC) Classification System.[9] Based on these aggregated data, the medicine changes were computed from the differences in the prescribed medicines at the different time points (baseline, after first visit, follow-up after 4 months, and follow-up after 13 months). If a medicine was still discontinued or prescribed with precisely the same dosage *after* the first visit and at a follow-up visit, then the medicine change at the first visit

was described as *persistent*. *Overprescribed* medicines were defined as medicines that were discontinued or reduced in dosage at the first visit in the outpatient clinic. *Underprescribed* medicines were defined as medicines that were prescribed or increased in dosage at the first visit in the outpatient clinic. *Rebounds* were defined as medicines that were prescribed again following discontinuation.

The number of medicines prescribed at baseline was summarized according to the therapeutic subgroups (second level ATC). The number of underprescribed and overprescribed medicines were then plotted as a function of the total number of medicines at baseline with trend lines using loess regression.[10] The medicine changes per group at the first visit were summarized descriptively along with the persistence of these changes. To identify the medicines that were more often discontinued during the medication review, we calculated the absolute difference in the proportions of discontinuations per medicine between groups. Only medicines prescribed to at least ten patients at baseline were included in the calculation. Rebounds were summarized for medicines with at least five discontinuations during the first visit. To compare the proportion of discontinuations and rebounds between groups, we plotted the ratio of the number of medicines prescribed at each time point to the number of medicines prescribed at baseline for pharmacological subgroups (third level ATC). Only subgroups with at least 40 medicines prescribed in both groups at baseline and at least 10 discontinuations in the medication review group during the first visit were included.

The reason(s) for discontinuations in the medication review group were registered prospectively, and based on these the *primary* reason for discontinuation was determined using the following hierarchy: 1) Treatment not indicated; 2) Treatment with no or poor effect; 3) Safety-related issues; 4) Patient preferences and circumstances; and 5) Unknown reason.

Lastly, to identify factors related to the number of overprescribed medicines, we created two exploratory models using all the subjects from the medication review group. One model included all patient baseline characteristics (to identify patient-related factors) and the other included all medicine groups (ATC fourth level, chemical subgroup) prescribed at baseline (to identify medicines that were associated with overprescribing). As the predicted variable was a count of overprescribed medicines, we fitted generalized linear models with a quasi-Poisson distribution (log link) using R version 3.6.3[11] with the tidymodel[12] and poissonreg[13] packages. For both models, we first fitted a full model using all variables excluding variables with near-zero variance. The statistically significant variables (defined as $P < 0.05$) from the full models were then further explored in univariate models. The models were purely exploratory and confidence limits and P-values were not adjusted for

multiple comparisons. To illustrate the results from the models, model predictions using estimated marginal means[14] were plotted for all patient baseline characteristics that were statistically significant in both the full and univariate models.

Results

The study included 196 patients randomized to medication review and 212 to usual care. The included patients had a median age of 81 years (IQR 75 to 85 years), were prescribed a median of 12 medicines (IQR 10 to 14) at baseline, and 71% were females. Detailed patient characteristics and patient flowchart have previously been reported.[3] Medicines prescribed at baseline are listed in Supporting Information Table S1. As reported in the primary publication,[3] medication review reduced the number of prescribed medicines by 18% after the first visit, by 16% after 4 months, and by 11% after 13 months compared with 5%, 5% and 2% in the usual care group. The medicine changes, and their corresponding persistence, that led to these differences in the number of prescribed medicines are described in detail in Table 1. The number of overprescribed and underprescribed medicines as a function of the number of baseline medicines is visualized in Figure 1. The primary reasons for discontinuations in the medication review group are listed in Table 2. The medicines that were more often discontinued in the medication review group compared with usual care are listed in Table 3. The medicines that were most often restarted after being discontinued in the medication review group are listed in Table 4. The proportions of prescribed medicines in pharmacological subgroups in the two groups at the different time points are shown in Figure 2. The numbers from the plots in Figure 2 are listed in Supporting Information Table S2. The factors that predicted the number of overprescribed medicines in the two models are listed in Table 5. The effect of the patient-related factors on predicted number of overprescribed medicines is visualized in Figure 3. For reference, the number of overprescribed medicines for patients referred from the geriatric department was a median (IQR) of 3 (2 to 5) compared with 4 (2 to 6) for patients referred from the GP, and for patients not motivated for medicine changes 3 (1 to 4) compared with 4 (2 to 6) for patients motivated for medicine changes.

