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Reducing the burden of anticholinergic and sedative medication in older patients on polypharmacy by medication review: A randomized controlled trial

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ABSTRACT

OBJECTIVE

To evaluate whether medication review is effective at reducing anticholinergic and sedative burden as measured by the Drug Burden Index (DBI).

DESIGN

Randomised controlled single blind trial.

SETTING

15 community pharmacies in the Northern Netherlands.

PARTICIPANTS

157 community-dwelling patients aged ≥ 65 years who used ≥ 5 medicines for ≥ 3 months, including at least one psycholeptic or psychoanaleptic medication, and having a DBI ≥ 1.

INTERVENTION

A medication review by the community pharmacist in collaboration with the patient's general practitioner and patient.

PRIMARY AND SECONDARY OUTCOMES MEASURES

The primary outcome was the proportion of patients whose DBI decreased by at least 0.5. Secondary outcomes were the presence of anticholinergic and/or sedative side effects, falls, cognitive function, activities of daily living, quality of life, hospital admission, and mortality. Data were collected at baseline and three-months follow-up.

RESULTS

Mean participant age was 75.7 (SD, 6.9) years in the intervention arm and 76.6 (SD, 6.7) years in the control arm, and the majority were female (respectively 69.3% and 72.0%). Linear mixed model analysis showed no difference in the proportion of patients with a ≥ 0.5 decrease in DBI between intervention arm (17.3%) and control arm (15.9%), (OR 1.04, CI 0.47 to 2.64, p=0.927). Intervention patients scored higher on the digit symbol substitution test, measure of cognitive function, (OR 2.02, CI 1.11 to 3.67, p=0.021), and reported fewer sedative side effects (OR 0.61, CI 0.40 to 0.94, p=0.024) at follow-up.

CONCLUSIONS

Medication review is not effective in reducing the burden of anticholinergic/sedative medication measured with the DBI. Preventive strategies, signalling a rising burden and taking action before chronic use of anticholinergic and/or sedative medication is established, may be more successful.

TRIAL REGISTRATION

Clinical trials NCT02317666.

STRENGTHS AND LIMITATION OF THIS STUDY

- A successfully completed randomized controlled trial, which was the first to focus on changing anticholinergic and sedative medication load by medication review.
- Appropriately powered to detect a clinically relevant medium difference.
- Showing the effect of "real world" practiced medication review, rather than the theoretical approach described in guidelines.
- Three-months follow-up might have been too short to detect full effects of medication review, e.g. due to stepwise reduction of medication, however very few dosage changes were seen.

BACKGROUND

Older people suffer from many medical conditions and use more medication than any other age group. Multiple medication use in combination with age-related physiological changes increase the risk of medication related harm including adverse drug events, drug-drug- and drug-disease-interactions. [1] Medications with anticholinergic and/or sedative properties are of particular concern in older people, because they worsen cognitive impairment and physical functioning, increase the risk of falls and negatively impact activities of daily living, hospitalization, and mortality. [23] Despite the risks, these medications are commonly prescribed to older individuals. [4] Different measures have been developed to quantify the anticholinergic burden in patients. [5] The Drug Burden Index (DBI) determines an individual's exposure to anticholinergic and sedative medication taking into account the dose. [67] A high DBI has been associated with impairments in both physical- and cognitive function among older individuals. [8] Hence, decreasing exposure to anticholinergic and sedative medication, as measured by the DBI, may have important health benefits in older people.

Two small Australian studies suggest that medication review could be a promising strategy in reducing the DBI. [910] A medication review is a structured assessment of a patient's medication by the community pharmacist in collaboration with the general practitioner (GP) and patient, in order to optimize prescribing. [11] While meta-analyses of studies in different settings show a lack of effectiveness on outcomes such as mortality or hospital (re-) admissions, [12-14] these studies included different types of medication review. Well-structured medication review with good cooperation between pharmacist and GP and involvement of the patient were most likely to be successful. [1516] Furthermore fee-for-pharmacist-led medication review seemed to have positive health benefits on the patient. [17] The most effective method for medication review remains unknown. Focusing on specific subgroups such as older people with multiple comorbidities and polypharmacy, [18] or patients suffering from pain [19] may be one strategy to optimize medication review associated benefits. To date, there is no consensus on the effectiveness of medication review as a strategy to reduce anticholinergic and sedative burden as measured by the DBI. Therefore, the primary aim of this study was to evaluate if a medication review is an effective strategy to reduce anticholinergic and sedative burden as measured by the DBI. Secondarily, we evaluated the effect of a medication review on patient outcomes including cognitive function, risk of falls, activities of daily living and quality of life.

METHODS

Study design, setting & participants

We conducted a randomized controlled, single blind trial in 15 community pharmacies from December 2014 until October 2015 in the Northern Netherlands. Pharmacies were recruited via the regional

association of pharmacists and per pharmacy one pharmacist was concerned with this study. Pharmacists were experienced in performing medication reviews and had an established working collaboration with GPs in the area. Patients who were aged ≥ 65 years, living independently, using ≥ 5 medications for ≥ 3 months, including at least one psycholeptic or psychoanaleptic medication (Anatomic Therapeutic Classification (ATC) code N05 or N06), [20] and with a DBI ≥ 1 were identified by the pharmacist and invited to participate in the study. Exclusion criteria were limited life expectancy (< 3 months), non-Dutch language speaker or advanced dementia. Patients who received a medication review within the past 9 months before the study period and patients who needed a medication review urgently were also excluded. Exclusion criteria were identified by the pharmacist. This study was approved by the Medical Ethical Committee of the University Medical Centre of Groningen, The Netherlands (protocol number METc 2014/392). The study protocol has been published elsewhere. [21]

Randomization, allocation & blinding

Eligible patients were approached by the pharmacist and asked to provide written informed consent. In each pharmacy, patients willing to participate were then matched in pairs by gender, age, DBI and number of medications. One patient of each pair was randomly assigned to the intervention condition. All participants gave written consent prior to the intervention allocation. The randomization process was conducted by the principal investigator, who was not involved in recruitment or data collection. The researchers who enrolled the patients and collected the data were kept blind to the allocation. Pharmacists and patients could not be kept blind. Therefore this was a single blind study.

Intervention

The intervention was a medication review conducted by the community pharmacist in close collaboration with the patient´s GP and, if needed, other medical specialists. The medication review, as described by Dutch guidelines comprised five steps. [11] First, the pharmacotherapeutical anamnesis, a face-to-face consultation between pharmacist and patient to discuss the medication use. Second, the pharmacotherapeutical medication review, the pharmacist identified pharmacotherapeutical problems and drafted recommendations for medication optimisation to discuss with the patients GP. Third, a multidisciplinary meeting, preferably face-to-face, between pharmacist and GP about the patients' medication and draft of a pharmaceutical action plan. Fourth, discussion of the pharmaceutical action plan between patient and pharmacist or GP. Patients' expectations and wishes were key elements in the decision-making process. Fifth, a follow-up of the pharmaceutical action plan. A detailed description of the guideline can be found in our previously published study protocol. [21] Pharmacists were familiar with the guideline, as medication reviews were widely performed and partly mandatory by agreements with health insurance companies. Nonetheless, we provided the guidelines to the pharmacists with the request to focus on anticholinergic and sedative medications. In order to get a reflection of 'real world' practice, we let the pharmacists perform the

medication review as they used to do, but we did check whether all steps were conducted. The medication review took place within days after the baseline measurement for the intervention patients. Patients in the control group received the medication review after the study period. Costs of the medication review were reimbursed by the patient's health insurance.

Outcomes

The primary outcome was defined as the difference in proportion of patients having a decrease of DBI ≥ 0.5 at 3-months follow-up. Our hypothesis was that this proportion would be higher in the intervention arm compared to the control arm. We chose 0.5, as this equals the cessation of one drug, which we considered clinically relevant. The DBI was calculated using the following formula [7]:

$$\text{DBI} = \sum \frac{D}{D+\delta}$$

D = daily dose, δ = minimum recommended daily dose were derived for the study from Dutch standard reference sources. [2223] Except for sensory and dermatological preparations, all chronic medications (i.e. those used for ≥ 3 months) with anticholinergic properties (dry mouth, constipation and urine retention) and sedative properties based on Dutch standard reference sources [22-24] were included in the calculation. Medication data were derived from electronic pharmacy dispensing data and were verified with the patient.

We included the following secondary outcomes: anticholinergic side effects, measured by the Udvalg for Kliniske Undersogelser (UKU) side effect rating scale, [25] sedative side effects, derived from a patient-reported adverse drug event questionnaire, [26] and risk of falls, determined by the Up & Go test. [27] Cognitive function was measured using validated tests for memory and executive function, namely the Seven Minute Screen (7MS), [28] the Trailmaking Test A & B, [29] and Digit Symbol Substitution Test (DSST). [30] The latter has also previously been used to examine the validity of the DBI. [7] Activities of daily living were derived using the validated Groningen Activity Restriction Scale (GARS), [3132] and quality of life was measured by the Euroqol-5 Dimension-3 Level (EQ-5D-3L) questionnaire, including visual analogue scale (VAS). [33] All tools were administered in Dutch and data were collected in a standardized manner, using data collection sheets, by researchers who were trained by a psychologist. Data collection took place at baseline and 3-months follow-up for both allocations. Patients with the inability to walk were excluded from the Up&Go test and the GARS questionnaire. At follow-up the number of fall incidents, hospital admission, and mortality was assessed based on patient/relative reporting.

Sample size calculation

To the best of our knowledge, only one randomized pilot study has been conducted assessing the DBI. [10] We therefore could not calculate the sample size 'a priori'. However we estimated a sample size based on a power of 80% at a significance of 0.05 and an intraclass correlation coefficient up to 0.2 to

detect a medium effect size on the primary outcome. [34] We chose a medium effect size as we considered a small effect size to be not clinically relevant and a power to detect a medium effect size also to be capable of detecting a large effect size. For this calculation around 160 participants (80 in control arm and 80 in intervention arm) were needed. We expected a non-response rate of 60% and therefore aimed to invite 400 patients to participate in the study.

Statistical analysis

We performed two analyses. In the first analysis we included all patients with a baseline measurement. In the second analysis, we included all patients who were not lost to follow-up, and who received the intervention as allocated. Descriptive statistics were calculated for both allocation arms at baseline. For the analysis of the primary outcome, we initially considered a generalized linear mixed model to adjust for dependence of observations (i.e. patients within pharmacies). However, as the intraclass correlation was not significant, extension of the model with random effects at the level of pharmacies was not necessary. Therefore only fixed effects were considered and standard regression models were applied. Most secondary outcomes were examined with linear mixed models. Depending on whether these were continuous, dichotomous, or count variables and their distribution was normal, we employed linear regression, logistic regression, or negative binomial regression. Variables with a skewed distribution were transformed before analysis. The Trailmaking Test A&B were log-transformed. Transformation did not normalize the distribution of the GARS and EQ-5D, we therefore dichotomized these data (cut-off points were 36 and 0.5 respectively). From the 7MS test, the Benton temporal orientation test had floor-effects, and the clock drawing and cued recall tests had ceiling-effects, therefore these variables were also dichotomized (cut-off points were 4, 6 and 15 respectively). Because of the high variance in the DSST, we ranked the scores per 5 percentiles and used these data in the analysis. For dichotomous variables we report percentages and numbers of patients in the highest scoring group, for skewed variables we report on the median and interquartile range and for normally distributed data we report the mean and standard deviation. Reported falls and hospitalization could be assessed from all patients who had a follow-up measurement and were analysed using Fisher's exact test, and we report the number and percentages of patients. Mortality was analysed in a similar way. We performed a sensitivity analysis on outliers and all analyses were adjusted for gender, age, and number of medication at baseline. Secondary outcomes were also adjusted for baseline scores. Analyses were done in SPSS 24 and MLwiN 2.36, statistical tests were one-sided and conducted on 5% significance level.

Missing data

Few data were missing for the primary outcome. For two patients, medication use at follow-up was unknown (lost to follow-up), therefore the baseline observation for medication use was carried forward. For eight patients, medication use could not be verified with the patient, as they could not be reached by telephone despite several attempts. For these patients, the medication data from the

pharmacy dispensing system were used. For secondary outcomes, 5.3% of data were missing in the complete dataset, mostly at follow-up (4.8%). In the intervention arm, 7.0% of data was missing (6.1% at follow-up) across 18 patients, whereas in the control arm 3.7% was missing (3.4% at follow-up) across 12 patients. In total 30 patients had missing data, of whom two were lost to follow-up. Eight patients were not able to complete one or more cognitive tests (0.5% of all data). Eleven patients could not be tested at follow-up within the study period, six patients due to sickness, four patients due to practical reasons (despite numerous attempts we were unsuccessful to arrange an appointment for the follow-up measurement), and one patient had died two days before the follow-up appointment. A few data were missing for other reasons across nine patients, for example patients forgetting their glasses, due to time constraints, or other reasons.

Missing data in cognitive tests due to inability of the patient to complete the task were replaced with the worst score for that specific group. Missing data of patients who could not be tested at follow-up within the study period, or who had missing data for other reasons were replaced by multiple imputation (five times) in SPSS 24. In this paper we report on the imputed dataset. Sensitivity analysis showed no difference between the dataset with and without missing data.

RESULTS

Participant flow

Overall, 498 patients were approached for participation, 164 patients provided informed consent (32.9% response rate), and 157 patients completed at least the baseline measurement. The baseline drop-out rate was 4.3% (Figure 1).

Participant characteristics

The average participant age was 75.7 (SD, 6.9) years in the intervention arm and 76.6 (SD, 6.7) years in the control arm, and the majority were female (respectively 69.3% and 72.0%). Participants in the control arm used slightly more medicines at baseline (9.3 (SD, 3.2) to 8.4 (SD,2.4)), and more control patients were living with a partner (53.6% to 44%) (Table 1).

Table 1 Demographic characteristics at baseline.

	Intervention (n=75)	Control (n=82)
Age (years)	75.7 (6.9)	76.6 (6.7)
Sex (female) (n (%))	52 (69.3)	59 (72.0)
Number of medicines	8.4 (2.4)	9.3 (3.2)
DBI	3.1 (1.0)	3.2 (1.0)
Marital status (n (%))		

Partner	33 (44.0%)	44 (53.6%)
Widow/widower/Divorced/single	34 (45.3%)	32 (39.0%)
Unknown	8 (10.6%)	6 (7.3%)
Level of education (n (%))		
No/ low/ middle	58 (77.3%)	64 (78.0%)
High	9 (12.0%)	13 (15.8%)
Unknown	8 (10.6%)	5 (6.0%)
Medication use at baseline (top 5 (n (%)))		
ATC Nervous system	75 (100%)	82 (100%)
ATC Cardiovascular	70 (93.3%)	74 (90.2%)
ATC Alimentary tract	64 (85.3%)	71 (86.6%)
ATC Blood/ blood forming organs	49 (65.3%)	46 (56.1%)
ATC Respiratory tract	20 (26.7%)	38 (46.3%)

*Data are means (SD) or numbers (%)

Primary outcome

In the first analysis, which included all patients with a baseline measurement, a higher proportion of patients in the intervention group had a decrease of DBI ≥0.5 (17.3% to 15.9%, OR 1.04, CI 0.47 to 2.64, p=0.927), however this finding was not statistically significant. Similar results were obtained in the second analysis, which included all patients who were not lost to follow-up, and who received the intervention as allocated (Table 2).

Table 2: Proportion of patients having a decrease in DBI ≥ 0.5 by analysis type

	Proportion with decrease of DBI ≥ 0.5 (%, n)		Odds ratio (95% CI) *	p-value
	Intervention	Control		
First analysis[#] (n=157)	17.3% (13)	15.9% (13)	1.04 (0.47 to 2.64)	0.927
Second analysis[+] (n=145)	18.5% (12)	16.3% (13)	1.09 (0.45 to 2.63)	0.857

* Binary logistic regression, adjusted for age, gender, number of medication at baseline.

First analysis: all patients with a baseline measurement

Second analysis: all patients who were not lost to follow-up, and who received the intervention as allocated

Secondary outcome

Secondary outcomes were analysed including all patients who were not lost to follow-up and who received the intervention as allocated (Table 3). A difference was seen in the DSST and reporting of sedative side effects between allocation arms. Patients in the intervention arm scored higher at follow-

up on average (3 (SD, 1) to 1 (SD, 0) point (s), OR 2.02, CI 1.11 to 3.67, p=0.021) and reported less sedative side effects at follow up compared to the control arm (-1 (IQR, -2) to 1 (IQR, 0) point(s), OR 0.61, CI 0.40 to 0.94, p=0.024). For all other secondary outcomes no difference was found between intervention and control arm.

Table 3: Secondary outcomes at follow-up

	Intervention (n=65)		Control (n=80)		Adjusted difference at follow-up (95% CI)
	Baseline	**Difference at follow-up**	**Baseline**	**Difference at follow-up**	
Trailmaking Test A[†]	59 (37)	-8 (-5)	61 (28)	-6 (2)	0.99 (0.90 to 1.09)
Trailmaking Test B[†]	149 (103)	-4 (24)	152 (103)	1 (19)	0.99 (0.87 to 1.11)
DSST	36 (12)	3 (1)	36 (13)	1 (0)	2.02 (1.11 to 3.67)*
7MS: enhanced cued recall[‡]	85 (55)	0 (0)	84 (71)	5 (4)	0.54 (0.15 to 1.90)
7MS: Benton temporal orientation[‡]	95 (62)	-3 (-2)	99 (79)	-4 (-3)	1.38 (0.28 to 6.88)
7MS: clock drawing[‡]	80 (52)	-8 (-5)	86 (69)	-6 (-5)	0.67 (0.28 to 1.62)
7MS: verbal fluency	16 (5)	0 (-1)	16 (5)	0 (0)	0.84 (0.21 to 3.28)
GARS[‡]□	72 (46)	2 (-1)	69 (54)	0 (0)	1.73 (0.62 to 4.84)
Sedative side effects[†]	3 (5)	-1 (-2)	2 (4)	1 (0)	0.61 (0.40 to 0.94)*
UKU[†]	17 (22)	-3 (1)	18 (27)	-2 (-2)	0.97 (0.67 to 1.39)
EQ-5D-3L[‡]	74 (48)	9 (6)	76 (61)	4 (3)	1.02 (0.95 to 1.09)
VAS	6.5 (1.5)	0 (0)	7.0 (1.5)	0 (0)	0.91 (0.61 to 1.37)
Up&Go[‡]□	66 (42)	0 (0)	64 (50)	4 (3)	1.37 (0.60 to

	3.14)

Data are given as means (standard deviation (SD)), median[†] (interquartile range (IQR)), and percentage (number) of patients in higher scoring group[‡]. DSST = Digit Symbol Substitution Test, 7MS = Seven Minute Screen, GARS = Groningen Activities Restriction Scale, UKU = Udvalg for Kliniske Undersogelser (measuring anticholinergic side effects), VAS = visual analogue scale (part of EQ-5D-3L). *Statistically significant difference (based on linear mixed model analysis, $p < 0.05$, adjusted for age, gender, number of medication at baseline. Deviation of number of patients, as 3 patients were excluded for this test/questionnaire: n=64 for intervention, n=78 for control.

Of all 144 patients, who did have a follow-up meeting, 60 falls were reported across 34 patients (15 in control arm (19.5%) and 19 from intervention arm (28.4%)). No significant relationship was found between reported falls and allocation (p=0.146). There was also no difference found between control- and intervention arm in hospitalization, 9 (11.7%) to 3 (4.5%) patients reported unplanned hospital admission, (p=0.103) and mortality, 1 (1.2%) to 1 (1.3%) patient died, (p=0.732).

DISCUSSION

We found that in our study medication review did not reduce the anticholinergic and/or sedative medication load in older people. In addition, medication review did not improve cognitive function, apart from the DSST. We also found that medication review had no effect on anticholinergic side effects, quality of life, activities of daily living, risk of falls, hospitalization, and mortality. However, intervention patients reported fewer sedative side effects.

Strengths and limitations of the study

This randomized controlled trial was the first to focus on changing anticholinergic and sedative medication load by medication review. The trial was completed successfully, allocation arms were comparable and we achieved a medium response rate, yet there are some methodological limitations that should be considered when interpreting our findings. First, the wide confidence intervals of our primary outcome suggest the study was underpowered to detect a small effect. However, we believe our study was appropriately powered to detect a clinically relevant medium difference between intervention and control arm. Second, although we did check whether all steps of the medication review were conducted, it was outside the scope of our study to investigate to what extent pharmacists adhered to communication methods recommended by the guideline on performing the medication review. Informal conversations with pharmacists suggested that although the guidelines insist on a face-to-face meeting between the pharmacist and GP, some pharmacists contacted the GP by phone, fax, or email due to lack of time. This might have had an effect on the implementation of medication suggestions, [16] but we believe that our results reflect "real-world" practice of how medication reviews

are carried out in Dutch health care practice. Third, we followed patients for three months after the intervention. One could suggest that more time was needed to determine the effect of the intervention, as changes in medication use may require more time, for example withdrawing of medication by step-wise reduction of dosing. However we found no indication for this, as few dosage changes were seen.

Comparison with other studies

The medication changes in both groups were comparable, suggesting that these reflect fluctuations of medication use over time as prescribing is a dynamic rather than a static process. We do not know the pattern of fluctuations in anticholinergic and sedative medication prescribing; this should be explored in longitudinal studies. Our results are in line with a number of meta-analyses, which also reported a lack of effect of medication reviews on a variety of patient outcomes. [12-14] Our results are in contrast to a number of studies, which found medication reviews to be effective in specific subgroups of patients with multiple comorbidities, polypharmacy and pain. [1819] The medication reviews in these studies however were not specifically focusing on medication with anticholinergic and/or sedative properties as we did. Two small Australian studies suggest that the DBI can be lowered, but these studies were based on pharmacist recommendations and did not investigate actual implementation of these by the GP. [910] Although some lowering of the DBI was seen, the latter study did find that GPs had difficulties in changing medications, for example with those medications initiated by specialists. A recent study also showed that while it was possible to optimize use for a number of medication classes, psychotropic medications were among the most difficult to adjust. [35] So, despite guidance how to reduce anticholinergic and sedative medication, [36-38] as highlighted by our findings, there seem to be important barriers preventing reduction in clinical practice.

Conclusions and implications for practice

Using the DBI, a highly vulnerable population group in need of medication optimization can be identified. The current strategy of multidisciplinary medication review does not appear effective in reducing the DBI. Despite some practical issues with the DBI, such as the lack of an international consensus-based list of anticholinergic/sedative medication including minimum doses, [39] we suggest to use the DBI as a tool to identify harmful medication users. This approach may be suitable for other patient groups and in other settings such as nursing homes. [40] Enlarging the multidisciplinary team should also be considered, for example psychiatrists advising GPs on lowering or ceasing medication and psychologists assisting patients during withdrawal. Furthermore, signalling a rising burden and taking action before chronic use of medication with anticholinergic and/or sedative properties is established may be the preferred approach.

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Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Contributors

KT initiated the study and HW and HGvdM contributed to the study conception, design, and to the intervention development. HGvdM, HW and KT reviewed the study parameters and contributed to the analysis plan; obtained ethical approval. KT did randomisation. HGvdM led the trial and collected the data. HGvdM and HW did the statistical analysis with input from KT. All authors contributed to the interpretation of the results. HGvdM drafted the manuscript. All the authors revised and approved the final manuscript. KT is the guarantor.

Data sharing

Data are available from corresponding author on request.

Ethics approval

This study was approved by the Medical Ethical Committee of the University Medical Centre of Groningen (protocol number METc 2014/392; in Dutch: Medisch Ethische Toetsingscommissie van het Universitair Medisch Centrum Groningen [METc UMCG]). Participants provided written informed consent before participating in the study.