Discussion

In this study, we deep-dived into the medicine changes that were implemented during the medication review intervention leading to improved HRQoL and reduced mortality.[3] The results in Table 1 show that even though there were three times the number of discontinuations (26% vs

8.7%) in the medication review group, the persistence of the discontinuations after 4 and 13 months were similar between groups (medication review: 91% at 4 months and 82% at 13 months; usual care: 83% at 4 months and 86% at 13 months). The high persistence in the medication review group despite the larger number of changes could be due to improved cross-sectoral communication as the patient's general practitioner (GP) was involved before implementation of the changes and notified of the changes after implementation.

While the overall persistence of changes was high, some medicines were more prone to rebound than others as evidenced in Table 4. Of note, even the highest rebound rates were roughly 1/3 meaning that even for these medicines, discontinuation attempts were successful for 2/3 of the patients. The rebounded medicines were almost exclusively symptomatic treatments where recurrence of symptoms could easily be identified and therapy reinitiated, while the two preventive medicines with high rebound rates both have easy monitoring options (bone mineral density for alendronate and blood pressure for bendroflumethiazide). Interestingly, discontinuation of opioids and benzodiazepines, which we consider symptomatic treatments, were more often successful than the opposite despite the added risk of withdrawal symptoms.

In Figure 2, other patterns regarding discontinuation and rebounding are apparent. For some medicine groups, the medication review results in fast and lasting reductions compared with usual care, i.e. for proton pump inhibitors (drugs for peptic ulcer and gastro-oesophagael reflux disease), opioids, paracetamol/acetaminophen (other analgesics and antipyretics), antithrombotic agents, antiepileptics, furosemide (high ceiling diuretics), and potassium (which follows furosemide prescriptions). For other medicines, the difference in discontinuations is not persistent, suggesting that the same changes will happen in the usual care group but over a longer time period, i.e. for drugs against constipation, vitamin B12 and folic acid, blood glucose-lowering drugs excl. insulins, statins (lipid modifying agents, plain), selective calcium channel blockers with many cardiovascular effects, and hypnotics and sedatives. For antidepressants and adrenergic inhalants, the medication review discontinuations seem to be unsuccessful with discontinuation of antidepressants being the least successful. Lastly, the calcium supplement discontinuations are outnumbered by new prescriptions leading to an overall and similar increase in prescriptions in both groups.

The reasons for the discontinuations in the medication review group listed in Table 2 clearly show that lack of indication is by far the most common reason to discontinue. Note that only the primary reason is listed, hence safety-related concerns may also apply when the primary reason for discontinuation was lack of indication. Nonetheless, it is evident that to reduce overprescription, a thorough review of the patient's

medical history is needed to understand the (original) indication for the patient's treatments. In cases where the indication is not obvious, the patient or the patient's family or GP may have this valuable information, further highlighting the need for a strong patient involvement and cross-sectoral collaboration when conducting medication reviews.

The results in Table 3 show that many of the medicines that were more often discontinued in the medication review group than in the usual care group are medicines which can negatively impact, especially older patients', HRQoL. For example, metoclopramide, citalopram, tramadol, tiotroprium and zopiclone may commonly cause dizziness and other important adverse effects. Even low dose aspirin may cause significant bleeding[15] and quinine may increase mortality risk in heart failure patients.[16] So, while a medication review is a complex intervention, the changes to the medicine may very well be one of the causes of the observed positive effects on HRQoL and mortality.