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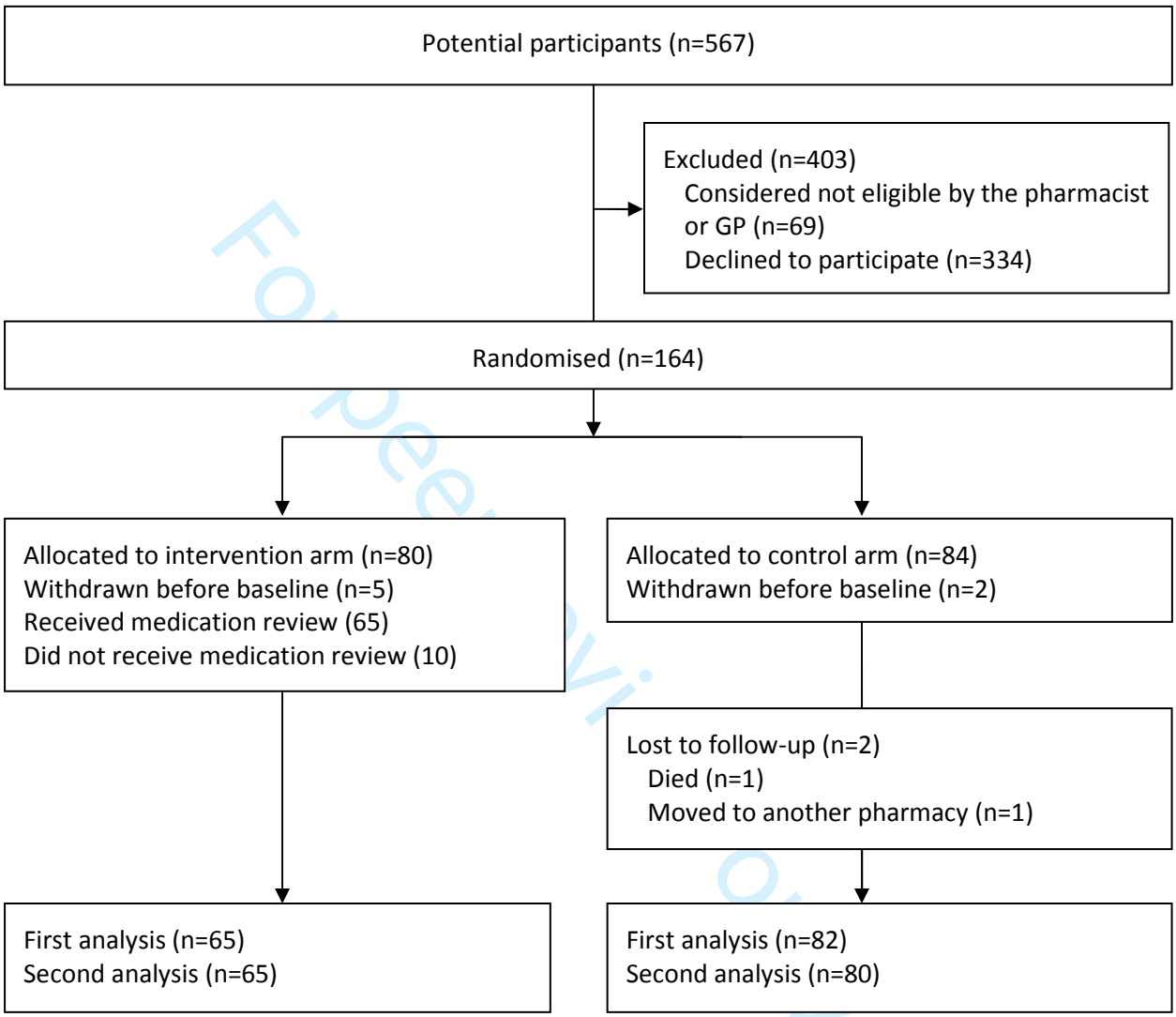
Potential participants (n=567)
Excluded (n=403)
Considered not eligible by the pharmacist or GP (n=69)
Declined to participate (n=334)
Randomised (n=164)
Allocated to intervention arm (n=80)
Withdrawn before baseline (n=5)
Received medication review (65)
Did not receive medication review (10)
Allocated to control arm (n=84)
Withdrawn before baseline (n=2)
Lost to follow-up (n=2)
Died (n=1)
Moved to another pharmacy (n=1)
First analysis (n=65)
Second analysis (n=65)
First analysis (n=82)
Second analysis (n=80)

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2-3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4-5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	4-5
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5-6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	6-7
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	5
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	5
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	5
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	5

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	7
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	7-8
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	8-9
	13b	For each group, losses and exclusions after randomisation, together with reasons	7-8 + figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	4
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	8-9
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	7-8 + figure 1
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	9-11
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	9-11
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	9-11
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	11-12
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	12
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	12
Other information			
Registration	23	Registration number and name of trial registry	3
Protocol	24	Where the full trial protocol can be accessed, if available	5
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	13

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Reducing the burden of anticholinergic and sedative medication in older patients on polypharmacy by pharmacist-led medication review: A randomized controlled trial

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Keywords:	AGED, DRUG BURDEN INDEX, MEDICATION REVIEW, MUSCARINIC ANTAGONISTS, POLYPHARMACY

Reducing the burden of anticholinergic and sedative medication in older patients on polypharmacy by pharmacist-led medication review: A randomized controlled trial

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Keywords: aged; drug burden index; medication review; muscarinic antagonists; polypharmacy

Word count: 3452

Tables: 3

Figure: 1

Appendices: 3

ABSTRACT

OBJECTIVE

To evaluate if a pharmacist-led medication review is effective at reducing anticholinergic and sedative burden, as measured by the Drug Burden Index (DBI).

DESIGN

Randomized controlled single blind trial.

SETTING

15 community pharmacies in the Northern Netherlands.

PARTICIPANTS

157 community-dwelling patients aged ≥ 65 years who used ≥ 5 medicines for ≥ 3 months, including at least one psycholeptic or psychoanaleptic medication, and who had a DBI ≥ 1.

INTERVENTION

A medication review by the community pharmacist in collaboration with the patient's general practitioner and patient.

PRIMARY AND SECONDARY OUTCOMES MEASURES

The primary outcome was the proportion of patients whose DBI decreased by at least 0.5. Secondary outcomes were the presence of anticholinergic and/or sedative side effects, falls, cognitive function, activities of daily living, quality of life, hospital admission, and mortality. Data were collected at baseline and three-months follow-up.

RESULTS

Mean participant age was 75.7 (SD, 6.9) years in the intervention arm and 76.6 (SD, 6.7) years in the control arm, and the majority were female (respectively 69.3% and 72.0%). Logistic regression analysis showed no difference in the proportion of patients with a ≥ 0.5 decrease in DBI between intervention arm (17.3%) and control arm (15.9%), (OR 1.04, CI 0.47 to 2.64, p=0.927). Intervention patients scored higher on the digit symbol substitution test, measure of cognitive function, (OR 2.02, CI 1.11 to 3.67, p=0.021), and reported fewer sedative side effects (OR 0.61, CI 0.40 to 0.94, p=0.024) at follow-up.

CONCLUSIONS

Pharmacist-led medication review as currently performed in the Netherlands was not effective in reducing the burden of anticholinergic/sedative medication measured with the DBI within the time frame of 3 months. Preventive strategies, signalling a rising burden and taking action before chronic use of anticholinergic and/or sedative medication is established, may be more successful.

TRIAL REGISTRATION

Clinical trials NCT02317666.

STRENGTHS AND LIMITATION OF THIS STUDY

- A successfully completed randomized controlled trial, which was the first to focus on changing anticholinergic and sedative medication load by medication review.
- Appropriately powered to detect a clinically relevant medium difference.
- Showing the effect of "real world" practiced medication review, rather than the theoretical approach described in guidelines.
- Three-months follow-up might have been too short to detect full effects of medication review, e.g. due to stepwise reduction of medication, however very few dosage changes were seen.

BACKGROUND

Older people suffer from many medical conditions and use more medication than any other age group. Multiple medication use in combination with age-related physiological changes increase the risk of medication related harm including adverse drug events, drug-drug- and drug-disease-interactions.[1] Medications with anticholinergic and/or sedative properties are of particular concern in older people, because they worsen cognitive impairment and physical functioning, increase the risk of falls and negatively impact activities of daily living, hospitalization, and mortality.[2, 3] Despite the risks, these medications are commonly prescribed to older individuals.[4] Different measures have been developed to quantify the anticholinergic burden in patients.[5] The Drug Burden Index (DBI) determines an individual's exposure to anticholinergic and sedative medication taking into account the dose.[6, 7] A high DBI has been associated with impairments in both physical- and cognitive function among older individuals.[8] Hence, decreasing exposure to anticholinergic and sedative medication, as measured by the DBI, may have important health benefits in older people.

Two small Australian studies suggest that medication review could be a promising strategy in reducing the DBI.[9, 10] In most countries a medication review is a structured assessment of a patient's medication, performed by the community pharmacist and/or general practitioner (GP), in order to optimize prescribing.[11] While meta-analyses of studies in different settings show a lack of effectiveness on outcomes such as mortality or hospital (re-) admissions,[12-14] these studies included different types of medication review. Well-structured medication review with good cooperation between pharmacist and GP and involvement of the patient were most likely to be successful.[15, 16] Furthermore fee-for-pharmacist-led medication review seemed to have positive health benefits on the patient.[17] The most effective method for medication review remains unknown. Focusing on specific subgroups such as older people with multiple comorbidities and polypharmacy,[18] or patients suffering from pain [19] may be one strategy to optimize medication review associated benefits. To date, there is no consensus on the effectiveness of medication review as a strategy to reduce anticholinergic and sedative burden as measured by the DBI. Therefore, the primary aim of this study was to evaluate if a medication review is an effective strategy to reduce anticholinergic and sedative burden as measured by the DBI. Secondarily, we evaluated the effect of a medication review on patient outcomes including cognitive function, risk of falls, activities of daily living and quality of life.

METHODS

Study design, setting & participants

We conducted a randomized controlled, single blind trial in 15 community pharmacies from December 2014 until October 2015 in the Northern Netherlands. Pharmacies were recruited via the regional

association of pharmacists and participation was voluntary. One pharmacist per pharmacy was involved in the study. In Dutch community pharmacy practice, all registered pharmacists are allowed to perform medication reviews. Furthermore, pharmacists collaborate with GPs in their area. This includes local regular meetings of pharmacists and GPs in pharmacotherapy counselling groups.[20] In the Netherlands, each individual is registered with a single pharmacy. Pharmacies hold a complete electronic medication history for each patient registered with them. When undertaking a medication review the pharmacists may request the patients' medical records from the GP. At the time of the study, all Dutch community pharmacists were required to perform medication reviews in cooperation with the GP for high risk patients according to the guidelines.[11]

Patients who were aged ≥ 65 years, living independently, using ≥ 5 medications for ≥ 3 months, including at least one psycholeptic or psychoanaleptic medication (Anatomic Therapeutic Classification (ATC) code N05 or N06),[21] and with a DBI ≥ 1 were identified by the pharmacist and invited to participate in the study. Exclusion criteria were limited life expectancy (< 3 months), non-Dutch language speaker or advanced dementia. Patients who had received a medication review within the past 9 months before the study period and patients who needed a medication review urgently were also excluded. Exclusion criteria were identified by the pharmacist with whom the patient was registered. This study was approved by the Medical Ethical Committee of the University Medical Centre of Groningen, The Netherlands (protocol number METc 2014/392). The study protocol has been published elsewhere.[22]

Randomization, allocation & blinding

Eligible patients were approached by the pharmacist and asked to provide written informed consent. In each pharmacy, patients willing to participate were then matched in pairs by gender, age, DBI and number of medications. One patient of each pair was randomly assigned to the intervention condition. All participants gave written consent prior to the intervention allocation. The randomization process was conducted by the principal investigator, who was not involved in recruitment or data collection. The researchers who enrolled the patients and collected the data were kept blind to the allocation. Pharmacists and patients could not be kept blind, but were explicitly asked not to reveal study allocation for individual patients to the researchers who collected the data. Therefore this was a single blind study.

Intervention

The intervention was a medication review conducted by the community pharmacist in close collaboration with the patients' GP and, if needed, other medical specialists. In the Netherlands medication review consists of five steps.[11] Step one is a face-to-face consultation between the pharmacist and patient to discuss medication use. Second, the pharmacist undertakes a pharmacotherapeutic medication review, identifying potential pharmacotherapeutic problems and

drafting written recommendations for medication optimisation to discuss with the patients' GP. Third, a multidisciplinary meeting, between pharmacist and GP is held. At this meeting, the potential medication problems of the patient are discussed and draft of a pharmacotherapeutic action plan is decided. Fourth, a discussion of the draft pharmacotherapeutic action plan between patient and pharmacist and/or GP. The patients' expectations and wishes are key elements in the decision-making process and are included in the final action plan. Fifth, a follow-up of the final pharmacotherapeutic action plan is undertaken. Further detail of the medication review process and the Dutch guideline underpinning the study can be found in our previously published study protocol.[22] The pharmacists participating in the study all undertook regular medication reviews as part of their practice and as such were familiar with the guideline. Nonetheless, we provided the guidelines to the pharmacists with the request to focus on anticholinergic and sedative medications. No additional educational material on anticholinergic and sedative medication was provided. In order to get a reflection of 'real world' practice, we let the pharmacists perform the medication reviews according to their routine practice, but we did check whether all 5 steps were conducted. The medication review took place within days after the baseline measurement for the intervention patients. In the control group, patients received the medication review after the study period.

Outcomes

The primary outcome was defined as the difference in proportion of patients having a decrease of DBI ≥ 0.5 at 3-months follow-up. We chose a 3-months follow-up because this was a reasonable time frame to detect medication changes by the medication review. A longer follow-up would have increased the chance of medication changes due to other reasons, such as changes in disease status. Our hypothesis was that the proportion with a 0.5 decrease in DBI would be higher in the intervention arm compared to the control arm. We chose 0.5, as this equals the cessation of one drug, which we considered a clinically relevant decrease. The DBI was calculated using the following formula [7]:

$$\text{DBI} = \sum \frac{D}{D+\delta}$$

D = daily dose, δ = minimum recommended daily dose were derived for the study from Dutch standard reference sources.[23, 24] Except for sensory and dermatological preparations, all chronic medications (i.e. those used for ≥ 3 months) with anticholinergic properties (dry mouth, constipation and urine retention) and sedative properties based on Dutch standard reference sources [23-25] were included in the calculation. Medication data were derived from electronic pharmacy dispensing data and were verified with the patient.

We included the following secondary outcomes: anticholinergic side effects, measured by the Udvalg for Kliniske Undersogelser (UKU) side effect rating scale,[26] sedative side effects, derived from a patient-reported adverse drug event questionnaire,[27] and risk of falls, determined by the Up & Go

test.[28] Cognitive function was measured using validated tests for memory and executive function, namely the Seven Minute Screen (7MS),[29] the Trailmaking Test A & B,[30] and Digit Symbol Substitution Test (DSST).[31] The latter has also previously been used to examine the validity of the DBI.[7] Activities of daily living were derived using the validated Groningen Activity Restriction Scale (GARS),[32, 33] and quality of life was measured by the Euroqol-5 Dimension-3 Level (EQ-5D-3L) questionnaire, including visual analogue scale (VAS).[34] All tools were administered in Dutch and data were collected in a standardized manner, using data collection sheets, by researchers who were trained by a psychologist. Data collection took place at baseline and 3-months follow-up for both allocations. Patients with the inability to walk were excluded from the Up&Go test and the GARS questionnaire. At follow-up the number of fall incidents, hospital admission, and mortality was assessed based on patient/relative reporting.

Sample size calculation

To the best of our knowledge, only one randomized pilot study has been conducted assessing the DBI.[10] We therefore could not calculate the sample size 'a priori'. However we estimated a sample size based on a power of 80% at a significance of 0.05 and an intra-class correlation coefficient up to 0.2 to detect a medium effect size on the primary outcome.[35] We chose a medium effect size as we considered a small effect size to be not clinically relevant and a power to detect a medium effect size also to be capable of detecting a large effect size. For this calculation around 160 participants (80 in control arm and 80 in intervention arm) were needed. We expected a non-response rate of 60% and therefore aimed to invite 400 patients to participate in the study.

Statistical analysis

We performed two analyses. In the first analysis we included all patients with a baseline measurement. In the second analysis, we included all patients who were not lost to follow-up, and who received the intervention as allocated. Descriptive statistics were calculated for both allocation arms at baseline. For the analysis of the primary outcome, we initially considered a generalized linear mixed effects model to adjust for dependence of observations (i.e. clustering of patients within pharmacies). However, as the intra-class correlation was not significant and no significant clustering was observed, extension of the model with random effects at the level of pharmacies was not necessary. Therefore, only fixed effects were considered and standard fixed effects logistic regression model applied. Most secondary outcomes were examined with standard regression models. Variables with a skewed distribution were transformed before analysis. For dichotomous variables we reported percentages and numbers of patients in the best scoring group, for skewed variables we report the median and interquartile range and for normally distributed data we report the mean and standard deviation. Further detail on the analysis of secondary outcome tests and –questionnaires data can be found in appendix table 1. Reported falls, hospitalization and mortality were only assessed from patients with a follow-up measurement. These variables were dichotomized, reported as number and percentages of

patients and analysed using Fisher's exact test. A sensitivity analysis was conducted on outliers (appendix table 2) and all analyses were adjusted for gender, age, and number of medication at baseline. Secondary outcomes were also adjusted for baseline scores. Analyses were done in SPSS 24 and MLwiN 2.36, statistical tests were two-sided and conducted at the 5% significance level.

Missing data

Few data were missing for the primary outcome. Of the two patients, who were lost to follow-up, the baseline observation for medication use was carried forward to follow-up. For eight patients, medication use could not be verified with the patient, as they could not be reached by telephone despite several attempts. For these patients, the medication data from the pharmacy dispensing system were used. For secondary outcomes, 5.3% of data were missing in the complete dataset, mostly at follow-up (4.8%). In the intervention arm, 7.0% of data was missing (6.1% at follow-up) across 18 patients, whereas in the control arm 3.7% was missing (3.4% at follow-up) across 12 patients. In total 30 patients had missing data, of whom two were lost to follow-up. Eight patients were not able to complete one or more cognitive tests (0.5% of all data). Eleven patients could not be tested at follow-up within the study period, six patients due to sickness, four patients due to practical reasons (despite numerous attempts we were unsuccessful to arrange an appointment for the follow-up measurement), and one patient had died two days before the follow-up appointment. A few data were missing for other reasons across nine patients, for example patients forgetting their glasses, due to time constraints, or other reasons.

Missing data in cognitive tests due to inability of the patient to complete the task were replaced with the worst score for that specific group. Missing data of patients who could not be tested at follow-up within the study period, or who had missing data for other reasons were replaced by multiple imputation (five times) in SPSS 24. In this paper we report on the imputed dataset. Sensitivity analysis showed no difference between the dataset with and without missing data.

RESULTS

Participant flow

Overall, 498 patients were approached for participation, 164 patients provided informed consent (32.9% response rate), and 157 patients completed at least the baseline measurement and were included in the first analysis (Figure 1). The drop-out rate was 4.3%.

Participant characteristics

The average participant age was 75.7 (SD, 6.9) years in the intervention arm and 76.6 (SD, 6.7) years in the control arm, and the majority were female (respectively 69.3% and 72.0%). Participants in the

control arm used slightly more medicines at baseline (9.3 (SD, 3.2) to 8.4 (SD,2.4)), and more control patients were living with a partner (53.6% to 44%) (Table 1).

Table 1 Demographic characteristics at baseline.

	Intervention (n=75)	Control (n=82)
Age (years) mean (SD)	75.7 (6.9)	76.6 (6.7)
Sex (female) (n (%))	52 (69.3)	59 (72.0)
Number of medicines (mean (SD)	8.4 (2.4)	9.3 (3.2)
DBI (mean (SD)	3.1 (1.0)	3.2 (1.0)
Marital status (n (%))		
Partner	33 (44.0)	44 (53.6)
Widow/widower/Divorced/single	34 (45.3)	32 (39.0)
Unknown	8 (10.6)	6 (7.3)
Level of education (n (%))		
No/ low/ middle	58 (77.3)	64 (78.0)
High	9 (12.0)	13 (15.8)
Unknown	8 (10.6)	5 (6.0)
Medication use at baseline (top 5 (n (%)))		
ATC Nervous system	75 (100)	82 (100)
ATC Cardiovascular	70 (93.3)	74 (90.2)
ATC Alimentary tract	64 (85.3)	71 (86.6)
ATC Blood/ blood forming organs	49 (65.3)	46 (56.1)
ATC Respiratory tract	20 (26.7)	38 (46.3)

Primary outcome

In the first analysis, which included all patients with a baseline measurement, the proportion of patients with a decrease of DBI ≥0.5 did not differ between patients in intervention- and control group (17.3% to 15.9%, OR 1.04, CI 0.47 to 2.64, p=0.927). Similar results were obtained in the second analysis, which included all patients who were not lost to follow-up, and who received the intervention as allocated (Table 2). A detailed description of medications started, stopped and changed in dose in both arms can be found in appendix table 3.

Table 2: Proportion of patients having a decrease in DBI ≥ 0.5 by analysis type

Analysis type	Proportion with decrease of DBI ≥ 0.5 (%, n)	Odds ratio (95% CI) *	p-value

	Intervention	Control		
First analysis (n=157)	17.3 (13)	15.9 (13)	1.04 (0.47 to 2.64)	0.927
Second analysis (n=145)	18.5 (12)	16.3 (13)	1.09 (0.45 to 2.63)	0.857

* Binary logistic regression, adjusted for age, gender, number of medication at baseline.

First analysis: all patients with a baseline measurement

Second analysis: all patients who were not lost to follow-up, and who received the intervention as allocated

Secondary outcome

Secondary outcome tests and - questionnaires were analysed including all patients who were not lost to follow-up and who received the intervention as allocated (Table 3). A difference was seen in the DSST and reporting of sedative side effects between allocation arms. Patients in the intervention arm scored higher at follow-up on average (3 (SD, 1) to 1 (SD, 0) point (s), OR 2.02, CI 1.11 to 3.67, p=0.021) and reported less sedative side effects at follow up compared to the control arm (-1 (IQR, -2) to 1 (IQR, 0) point(s), OR 0.61, CI 0.40 to 0.94, p=0.024). For all other secondary outcomes no difference was found between intervention and control arm.

Table 3: Secondary outcome tests and - questionnaires at follow-up

Outcome	Intervention (n=65)		Control (n=80)		Treatment difference at FU (95% CI)
	BL score	Δ with FU	BL score	Δ with FU	
Trailmaking Test A, median (IQR)	59.0 (36.9)	-8.4 (-4.8)	61.0 (27.8)	-6.0 (1.6)	-0.01 (-0.11 - 0.09)†
Trailmaking Test B, median (IQR)	149.0 (103.0)	-3.9 (24.1)	152.0 (103.0)	1.0 (19.0)	-0.01 (-0.14 - 0.11)†
DSST, mean (SD)	36.4 (12.2)	2.6 (1.2)	36.4 (13.2)	1.0 (-0.3)	0.70 (0.11 - 1.30)†*
7MS enhanced cued recall, % (n) best scoring	85 (55)	0 (0)	84 (71)	5 (4)	0.54 (0.15 - 1.90)‡
7MS Benton temporal orientation, % (n) best scoring	95 (62)	-3 (-2)	99 (79)	-4 (-3)	1.38 (0.28 - 6.88)‡
7MS clock drawing, % (n) best scoring	80 (52)	-8 (-5)	86 (69)	-6 (-5)	0.67 (0.28 - 1.62)‡
7MS category fluency, mean (SD)	16.1 (5.5)	0.1 (-0.6)	15.9 (5.0)	0.4 (-0.3)	-0.18 (-1.55 - 1.20)†

GARS, % (n) best scoring	72 (46)	2 (-1)	69 (54)	0 (0)	1.73 (0.62 - 4.84) ‡0
Sedative side effects, median (IQR)	3.0 (5.0)	-1.0 (-2.0)	2.0 (4.0)	1 (0)	0.61 (0.40 - 0.94) §*
UKU, median (IQR)	17.0 (22.0)	-3.0 (1.0)	18.0 (27.0)	-1.6 (-2.4)	0.97 (0.67 - 1.39) §
EQ-5D-3L, % (n) best scoring	74 (48)	9 (6)	76 (61)	4 (3)	1.43 (0.51 - 4.03)‡
VAS, mean (SD)	6.6 (1.6)	-0.2 (0.0)	6.8 (1.4)	-0.1 (0.1)	-0.09 (-0.50 - 0.32)†
Up&Go, % (n) best scoring	66 (42)	0 (0)	64 (50)	4 (3)	1.37 (0.60 - 3.14) ‡0

BL = Baseline, FU = Follow-up, DSST = Digit Symbol Substitution Test; 7MS = Seven Minute Screen; GARS = Groningen Activities Restriction Scale; UKU = Udvalg for Kliniske Undersogelser (measuring anticholinergic side effects); VAS = visual analogue scale (part of EQ-5D-3L).
†Linear regression analysis (reporting unstandardized b), ‡logistic regression analysis (reporting odds ratio), §negative binomial regression analysis (reporting incident rate ratio) used, all adjusted for age, gender, number of medication at baseline. *Statistically significant difference ($p < 0.05$). 0Deviation of number of patients: n=64 for intervention, n=78 for control, 3 patients were excluded from this test/questionnaire.