Medication reviews are labor intensive as they require a comprehensive evaluation of the patient's medical history and prescriptions to accurately evaluate their current medication use and indications. Therefore, it is important to identify the patients that would benefit most from medication reviews to optimize the allocation of health resources. Table 5 lists the factors that were statistically significantly associated with the number of overprescribed medicines for this population. Only two factors were associated with fewer overprescribed medicines; not being motivated for medicine changes or being referred from the geriatric department. Patients who were not motivated for medication changes had 26% fewer overprescribed medicines at the first visit. It is unknown whether this is due to them having fewer overprescribed medicines prescribed or an unwillingness to consent to the proposed medicine changes. Still, even patients that were not motivated for medicine changes had a median of 3 medicines discontinued or reduced in dosage. Patients referred from the geriatric department had 25% fewer overprescribed medicines, most likely due to some extent of medication reviews being performed prior to referral. Multiple factors were associated with an increased number of overprescribed medicines. The number of medicines was an important factor with 8% more overprescribed medicines per additional medicine prescribed at baseline. This is similar to the finding by Steinman et al.[17] and intuitively makes sense as more medicines impair overview while offering more opportunities for mistakes. However, not only the number of medicines but also the sedative and anticholinergic burden of the medicines (as measured with the Drug Burden Index) impacted the number of overprescribed medicines with 15%–26% (full model or univariate model) more overprescribed medicines per one increase in Drug Burden Index. Besides the patient characteristics, we also identified some medicines that seem to be proxies for suboptimal medicine treatment. Thus, a prescription of metoclopramide was as-

sociated with a 42%–73% (full model or univariate model) increase in overprescribed medicines. Thus, metoclopramide, non-steroid anti-inflammatory drugs (propionic acid derivatives), and drugs for urinary frequency and incontinence are all medicines that should serve as an alarm bell that may prompt medication reviews in patients exposed to polypharmacy.

Strengths and limitations

The strength of this study is the completeness of data and long follow-up of medicine changes due to medication reviews that *overall* resulted in improved clinical outcomes for the patients. The main limitation is that we cannot correlate individual medicine changes to these outcomes due to the design of the study. Also, all analyses in this paper are post-hoc explorative studies that require further confirmative studies.

Conclusion

In conclusion, the most frequent medicine change was discontinuation due to lack of indication and most of the discontinued medicines were medicines that may cause adverse effects in older patients. A higher number of medicines, higher sedative and higher anticholinergic burden of the medicines, if the patient was motivated for medicine changes or had a prescription of metoclopramide, an iron preparation, other antidepressant (i.e. not selective serotonin reuptake inhibitors), non-steroid anti-inflammatory drug, or drug for urinary frequency and incontinence was associated with a higher number of overprescribed medicines. These patient- and medication-related factors could aid in identifying patients that will benefit most from medication reviews.

Acknowledgements

We would like to thank Ditte-Marie Schärfe Kjærgaard and Linea Fugmann Thamdrup for assistance with data collection. We would like to thank all the physicians, nurses and medical secretaries at the geriatric outpatient clinic at Copenhagen University Hospital, Bispebjerg and Frederiksberg for assistance with the conduct of this study. This work was supported by the Velux Foundation [00025835] and the Capital Region of Denmark [E-12825-01-12-01]. The funders had no role in the design and conduct of the study, the collection, management, analysis and interpretation of the data, the preparation, review or approval of the manuscript or the decision to submit the manuscript for publication.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Funding information

This study was funded by the Velux Foundation (00025835) and the Capital Region of Denmark (E-12825-01-12-01).

Data availability statement

Data available on request from the authors.

References

1. Blenkinsopp A, Bond C, Raynor DK. Medication reviews. *Br J Clin Pharmacol* . 2012;74(4):573-580. doi:10.1111/j.1365-2125.2012.04331.x

2. Rankin A, Cadogan, CA, Patterson, SM, Kerse, N, Cardwell, CR, Bradley, MC, Ryan, C, Hughes C. Interventions to improve the appropriate use of polypharmacy for older people. *Cochrane Database Syst Rev* . 2018;(9). doi:10.1002/14651858.CD008165.pub4

3. Kornholt J, Feizi ST, Hansen AS, et al. Effects of a comprehensive medication review intervention on health-related quality of life and other clinical outcomes in geriatric outpatients with polypharmacy: A pragmatic randomized clinical trial. *Br J Clin Pharmacol* . 2022;88(7):3360-3369. doi:10.1111/bcp.15287

4. Hilmer SN, Mager DE, Simonsick EM, et al. A Drug Burden Index to Define the Functional Burden of Medications in Older People. *Arch Intern Med* . 2007;167(8):781-787. doi:10.1001/archinte.167.8.781

5. Byrne CJ, Walsh C, Cahir C, Ryan C, Williams DJ, Bennett K. Anticholinergic and sedative drug burden in community-dwelling older people: a national database study. *BMJ Open* . 2018;8(7). doi:10.1136/bmjopen-2018-022500

6. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* . 1987;40(5):373-383. doi:10.1016/0021-9681(87)90171-8

7. Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. *J Nutr Health Aging* . 2012;16(7):601-608. doi:10.1007/s12603-012-0084-2

8. Munck LK, Hansen KR, Mølbak AG, Balle H, Kongsgren S. The use of shared medication record as part of medication reconciliation at hospital admission is feasible. *Dan Med J* . 2014;61(5):A4817.