Reported falls and hospitalization could be assessed from 136 patients who were included in the second analysis. No significant difference was found in reported falls between control- and intervention group, respectively 15 patients (19.5%) versus 18 patients (30.5%), (p=0.100). There was also no difference found between control- and intervention arm in hospitalization, 9 (11.7%) versus 3 (5.1%) patients reported unplanned hospital admission, (p=0.149). Of all patients who were included in the study, 2 died, 1 (1.2%) in control group to 1 (1.3%) intervention group, (p=0.732).

DISCUSSION

In our study pharmacist-led medication review did not reduce the anticholinergic and/or sedative medication load in older people within the first 3-months following review. In addition, medication review did not improve cognitive function, apart from the DSST. We also found that medication review had no effect on anticholinergic side effects, quality of life, activities of daily living, risk of falls, hospitalization, and mortality. However, intervention patients reported fewer sedative side effects.

Strengths and limitations of the study

This randomized controlled trial was the first to focus on changing anticholinergic and sedative medication load by medication review. The trial was completed successfully, allocation arms were comparable and we achieved a medium response rate. We also believe our study was appropriately

powered to detect a clinically relevant medium difference between intervention and control arm. Yet there are some methodological limitations that should be considered when interpreting our findings. Firstly, our study design might have introduced a risk of contamination between intervention- and control arm, as pharmacists and GPs could have been triggered to optimize medication use also for patients in the control arm during the study period. We know from the pharmacists that no structured medication reviews were performed for control patients during the study period. Therefore we believe that changes we observed in control patients were due to usual care. Cluster randomization may have prevented the chance of contamination, but this method has other disadvantages.[36] Second, although we did check whether all steps of the medication review were conducted, it was outside the scope of our study to investigate to what extent pharmacists adhered to communication methods recommended by the guideline on performing the medication review. Informal conversations with pharmacists suggested that although the guidelines recommend a face-to-face meeting between the pharmacist and GP, some pharmacists contacted the GP by phone, fax, or email due to lack of time. This might have had an effect on the implementation of medication suggestions.[16] A full process evaluation might have given insight in this, but also might have changed the normal practice of pharmacists to carry out medication reviews.[37] We believe that our results reflect "real-world" practice of how medication reviews were carried out in Dutch health care practice at the time of the study. Third, we followed patients for three months after the intervention. One could suggest that more time was needed to determine the effect of the intervention, as changes in medication use may require more time, for example withdrawing of medication by step-wise reduction of dosing. However, there did not seem to be a difference in dosage changes between intervention- and control arm. Finally, one third of all eligible patients were willing to participate in the study. Given the frailty of this population and the time consuming nature of participation, we think this is a very reasonable response rate. Nevertheless, our results may not be generalizable to the total population.

Comparison with other studies

The medication changes in both groups were comparable, suggesting that these reflect fluctuations of medication use over time as prescribing is a dynamic - rather than a static process. We do not know the pattern of fluctuations in anticholinergic and sedative medication prescribing; this should be explored in longitudinal studies. Our results are in line with a number of meta-analyses, which also reported a lack of effect of medication reviews on a variety of patient outcomes.[12-14] Our results are in contrast to a number of studies, which found medication reviews to be effective in specific subgroups of patients with multiple comorbidities, polypharmacy and pain.[18, 19] The medication reviews in these studies however were not specifically focusing on medication with anticholinergic and/or sedative properties as we did. Two small Australian studies suggest that the DBI can be lowered, but these studies were based on pharmacist recommendations and did not investigate actual implementation of these by the GP.[9, 10] Although some lowering of the DBI was seen, the latter

study did find that GPs had difficulties in changing medications, for example with those medications initiated by specialists. A recent study also showed that while it was possible to optimize use for a number of medication classes, psychotropic medications were among the most difficult to adjust.[38] So, despite guidance how to reduce anticholinergic and sedative medication,[39-41] as highlighted by our findings, there seem to be important barriers preventing reduction in clinical practice.

Conclusions and implications for practice

Using the DBI, a highly vulnerable population group in need of medication optimization can be identified. Pharmacist-led medication review as currently performed in the Netherlands did not appear effective in reducing the DBI. Despite some practical issues with the DBI, such as the lack of an international consensus-based list of anticholinergic/sedative medication including minimum doses,[42] we suggest to use the DBI as a tool to identify harmful medication users. This approach may be suitable for other patient groups and in other settings such as nursing homes or GP practice with co-located pharmacist.[43, 44] Enlarging the multidisciplinary team should also be considered, for example psychiatrists advising GPs on lowering or ceasing medication and psychologists assisting patients during withdrawal. Furthermore, signalling a rising burden and taking action before chronic use of medication with anticholinergic and/or sedative properties is established may be the preferred approach.

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Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Contributors

KT initiated the study and HW and HGvdM contributed to the study conception, design, and to the intervention development. HGvdM, HW and KT reviewed the study parameters and contributed to the analysis plan; obtained ethical approval. KT did randomisation. HGvdM led the trial and collected the data. HGvdM and HW did the statistical analysis with input from KT. All authors contributed to the interpretation of the results. HGvdM drafted the manuscript. All the authors revised and approved the final manuscript. KT is the guarantor.

Data sharing

Data are available from corresponding author on request.

Ethics approval

This study was approved by the Medical Ethical Committee of the University Medical Centre of Groningen (protocol number METc 2014/392; in Dutch: Medisch Ethische Toetsingscommissie van het Universitair Medisch Centrum Groningen [METc UMCG]). Participants provided written informed consent before participating in the study.

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Figure 1: Participant flow

*All patients who had a baseline measurement.
†All patients who were not lost to follow-up and received the intervention as allocated.

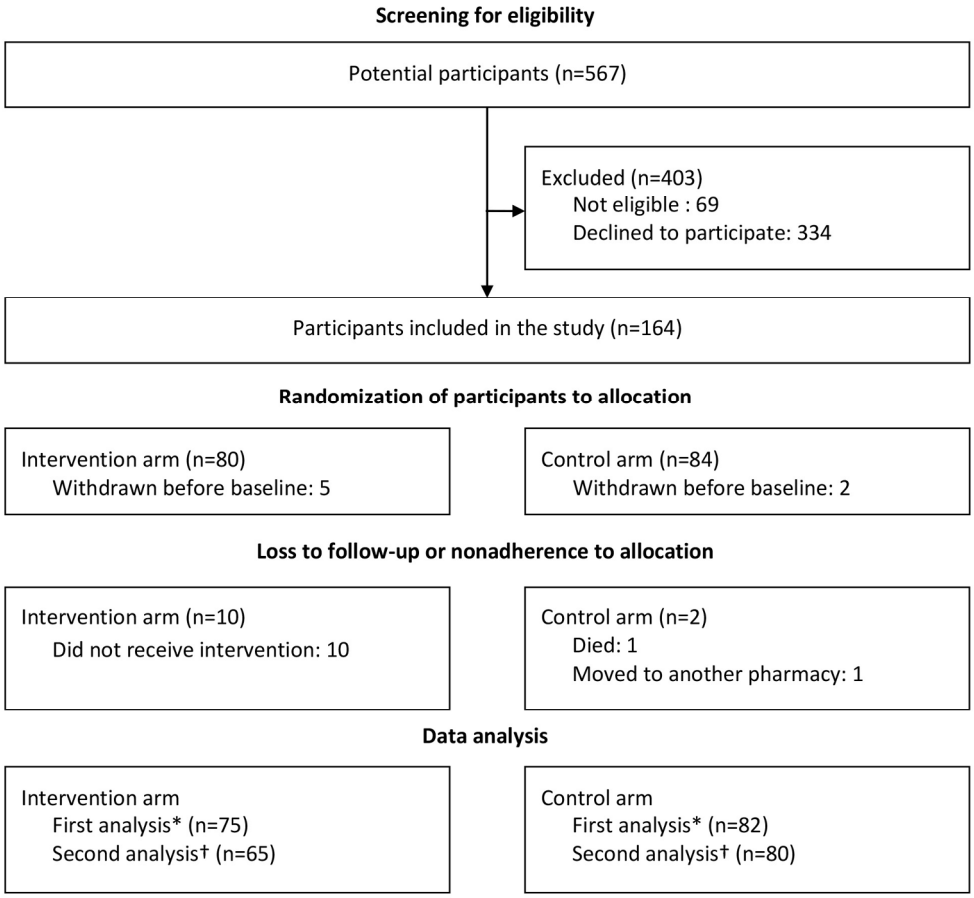

Figure 1: Participant flow/ *All patients who had a baseline measurement.
†All patients who were not lost to follow-up and received the intervention as allocated.

168x156mm (300 x 300 DPI)

Appendix table 1: Secondary outcomes distribution and treatment in our study.

Outcome	Measurement scale	Best score measured	Worst score measured	Distribution	Transformation	Cut-off points	Regression type	Reporting
Cognitive function								
Trailmaking Test A	Time in seconds to finish	26	202	Left skewed	logarithmic	N/A	linear	median (IQR)
Trailmaking Test B	Time in seconds to finish	55	439	Left skewed	logarithmic	N/A	linear	median (IQR)
DSST	Number of symbols correct	75	7	Normal, with high variance	5% classes	N/A	linear	mean (SD)
7MS enhanced cued recall	Number of items recalled	16	5	Ceiling effects	dichotomized	15	logistic	% (n) in best scoring group
7MS Benton temporal orientation	Number of error points	0	106	Floor effects	dichotomized	5	logistic	% (n) in best scoring group
7MS clock drawing	Number of correct items drawn	7	1	Ceiling effects	dichotomized	6	logistic	% (n) in best scoring group
7MS category fluency	Number of animal names produced	32	5	Normal	N/A	N/A	linear	mean (SD)
Activities of daily living								
Groningen Activity Restriction Scale	Severity of problems	18	66	Left skewed	dichotomized	36	logistic	% (n) in best scoring group
Side effects								
Sedative side effects	Severity/number of side effects	0	12	Negative binomial	N/A	N/A	negative binomial	median (IQR)
UKU	Severity/number of side effects	0	84	Negative binomial	N/A	N/A	negative binomial	median (IQR)
Quality of life								
EQ-5D-3L	Utilities	1	-0.204	Right skewed	dichotomized	0,5	logistic	% (n) in best scoring group
EQ-5D-3L: Visual Analogue Scale	Points on scale	10	2	Normal	N/A	N/A	linear	mean (SD)
Risk of falls								
Up&Go test	Time in seconds	6	43	Dichotomous	≥15	N/A	logistic	% (n) in best scoring group

Appendix table 2: Sensitivity analysis of proportion of patients having a decrease in DBI ≥ 0.5

	Proportion with decrease of DBI ≥ 0.5, n/N (%)		Odds ratio (95% CI) *	p-value
	Intervention	Control		
DBI > 1.5	12/64 (18.8)	13/78 (16.7)	1.15 (0.49 to 2.74)	0.746
DBI < 6	12/64 (18.8)	13/79 (16.5)	1.17 (0.49 to 2.78)	0.720
Number of medications at baseline >5	12/61 (19.7)	12/78 (15.4)	1.35 (0.56 to 3.25)	0.508
Number of medications at baseline <20	12/65 (18.5)	13/79 (16.5)	1.15 (0.48 to 2.73)	0.752
Age >66	12/65 (18.5)	12/77 (15.6)	1.23 (0.51 to 2.95)	0.649
Age <93	12/64 (18.8)	13/79 (16.5)	1.17 (0.49 to 2.78)	0.720

* Binary logistic regression, unadjusted, according to second analysis.