9. WHO Collaborating Centre for Drug Statistics Methodology. *ATC Classification Index with DDDs* . Vol 2021. Oslo, Norway; 2020.

10. Jacoby WG. Loess: a nonparametric, graphical tool for depicting relationships between variables. *Elect Stud* . 2000;19(4):577-613. doi:10.1016/S0261-3794(99)00028-1

11. R Core Team. *R: A Language and Environment for Statistical Computing* . R Foundation for Statistical Computing; 2020. https://www.R-project.org/

12. Kuhn M, Wickham H. *Tidymodels: A Collection of Packages for Modeling and Machine Learning Using Tidyverse Principles.* ; 2020. https://www.tidymodels.org

13. Kuhn M. *Poissonreg: Model Wrappers for Poisson Regression* .; 2020. https://CRAN.R-project.org/package=poissonreg

14. Lenth R. *Emmeans: Estimated Marginal Means, Aka Least-Squares Means* .; 2020. https://CRAN.R-project.org/package=emmeans

15. McNeil JJ, Wolfe R, Woods RL, et al. Effect of Aspirin on Cardiovascular Events and Bleeding in the Healthy Elderly. *N Engl J Med* . 2018;379(16):1509-1518. doi:10.1056/NEJMoa1805819

16. Gjesing A, Gislason GH, Christensen SB, et al. Use of quinine and mortality-risk in patients with heart failure–a Danish nationwide observational study. *Pharmacoepidemiol Drug Saf* . 2015;24(3):310-318. doi:10.1002/pds.3746

17. Steinman MA, Landefeld CS, Rosenthal GE, Berthenthal D, Sen S, Kaboli PJ. Polypharmacy and Prescribing Quality in Older People. *J Am Geriatr Soc* . 2006;54(10):1516-1523. doi:https://doi.org/10.1111/j.1532-5415.2006.00889.x

Tables

Table 1: Changes to the medicine and persistence of changes. For the change to be persistent, the medicine must be prescribed at the same dosage at follow-up as after the first visit. This means that if e.g., a medicine is reduced in dosage at the first visit and then discontinued at 4 months, then the change is not persistent. Medicine data is only available for patients that were alive at follow-up. When calculating the proportion of persistent changes, the denominator is therefore not identical to the number of changes at first visit. *Other change* includes changes in medicines with multiple prescriptions with the same substance(s) where the changes are in opposite directions, e.g. reducing regular and increasing as-needed at the same time.

	Changes at first visit, No. (% of medicines prescribed at baseline)		**Persistent changes at 4 months, No. (% of changes at first visit)**		**Persistent changes at 13 months, No. (% of changes at first visit)**	
	Medication review	**Usual care**	**Medication review**	**Usual care**	**Medication review**	**Usual care**
Overprescribed medicines						
Discontinued	628 (26)	224 (8.7)	565 (91)	191 (86)	481 (82)	176 (83)
Reduced dosage	202 (8.3)	83 (3.2)	154 (78)	61 (76)	96 (54)	45 (61)
Underprescribed medicines						
New medication	175	92	132 (75)	62 (67)	103 (62)	43 (49)
Increased dosage	52 (2.1)	27 (1)	39 (75)	21 (78)	28 (59)	15 (58)
Other						
Other change	113 (4.7)	24 (0.9)	86 (76)	22 (92)	63 (59)	13 (59)
Unchanged	1429 (59)	2230 (86)	1159 (81)	1751 (82)	929 (68)	1329 (67)

Table 2: Primary reasons for discontinuation of medicine in the medication review group. Primary was determined using the following hierarchy: 1) Indication; 2) Efficacy; 3) Safety; 4) Patient preferences and circumstances; and 5) Unknown reason.