Appendix table 3: Patients who had medications started, stopped and changed in dose at follow-up in intervention- and control arm.

ATC code class	Intervention (n=65)		Control (n=80)	
	DBI medication (%, n)	All medication (%, n)	DBI medication (%, n)	All medication (%, n)
Started				
A (alimentary tract and metabolism)	7.7 (5)	20.0 (13)	3.7 (3)	11.3 (9)
R (respiratory system)	4.6 (3)	12.3 (8)	3.7 (3)	7.5 (6)
N (nervous system)	4.6 (3)	6.2 (4)	3.7 (3)	7.5 (6)
M (musculo-skeletal system)	0 (0)	6.2 (4)	3.7 (3)	5.0 (4)
C (cardiovascular system)	4.6 (3)	6.2 (4)	1.3 (1)	2.5 (2)
B (blood and blood forming organs)	0 (0)	10.8 (7)	0 (0)	7.5 (6)
L (antineoplastic and immune-modulating agents)	1.5 (1)	3.1 (2)	0 (0)	0 (0)
H (systemic hormonal preparations, excl. sex hormones and insulins)	0 (0)	1.5 (1)	0 (0)	0 (0)
G (genito urinary system and sex hormones)	0 (0)	0 (0)	1.3 (1)	1.3 (1)
S (sensory organs)	0 (0)	0 (0)	0 (0)	1.3 (1)
Total*	20.0 (13)	43.1 (28)	13.8 (11)	33.8 (27)
Stopped				
A (alimentary tract and metabolism)	9.2 (6)	21.5 (14)	2.5 (2)	6.3 (5)
N (nervous system)	13.8 (9)	15.4 (10)	12.5 (10)	15.0 (12)
C (cardiovascular system)	6.2 (4)	9.2 (6)	7.5 (6)	10.0 (8)
B (blood and blood forming organs)	0 (0)	9.2 (6)	0 (0)	6.3 (5)
R (respiratory system)	0 (0)	7.7 (5)	3.7 (3)	13.8 (11)
M (musculo-skeletal system)	3.1 (2)	4.6 (3)	5.0 (4)	5.0 (4)
G (genito urinary system and sex hormones)	3.1 (2)	4.6 (3)	1.3 (1)	1.3 (1)
D (dermatologicals)	0 (0)	1.5 (1)	0 (0)	0 (0)
H (systemic hormonal preparations, excl. sex hormones and insulins)	0 (0)	0 (0)	0 (0)	2.4 (2)
L (antineoplastic and immune-modulating agents)	0 (0)	0 (0)	1.3 (1)	1.3 (1)
S (sensory organs)	0 (0)	0 (0)	0 (0)	1.3 (1)
Total*	30.8 (20)	46.2 (30)	22.5 (18)	41.3 (33)
Dose change				
N (nervous system)	21.5 (14)	23.1 (15)	21.3 (17)	22.5 (18)
C (cardiovascular system)	10.8 (7)	15.4 (10)	1.3 (1)	2.5 (2)
A (alimentary tract and metabolism)	1.5 (1)	4.6 (3)	3.7 (3)	3.8 (3)
R (respiratory system)	0 (0)	1.5 (1)	1.3 (1)	1.3 (1)
B (blood and blood forming organs)	0 (0)	1.5 (1)	0 (0)	0 (0)
M (musculo-skeletal system)	0 (0)	1.5 (1)	0 (0)	0 (0)
H (systemic hormonal preparations, excl. sex hormones and insulins)	0 (0)	0 (0)	0 (0)	3.8 (3)
J (antiinfectives for systemic use)	0 (0)	0 (0)	1.3 (1)	1.3 (1)
Total*	27.7 (18)	38.5 (25)	23.8 (19)	28.0 (23)
Total interventions	53.8 (35)	72.3 (47)	45.0 (36)	66.3 (53)

ATC = Anatomical Therapeutic Chemical, classification by the WHO Collaborating Centre for Drug Statistics Methodology. Based on second analysis. *Not sum of subtotals, as some patients had several interventions.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2-3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4-5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	4-5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5-6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6-7
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	7
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	5
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	5
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	5
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	5

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	7-8
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	7-8
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	8-9
	13b	For each group, losses and exclusions after randomisation, together with reasons	7-8 + figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	4
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	9
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	8-9 + figure 1
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	9-11
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	9-11
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	9-11
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	11-12
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	12
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	12-13
Other information			
Registration	23	Registration number and name of trial registry	3
Protocol	24	Where the full trial protocol can be accessed, if available	5
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	14

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Reducing the anticholinergic and sedative load in older patients on polypharmacy by pharmacist-led medication review: A randomized controlled trial

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Reducing the anticholinergic and sedative load in older patients on polypharmacy by pharmacist-led medication review: A randomized controlled trial

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Keywords: aged; drug burden index; medication review; muscarinic antagonists; polypharmacy; deprescribing

Word count: 3768

Tables: 3

Figure: 1

Appendices: 3

ABSTRACT

OBJECTIVE

To evaluate if a pharmacist-led medication review is effective at reducing the anticholinergic/sedative load, as measured by the Drug Burden Index (DBI).

DESIGN

Randomized controlled single blind trial.

SETTING

15 community pharmacies in the Northern Netherlands.

PARTICIPANTS

157 community-dwelling patients aged ≥ 65 years who used ≥ 5 medicines for ≥ 3 months, including at least one psycholeptic/psychoanaleptic medication, and who had a DBI ≥ 1.

INTERVENTION

A medication review by the community pharmacist in collaboration with the patient's general practitioner and patient.

PRIMARY AND SECONDARY OUTCOMES MEASURES

The primary outcome was the proportion of patients whose DBI decreased by at least 0.5. Secondary outcomes were the presence of anticholinergic/sedative side effects, falls, cognitive function, activities of daily living, quality of life, hospital admission, and mortality. Data were collected at baseline and three-months follow-up.

RESULTS

Mean participant age was 75.7 (SD, 6.9) years in the intervention arm and 76.6 (SD, 6.7) years in the control arm, the majority were female (respectively 69.3% and 72.0%). Logistic regression analysis showed no difference in the proportion of patients with a ≥ 0.5 decrease in DBI between intervention arm (17.3%) and control arm (15.9%), (OR 1.04, CI 0.47 to 2.64, p=0.927). Intervention patients scored higher on the digit symbol substitution test, measure of cognitive function, (OR 2.02, CI 1.11 to 3.67, p=0.021), and reported fewer sedative side effects (OR 0.61, CI 0.40 to 0.94, p=0.024) at follow-up. No significant difference was found for other secondary outcomes.

CONCLUSIONS

Pharmacist-led medication review as currently performed in the Netherlands was not effective in reducing the anticholinergic/sedative load, measured with the DBI, within the time frame of 3 months. Preventive strategies, signalling a rising load and taking action before chronic use of anticholinergic/sedative medication is established, may be more successful.

TRIAL REGISTRATION

Clinical trials NCT02317666.

STRENGTHS AND LIMITATION OF THIS STUDY

- A successfully completed randomized controlled trial, which was the first to focus on changing anticholinergic and sedative load by medication review.
- Appropriately powered to detect a clinically relevant medium difference.
- Showing the effect of "real world" practiced medication review, rather than the theoretical approach described in guidelines.
- Three-months follow-up might have been too short to detect full effects of medication review, e.g. due to stepwise reduction of medication, however very few dosage changes were seen.

BACKGROUND

Older people suffer from many medical conditions and use more medication than any other age group. Multiple medication use in combination with age-related physiological changes increase the risk of medication related harm including adverse drug events, drug-drug- and drug-disease-interactions. [1] Medications with anticholinergic and/or sedative properties are of particular concern in older people, because they worsen cognitive impairment and physical functioning, increase the risk of falls and negatively impact activities of daily living, hospitalization, and mortality. [2, 3] Despite the risks, these medications are commonly prescribed to older individuals. [4, 5] Different measures have been developed to quantify the anticholinergic load in patients. [6] The Drug Burden Index (DBI) determines an individual's exposure to anticholinergic and sedative medication taking into account the dose. [7, 8] A high DBI has been associated with impairments in both physical- and cognitive function among older individuals. [9, 10] Hence, decreasing exposure to anticholinergic and sedative medication, as measured by the DBI, may have important health benefits in older people.

Two small Australian studies suggest that medication review could be a promising strategy in reducing the DBI in community dwelling older people. [11, 12] Medication review is 'a structured critical examination of a person's medicines with the objective of reaching an agreement with the person about treatment, optimising the impact of medicines, minimising the number of medication-related problems and reducing waste'. [13] While meta-analyses of studies in different settings show a lack of effectiveness on outcomes such as mortality or hospital (re-) admissions, [14-16] these studies included different types of medication review. Well-structured medication review with good cooperation between pharmacist and GP and involvement of the patient were most likely to be successful. [17, 18] Furthermore fee-for-pharmacist-led medication review seemed to have positive health benefits on the patient. [19] The most effective method for medication review remains unknown. Focusing on specific subgroups such as older people with multiple comorbidities and polypharmacy, [20] or patients suffering from pain [21] may be one strategy to optimize medication review associated benefits. To date, there is no consensus on the effectiveness of medication review as a strategy to reduce anticholinergic and sedative load as measured by the DBI. Therefore, the primary aim of this study was to evaluate if a medication review is an effective strategy to reduce anticholinergic and sedative load as measured by the DBI. Secondarily, we evaluated the effect of a medication review on patient outcomes including cognitive function, risk of falls, activities of daily living and quality of life.

METHODS

Study design, setting & participants

We conducted a randomized controlled, single blind trial in 15 community pharmacies from December 2014 until October 2015 in the Northern Netherlands. Pharmacies were recruited via the regional association of pharmacists and participation was voluntary. One pharmacist per pharmacy was involved in the study. In Dutch community pharmacy practice, all registered pharmacists are allowed to perform medication reviews. Furthermore, pharmacists collaborate with GPs in their area. This includes local regular meetings of pharmacists and GPs in pharmacotherapy counselling groups. [22] In the Netherlands, each individual is registered with a single pharmacy. [23] Pharmacies hold a complete electronic medication history for each patient registered with them. When undertaking a medication review it is routine practice of pharmacists to obtain an extensive summary of the electronic patients' medical records, including latest recorded episodes and lab-values, from the GP. [24] At the time of the study, all Dutch community pharmacists were required to perform medication reviews in cooperation with the GP for high-risk patients according to the guidelines. [25] Patients who were aged ≥ 65 years, living independently, using ≥ 5 medications for ≥ 3 months, including at least one psycholeptic or psychoanaleptic medication (Anatomic Therapeutic Classification (ATC) code N05 or N06), [26] and with a DBI ≥ 1 were identified by the pharmacist and invited to participate in the study. Exclusion criteria were limited life expectancy (< 3 months), non-Dutch language speaker or advanced dementia. Patients who had received a medication review within the past 9 months before the study period and patients who needed a medication review urgently were also excluded. Exclusion criteria were identified by the pharmacist with whom the patient was registered. This study was approved by the Medical Ethical Committee of the University Medical Centre of Groningen, The Netherlands (protocol number METc 2014/392). The study protocol has been published elsewhere. [27]

Randomization, allocation & blinding

Eligible patients were approached by the pharmacist and asked to provide written informed consent. In each pharmacy, patients willing to participate were then matched in pairs by gender, age, DBI and number of medications. One patient of each pair was randomly assigned to the intervention condition. All participants gave written consent prior to the intervention allocation. The randomization process was conducted by the principal investigator, who was not involved in recruitment or data collection. The researchers who enrolled the patients and collected the data were kept blind to the allocation. Pharmacists and patients could not be kept blind, but were explicitly asked not to reveal study allocation for individual patients to the researchers who collected the data. Therefore this was a single blind study.

Intervention

The intervention was a medication review conducted by the community pharmacist in close collaboration with the patients' GP and, if needed, other medical specialists. In the Netherlands medication review consisted of five steps. [25] Step one was a face-to-face consultation between the

pharmacist and patient to discuss medication use. Second, the pharmacist undertook a pharmacotherapeutic medication review, identified potential pharmacotherapeutic problems taking into account the patient's medical records, including latest recorded episodes and lab-values. Accordingly the pharmacist drafted written recommendations for medication optimisation to discuss with the patients' GP. Third, a multidisciplinary meeting, between pharmacist and GP was held. At this meeting, the potential medication problems of the patient were discussed and draft of a pharmacotherapeutic action plan was decided. Fourth, a discussion of the draft pharmacotherapeutic action plan between patient and pharmacist and/or GP. The patients' expectations and wishes were key elements in the decision-making process and were included in the final action plan. Fifth, a follow-up of the final pharmacotherapeutic action plan was undertaken. Further detail of the medication review process and the Dutch guideline underpinning the study can be found in our previously published study protocol. [27] The pharmacists participating in the study all undertook regular medication reviews as part of their practice and as such were familiar with the guideline. Nonetheless, we provided the guidelines to the pharmacists with the request to focus on anticholinergic and sedative medications. No additional educational material on anticholinergic and sedative medication was provided. In order to get a reflection of 'real world' practice, we let the pharmacists perform the medication reviews according to their routine practice, but we did check whether all 5 steps were conducted. The medication review took place within days after the baseline measurement for the intervention patients. In the control arm, patients received the medication review after the study period.

Outcomes

The primary outcome was defined as the difference in proportion of patients having a decrease of DBI ≥ 0.5 at 3-months follow-up. We chose a 3-months follow-up because this was a reasonable time frame to detect medication changes by the medication review. A longer follow-up would have increased the chance of medication changes due to other reasons, such as changes in disease status. Our hypothesis was that the proportion with a 0.5 decrease in DBI would be higher in the intervention arm compared to the control arm. We chose 0.5, as this equals the cessation of one drug, which we considered a clinically relevant decrease. The DBI was calculated using the following formula [8]:

$$\text{DBI} = \sum \frac{D}{D+\delta}$$

D = daily dose, δ = minimum recommended daily dose were derived for the study from Dutch standard reference sources. [28, 29] Except for sensory and dermatological preparations, all chronic medications (i.e. those used for ≥ 3 months) with anticholinergic properties (dry mouth, constipation and urine retention) and sedative properties based on Dutch standard reference sources [28-30] were included in the calculation. Medication data were derived from electronic pharmacy dispensing data and were verified with the patient.

We included the following secondary outcomes: anticholinergic side effects, measured by the Udvalg for Kliniske Undersogelser (UKU) side effect rating scale, [31] sedative side effects, derived from a patient-reported adverse drug event questionnaire, [32] and risk of falls, determined by the Up & Go test. [33] Cognitive function was measured using validated tests for memory and executive function, namely the Seven Minute Screen (7MS), [34] the Trailmaking Test A & B, [35] and Digit Symbol Substitution Test (DSST). [36] The latter has also previously been used to examine the validity of the DBI. [8] Activities of daily living were derived using the validated Groningen Activity Restriction Scale (GARS), [37, 38] and quality of life was measured by the Euroqol-5 Dimension-3 Level (EQ-5D-3L) questionnaire, including visual analogue scale (VAS). [39] All tools were administered in Dutch and data were collected in a standardized manner, using data collection sheets, by researchers who were trained by a psychologist. Data collection took place at baseline and 3-months follow-up for both allocations. Patients with the inability to walk were excluded from the Up&Go test and the GARS questionnaire. At follow-up the number of fall incidents, hospital admission, and mortality was assessed based on patient/relative reporting.

Sample size calculation

To the best of our knowledge, only one randomized pilot study has been conducted assessing the DBI. [12] We therefore could not calculate the sample size 'a priori'. However we estimated a sample size based on a power of 80% at a significance of 0.05 and an intra-class correlation coefficient up to 0.2 to detect a medium effect size on the primary outcome. [40] We chose a medium effect size as we considered a small effect size to be not clinically relevant and a power to detect a medium effect size also to be capable of detecting a large effect size. For this calculation around 160 participants (80 in control arm and 80 in intervention arm) were needed. We expected a non-response rate of 60% and therefore aimed to invite 400 patients to participate in the study.

Statistical analysis

We performed two analyses. In the first analysis we included all patients with a baseline measurement. In the second analysis, we included all patients who were not lost to follow-up, and who received the intervention as allocated. Descriptive statistics were calculated for both allocation arms at baseline. For the analysis of the primary outcome, we initially considered a generalized linear mixed effects model to adjust for dependence of observations (i.e. clustering of patients within pharmacies). However, as the intra-class correlation was not significant and no significant clustering was observed, extension of the model with random effects at the level of pharmacies was not necessary. Therefore, only fixed effects were considered and standard fixed effects logistic regression model applied. Most secondary outcomes were examined with standard regression models. Variables with a skewed distribution were transformed before analysis. For dichotomous variables we reported percentages and numbers of patients in the best scoring group, for skewed variables we report the median and interquartile range and for normally distributed data we report the mean and standard deviation.

Further detail on the analysis of secondary outcome tests and –questionnaires data can be found in appendix table 1. Reported falls, hospitalization and mortality were only assessed from patients with a follow-up measurement. These variables were dichotomized, reported as number and percentages of patients and analysed using Fisher's exact test. A sensitivity analysis was conducted on outliers (appendix table 2) and all analyses were adjusted for gender, age, and number of medication at baseline. Secondary outcomes were also adjusted for baseline scores. Analyses were done in SPSS 24 and MLwiN 2.36, statistical tests were two-sided and conducted at the 5% significance level.

Missing data

Few data were missing for the primary outcome. Of the two patients, who were lost to follow-up, the baseline observation for medication use was carried forward to follow-up. For eight patients, medication use could not be verified with the patient, as they could not be reached by telephone despite several attempts. For these patients, the medication data from the pharmacy dispensing system were used. For secondary outcomes, 5.3% of data were missing in the complete dataset, mostly at follow-up (4.8%). In the intervention arm, 7.0% of data was missing (6.1% at follow-up) across 18 patients, whereas in the control arm 3.7% was missing (3.4% at follow-up) across 12 patients. In total 30 patients had missing data, of whom two were lost to follow-up. Eight patients were not able to complete one or more cognitive tests (0.5% of all data). Eleven patients could not be tested at follow-up within the study period, six patients due to sickness, four patients due to practical reasons (despite numerous attempts we were unsuccessful to arrange an appointment for the follow-up measurement), and one patient had died two days before the follow-up appointment. A few data were missing for other reasons across nine patients, for example patients forgetting their glasses, due to time constraints, or other reasons.

Missing data in cognitive tests due to inability of the patient to complete the task were replaced with the worst score for that specific group. Missing data of patients who could not be tested at follow-up within the study period, or who had missing data for other reasons were replaced by multiple imputation (five times) in SPSS 24. In this paper we report on the imputed dataset. Sensitivity analysis showed no difference between the dataset with and without missing data.

Patient and Public involvement

Patients and or public were not involved in the design or conduct of the study. After the study period all participants received a thank you letter including a brief summary of the overall results.

RESULTS

Participant flow

Overall, 498 patients were approached for participation, 164 patients provided informed consent (32.9% response rate), and 157 patients completed at least the baseline measurement and were included in the first analysis (Figure 1). The drop-out rate was 4.3%.

Participant characteristics

The average participant age was 75.7 (SD, 6.9) years in the intervention arm and 76.6 (SD, 6.7) years in the control arm, and the majority were female (respectively 69.3% and 72.0%). Participants in the control arm used slightly more medicines at baseline (9.3 (SD, 3.2) to 8.4 (SD,2.4)), and more control patients were living with a partner (53.6% to 44%) (Table 1).

Table 1 Demographic characteristics at baseline.

	Intervention (n=75)	Control (n=82)
Age (years) mean (SD)	75.7 (6.9)	76.6 (6.7)
Sex (female) (n (%))	52 (69.3)	59 (72.0)
Number of medicines (mean (SD)	8.4 (2.4)	9.3 (3.2)
DBI (mean (SD)	3.1 (1.0)	3.2 (1.0)
Marital status (n (%))		
Partner	33 (44.0)	44 (53.6)
Widow/widower/Divorced/single	34 (45.3)	32 (39.0)
Unknown	8 (10.6)	6 (7.3)
Level of education (n (%))		
No/ low/ middle	58 (77.3)	64 (78.0)
High	9 (12.0)	13 (15.8)
Unknown	8 (10.6)	5 (6.0)
Medication use at baseline (top 5 (n (%)))		
ATC Nervous system	75 (100)	82 (100)
ATC Cardiovascular	70 (93.3)	74 (90.2)
ATC Alimentary tract	64 (85.3)	71 (86.6)
ATC Blood/ blood forming organs	49 (65.3)	46 (56.1)
ATC Respiratory tract	20 (26.7)	38 (46.3)

Primary outcome

In the first analysis, which included all patients with a baseline measurement, the proportion of patients with a decrease of DBI ≥0.5 did not differ between patients in intervention- and control arm (17.3% to 15.9%, OR 1.04, CI 0.47 to 2.64, p=0.927). Similar results were obtained in the second analysis, which included all patients who were not lost to follow-up, and who received the intervention

as allocated (Table 2). Descriptive analysis showed medication changes (starting, stopping, dosage change) of DBI medications on ATC code level 1 in 53.8% of patients from intervention arm and in 45.0% of patients from control arm. For cardiovascular DBI medications, dose increases and – decreases of different medications occurred in 10.8% patients from intervention arm compared to 1.3% of patients from control arm (Appendix table 3).

Table 2: Proportion of patients having a decrease in DBI ≥ 0.5 by analysis type

Analysis type	Proportion with decrease of DBI ≥ 0.5 (%, n)		Odds ratio (95% CI) *	p-value
	Intervention	Control		
First analysis (n=157)	17.3 (13)	15.9 (13)	1.04 (0.47 to 2.64)	0.927
Second analysis (n=145)	18.5 (12)	16.3 (13)	1.09 (0.45 to 2.63)	0.857

* Binary logistic regression, adjusted for age, gender, number of medication at baseline.

First analysis: all patients with a baseline measurement

Second analysis: all patients who were not lost to follow-up, and who received the intervention as allocated

Secondary outcome

Secondary outcome tests and - questionnaires were analysed including all patients who were not lost to follow-up and who received the intervention as allocated (Table 3). A difference was seen in the DSST and reporting of sedative side effects between allocation arms. Patients in the intervention arm scored higher at follow-up on average (3 (SD, 1) to 1 (SD, 0) point (s), OR 2.02, CI 1.11 to 3.67, p=0.021) and reported less sedative side effects at follow up compared to the control arm (-1 (IQR, -2) to 1 (IQR, 0) point(s), OR 0.61, CI 0.40 to 0.94, p=0.024). For all other secondary outcomes no difference was found between intervention and control arm.