Primary reason for discontinuation	**Number of medicines**
Indication	455 (72%)
Treatment no longer indicated	
Unknown	48 (8%)
Reason for discontinuation not described	
Safety	47 (7%)
Adverse drug reaction	
Risk of adverse drug reaction	
Risk due to drug-drug interactions	
Risk due to drug-disease interactions	
Efficacy	39 (6%)
Poor or no effect of the treatment	
Patient preferences and circumstances	39 (6%)
Treatment too expensive	
Patient does not wish to take the medicine	
Patient cannot administer the medicine	

Table 3: Top 10 medicines with the highest absolute difference in the proportion of discontinuations between the groups. Only medicines prescribed to at least 10 patients at baseline are included.

	Discontinued at first visit, No. discontinued / No. at baseline = % discontinued		
Medicine	**Medication review (n = 196)**	**Usual care (n = 212)**	**Absolute difference, No. (%)**
Metoclopramide	11 / 15 = 73%	1 / 12 = 8%	10 (65)
Acetylsalicylic acid	20 / 48 = 42%	2 / 47 = 4%	18 (37)
Simvastatin	18 / 48 = 38%	2 / 58 = 3%	16 (34)
Formoterol and budesonide	5 / 15 = 33%	0 / 16 = 0%	5 (33)
Zopiclone	23 / 59 = 39%	4 / 54 = 7%	19 (32)
Tiotropium bromide	4 / 14 = 29%	0 / 17 = 0%	4 (29)
Allopurinol	3 / 11 = 27%	0 / 12 = 0%	3 (27)
Quinine	9 / 14 = 64%	6 / 16 = 38%	3 (27)
Citalopram	4 / 18 = 22%	0 / 20 = 0%	4 (22)
Tramadol	18 / 37 = 49%	8 / 30 = 27%	10 (22)

Table 4: Rebounds after discontinuation of medicines during medication review. Only includes data from the medication review group and medicines with at least 5 discontinuations at the first visit. The denominator in *proportion restarted* can differ from the number discontinued at first visit since medicine data was not collected for patients who died.

Medicine	**Discontinued at first visit, No. discontinued / No. at baseline = % discontinued**	**Proportion restarted, No. restarted / No. discontinued at first visit = % restarted**	
		Follow-up at 4 months	**Follow-up at 13 months**
Paracetamol (acetaminophen)	26 / 180 = 14%	2 / 24 = 8%	9 / 24 = 38%
Alendronic acid	6 / 30 = 20%	1 / 6 = 17%	2 / 6 = 33%
Quinine	9 / 14 = 64%	1 / 9 = 11%	3 / 9 = 33%
Furosemide	15 / 59 = 25%	3 / 14 = 21%	4 / 14 = 29%
Metoprolol	8 / 68 = 12%	1 / 8 = 12%	2 / 8 = 25%
Zopiclone	23 / 59 = 39%	3 / 21 = 14%	5 / 21 = 24%
Macrogol, combinations	27 / 96 = 28%	2 / 27 = 7%	6 / 27 = 22%
Morphine	5 / 23 = 22%	1 / 5 = 20%	1 / 5 = 20%
Codeine	5 / 16 = 31%	0 / 5 = 0%	1 / 5 = 20%
Bendroflumethiazide and potassium	6 / 21 = 29%	2 / 6 = 33%	1 / 6 = 17%
Amlodipine	7 / 40 = 18%	2 / 6 = 33%	1 / 6 = 17%
Oxazepam	5 / 21 = 24%	1 / 5 = 20%	0 / 5 = 0%

Table 5: Factors predicting the number of overprescribed medicines in the medication review group. Results from the full and univariate analysis are presented for the model with patient-related factors and the model with medication-related factors. All models were generalized linear models with quasi-Poisson distribution (log link). The full models included all medicine groups or all patient-related baseline characteristics without near-zero variance. Confidence limits and P-values are not adjusted for multiple comparisons. The exponentiated β is the ratio between the predicted number of overprescribed medicines for patients "having" the factor versus patients not "having" the factor (with all other factors being equal). The reference level (i.e. what is meant by not "having" the factor) is listed in parentheses for binary and categorical factors. For example, patients referred from the geriatric department have 74% (or 26% fewer) the number of overprescribed medicines compared with patients referred from their GP. For continuous variables, an increase of one is used, e.g. patients with a Drug Burden Index of 1 have 115% (or 15% more) overprescribed medicines compared with patients with a Drug Burden Index of 0, and patients with a Drug Burden Index of 2 have 15% more overprescribed medicines compared with patients with a Drug Burden Index of 1 (or 115% × 115% = 132% overprescribed medicines compared with a patient with a Drug Burden Index of 0).

		Full model		**Univariate model**	
	Descriptive statistics	**Exponentiated β (95% CI)**	***P* value**	**Exponentiated β (95% CI)**	***P* value**
Model: Baseline characteristics					
Not motivated for medicine changes (ref. Motivated for medicine changes), No. (%)	39 (19.9%)	0.74 (0.59 to 0.92)	.009	0.72 (0.55 to 0.93)	.016
Referred from the geriatric department (ref. Referred from GP), No. (%)	59 (30.1%)	0.75 (0.58 to 0.96)	.024	0.78 (0.63 to 0.97)	.026
Age in years (continuous), median (IQR)	80 (74 to 85)	1.02 (1.00 to 1.03)	0.009	1.003 (0.99 to 1.02)	.63
No. of medicines at baseline, median (IQR)	12 (10 to 14)	1.08 (1.05 to 1.11)	<.001	1.09 (1.07 to 1.12)	<.001
Drug Burden Index, median (IQR)	0.5 (0 to 1)	1.15 (1.03 to 1.29)	.015	1.26 (1.13 to 1.40)	<.001
Model: Medicine groups					
(ref. Medicine group not used), No. (%)					
Propulsives	15 (7.7%)	1.42 (1.02 to 1.97)	.038	1.73 (1.30 to 2.26)	<.001
Metoclopramid	15				
Iron bivalent, oral preparations	28 (14.3%)	1.51 (1.14 to 2.01)	.005	1.40 (1.07 to 1.80)	.013
Ferrous fumarate	16				
Ferrous sulphate	11				
Ferrous tartrate	1				
Other antidepressants	26 (13.3%)	1.52 (1.13 to 2.04)	.006	1.66 (1.29 to 2.11)	<.001
Mirtazapin	14				
Venlafaxin	5				
Duloxetin	4				
Mianserin	2				
Agomelatin	1				
Propionic acid derivatives	19 (9.7%)	1.54 (1.14 to 2.07)	.005	1.47 (1.11 to 1.91)	.006
Ibuprofen	18				
Dexibuprofen	1				
Drugs for urinary frequency and incontinence	14 (7.1%)	1.97 (1.37 to 2.79)	<.001	1.36 (0.95 to 1.87)	.076
Mirabegron	8				
Tolterodine	4				
Solifenacin	1				
Trospium	1				

Figures

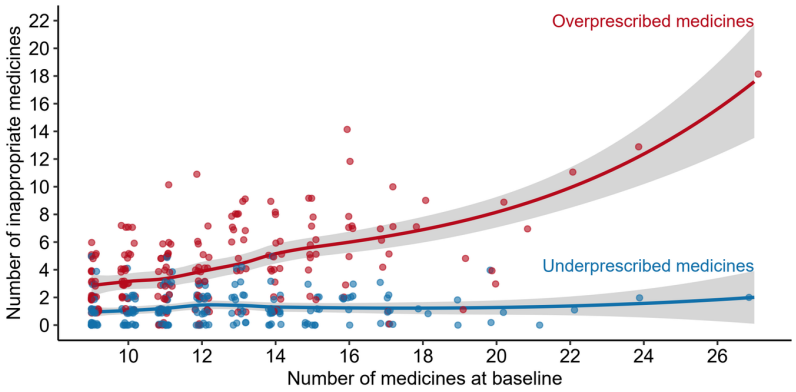

Figure 1: Observed number of overprescribed medicines and underprescribed medicines in the medication review group as a function of the number of medicines prescribed at baseline. Overprescribed medicines are medicines that were reduced in dosage or discontinued during the first visit. Underprescribed medicines are medicines that were increased in dosage or prescribed during the first visit. The fitted lines are loess regressions with 95% confidence intervals shaded in grey. All points are jittered slightly to reduce overplotting.

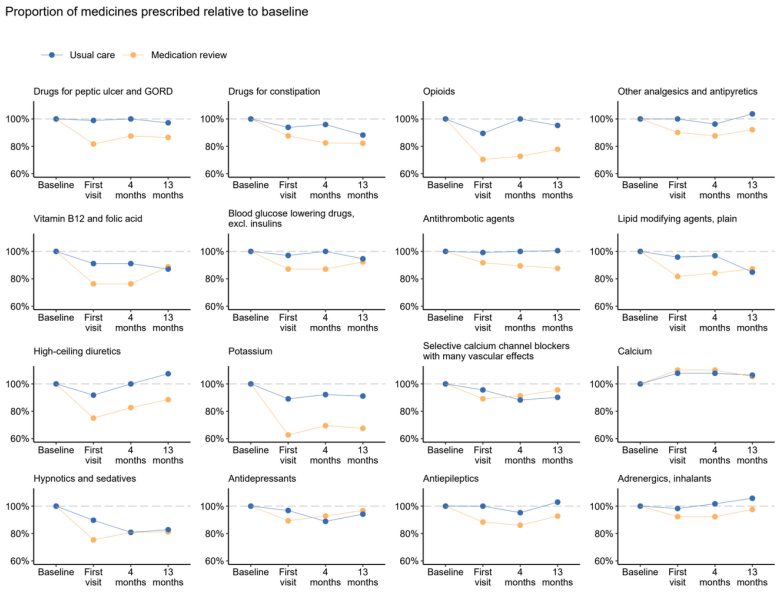

Figure 2: The ratio of the number of medicines prescribed at each timepoint relative to the number prescribed at baseline. The figures present pharmacological subgroups (third level ATC groups) with at least 40 medicines prescribed in both groups at baseline and at least 10 discontinuations in the medication review group during the first visit. Abbreviations: GORD, gastro-oesophageal reflux disease.

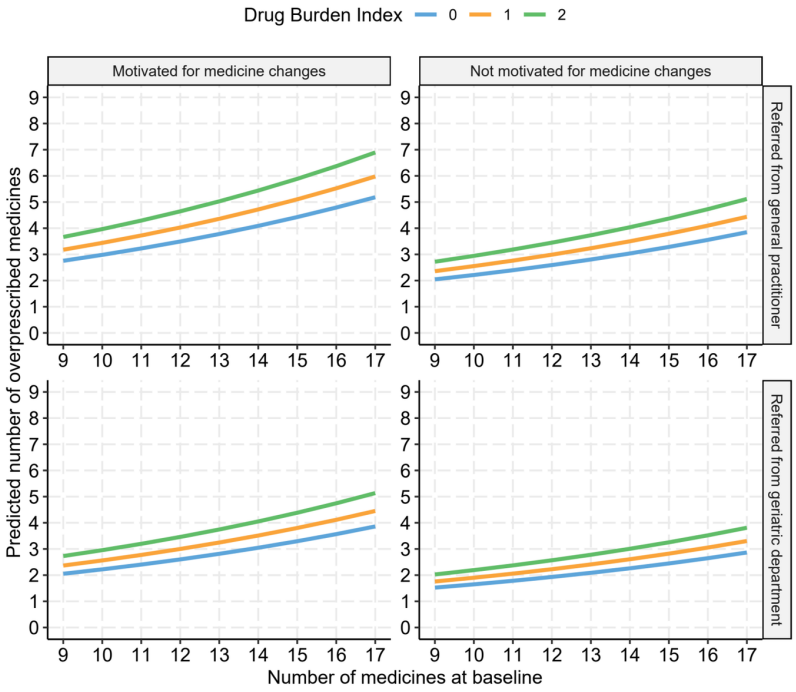

Figure 3: Visualization of the results from the full model using the patient-related baseline characteristics. The lines show the predicted number of overprescribed medicines (i.e., medicines with reduced dosage or discontinuation at first visit) for different combinations of all the variables that were statistically significant in both the full and univariate models. The full model was a generalized linear model with quasi-Poisson distribution (log link) including all patient-related baseline characteristics without near-zero variance.

Supporting information

Hosted file

`supporting_information.docx` available at https://authorea.com/users/522596/articles/595019-medication-changes-implemented-during-medication-reviews-and-factors-related-to-overprescribing-post-hoc-analyses-of-a-randomized-clinical-trial-in-geriatric-outpatients-with-polypharmacy