Table 3: Secondary outcome tests and - questionnaires at follow-up

Outcome	Intervention (n=65)		Control (n=80)		Treatment difference at FU (95% CI)
	BL score	Δ with FU	BL score	Δ with FU	
Trailmaking Test A, median (IQR)	59.0 (36.9)	-8.4 (-4.8)	61.0 (27.8)	-6.0 (1.6)	-0.01 (-0.11 - 0.09)†
Trailmaking Test B, median (IQR)	149.0 (103.0)	-3.9 (24.1)	152.0 (103.0)	1.0 (19.0)	-0.01 (-0.14 - 0.11)†
DSST, mean (SD)	36.4 (12.2)	2.6 (1.2)	36.4 (13.2)	1.0 (-0.3)	0.70 (0.11 - 1.30)†*
7MS enhanced cued recall, % (n) best	85 (55)	0 (0)	84 (71)	5 (4)	0.54 (0.15 - 1.90)‡

scoring					
7MS Benton temporal orientation, % (n) best scoring	95 (62)	-3 (-2)	99 (79)	-4 (-3)	1.38 (0.28 - 6.88) ‡
7MS clock drawing, % (n) best scoring	80 (52)	-8 (-5)	86 (69)	-6 (-5)	0.67 (0.28 - 1.62) ‡
7MS category fluency, mean (SD)	16.1 (5.5)	0.1 (-0.6)	15.9 (5.0)	0.4 (-0.3)	-0.18 (-1.55 - 1.20) †
GARS, % (n) best scoring	72 (46)	2 (-1)	69 (54)	0 (0)	1.73 (0.62 - 4.84) ‡0
Sedative side effects, median (IQR)	3.0 (5.0)	-1.0 (-2.0)	2.0 (4.0)	1 (0)	0.61 (0.40 - 0.94) §*
UKU, median (IQR)	17.0 (22.0)	-3.0 (1.0)	18.0 (27.0)	-1.6 (-2.4)	0.97 (0.67 - 1.39) §
EQ-5D-3L, % (n) best scoring	74 (48)	9 (6)	76 (61)	4 (3)	1.43 (0.51 - 4.03) ‡
VAS, mean (SD)	6.6 (1.6)	-0.2 (0.0)	6.8 (1.4)	-0.1 (0.1)	-0.09 (-0.50 - 0.32) †
Up&Go, % (n) best scoring	66 (42)	0 (0)	64 (50)	4 (3)	1.37 (0.60 - 3.14) ‡0

BL = Baseline, FU = Follow-up, DSST = Digit Symbol Substitution Test; 7MS = Seven Minute Screen; GARS = Groningen Activities Restriction Scale; UKU = Udvalg for Kliniske Undersogelser (measuring anticholinergic side effects); VAS = visual analogue scale (part of EQ-5D-3L).
†Linear regression analysis (reporting unstandardized b), ‡logistic regression analysis (reporting odds ratio), §negative binomial regression analysis (reporting incident rate ratio) used, all adjusted for age, gender, number of medication at baseline. *Statistically significant difference ($p < 0.05$). 0Deviation of number of patients: n=64 for intervention, n=78 for control, 3 patients were excluded from this test/questionnaire.

Reported falls and hospitalization could be assessed from 136 patients who were included in the second analysis. No significant difference was found in reported falls between control- and intervention arm, respectively 15 patients (19.5%) versus 18 patients (30.5%), (p=0.100). There was also no difference found between control- and intervention arm in hospitalization, 9 (11.7%) versus 3 (5.1%) patients reported unplanned hospital admission, (p=0.149). Of all patients who were included in the study, 2 died, 1 (1.2%) in control arm to 1 (1.3%) intervention arm, (p=0.732).

DISCUSSION

In our study pharmacist-led medication review did not reduce the anticholinergic and/or sedative medication load in older people within the first 3-months following review. In addition, medication review did not improve cognitive function, apart from the DSST. We also found that medication review had no effect on anticholinergic side effects, quality of life, activities of daily living, risk of falls, hospitalization, and mortality. However, intervention patients reported fewer sedative side effects.

Strengths and limitations of the study

This randomized controlled trial was the first to focus on changing anticholinergic and sedative medication load by medication review. The trial was completed successfully, allocation arms were comparable and we achieved a medium response rate. We also believe our study was appropriately powered to detect a clinically relevant medium difference between intervention and control arm. Yet there are some methodological limitations that should be considered when interpreting our findings. Firstly, our study design might have introduced a risk of contamination between intervention- and control arm, as pharmacists and GPs could have been triggered to optimize medication use also for patients in the control arm during the study period. We know from the pharmacists that no structured medication reviews were performed for control patients during the study period. Therefore we believe that changes we observed in control patients were due to usual care. Cluster randomization may have prevented the chance of contamination, but this method has other disadvantages. [41] Second, although we did check whether all steps of the medication review were conducted, it was outside the scope of our study to investigate to what extent pharmacists adhered to methods recommended by the guideline on performing the medication review. Informal conversations with pharmacists suggested that although the guidelines recommend a face-to-face meeting between the pharmacist and GP, some pharmacists contacted the GP by phone, fax, or email due to lack of time. This might have had an effect on the implementation of medication suggestions. [18] Furthermore, while as part of the established collaboration between pharmacists and GPs in Dutch primary care, Dutch pharmacists routinely request an extensive summary of the electronic patient's medical records from the GP to perform a medication review, it is possible that some pharmacists did not do this. We performed a pragmatic trial and therefore our results reflect "real-world" practice of how medication reviews were carried out in Dutch health care practice at the time of the study. Third, we followed patients for three months after the intervention. Possibly, more time may have been necessary to determine the effect of the intervention. We were not able to collect data about timing of the medication review steps, so in some cases there may have been delay in performing all steps. But in Dutch primary care, pharmacists and GP's have an established close collaboration and therefore we believe that long delays were unlikely. Another argument for a longer follow-up could be that changes in medication use may require more time, for example withdrawing of medication by step-wise reduction of dosing. However, there did not seem to be a difference in dosage changes between intervention- and control

arm. Finally, one third of all eligible patients were willing to participate in the study. Given the frailty of this population and the time consuming nature of participation, we think this is a very reasonable response rate. Nevertheless, our results may not be generalizable to the total population.

Comparison with other studies

The medication changes in both arms were comparable. Small changes in different therapeutic medication groups suggest fluctuations of medication use over time as prescribing is a dynamic - rather than a static process. We do not know the pattern of fluctuations in anticholinergic and sedative medication prescribing; this should be explored in longitudinal studies powered to detect changes at medication level. Our results are in line with a number of meta-analyses, which also reported a lack of effect of medication reviews on a variety of patient outcomes. [14-16] Our results are in contrast to a number of studies, which found medication reviews to be effective in specific subgroups of patients with multiple comorbidities, polypharmacy and pain. [20, 21] The medication reviews in these studies however were not specifically focusing on medication with anticholinergic and/or sedative properties as we did. Two small Australian studies suggest that the DBI can be lowered, but these studies were based on pharmacist recommendations and did not investigate actual implementation of these by the GP. [11, 12] Although some lowering of the DBI was seen, the latter study did find that GPs had difficulties in changing medications, for example with those medications initiated by specialists. A recent study also showed that while it was possible to optimize use for a number of medication classes, psychotropic medications were among the most difficult to adjust. [42] So, despite guidance how to reduce anticholinergic and sedative medication, [43-45] as highlighted by our findings, there seem to be important barriers preventing reduction in clinical practice.

Conclusions and implications

Using the DBI, a highly vulnerable population group in need of medication optimization can be identified. Pharmacist-led medication review as currently performed in the Netherlands did not appear effective in reducing the DBI. While our study was powered to detect a difference in medication use, it should be acknowledged that other patient outcomes, like geriatric syndromes (e.g. risk of falls) and adverse events (e.g. drug-related hospital admission) are very important for the evaluation of medication review in older patients. Further studies should ensure sufficient sample sizes to study these outcomes. [46, 47] Despite some practical issues with the DBI, such as the lack of an international consensus-based list of anticholinergic/sedative medication including minimum doses, [10] we suggest to use the DBI as a tool to identify harmful medication users. This deprescribing approach may be suitable for other patient groups and in other settings such as nursing homes or GP practice with co-located pharmacist. [4, 48-50] Enlarging the multidisciplinary team should also be considered, for example psychiatrists advising GPs on lowering or ceasing medication and psychologists assisting patients during withdrawal. Furthermore, signalling a rising load and taking

action before chronic use of medication with anticholinergic and/or sedative properties is established may be the preferred approach.

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Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Contributors

KT initiated the study and HW and HGvdM contributed to the study conception, design, and to the intervention development. HGvdM, HW and KT reviewed the study parameters and contributed to the analysis plan; obtained ethical approval. KT did randomisation. HGvdM led the trial and collected the data. HGvdM and HW did the statistical analysis with input from KT. HGvdM, HW, KT and LP contributed to the interpretation of the results. HGvdM drafted the manuscript. HGvdM, HW, KT and LP revised and approved the final manuscript. KT is the guarantor.

Data sharing

Data are available from corresponding author on request.

Ethics approval

This study was approved by the Medical Ethical Committee of the University Medical Centre of Groningen (protocol number METc 2014/392; in Dutch: Medisch Ethische Toetsingscommissie van het Universitair Medisch Centrum Groningen [METc UMCG]). Participants provided written informed consent before participating in the study.

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Figure 1: Participant flow

*All patients who had a baseline measurement.
†All patients who were not lost to follow-up and received the intervention as allocated.

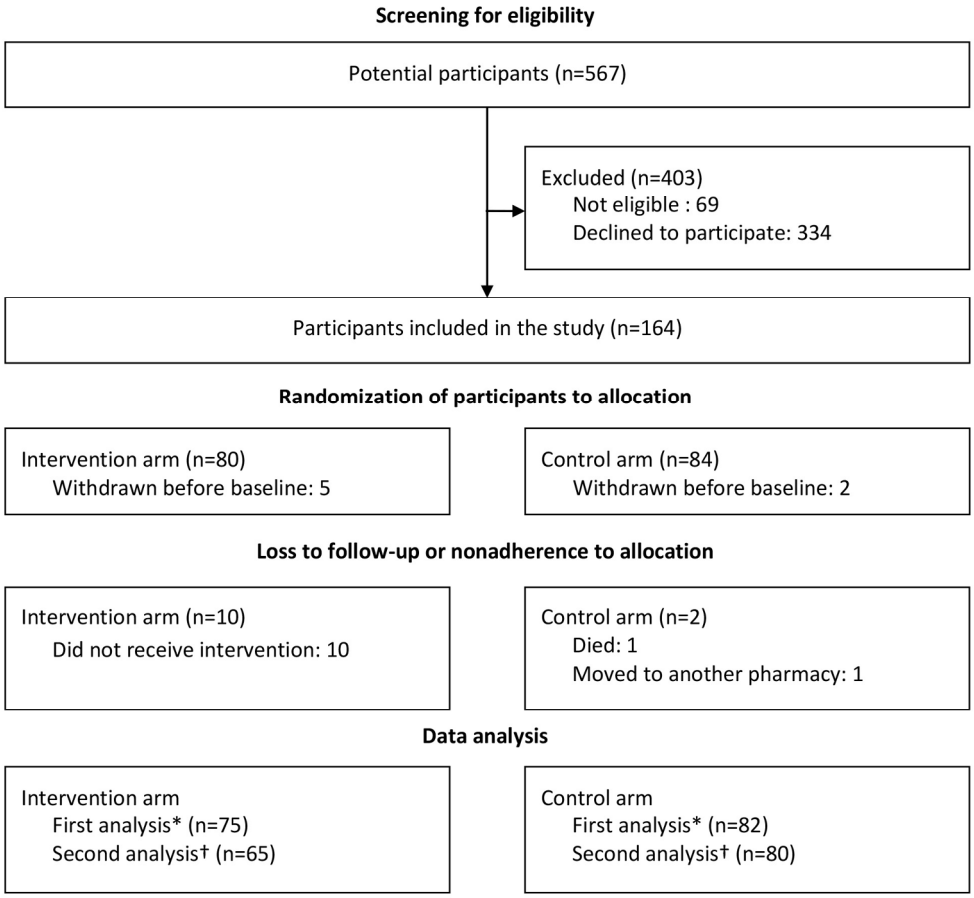

Figure 1: Participant flow/ *All patients who had a baseline measurement.
†All patients who were not lost to follow-up and received the intervention as allocated.

168x156mm (300 x 300 DPI)

Appendix table 1: Secondary outcomes distribution and treatment in our study.

Outcome	Description of test	Measurement scale	Best-worst score achievable	Best-worst score measured	Distribution	Transformation	Cut-off points	Regression type	Reporting
Cognitive function									
Trailmaking Test A	Connecting a series of numbers in the correct increasing order.	Time in seconds to complete	1-300	26-202	Left skewed	logarithmic	N/A	linear	median (IQR)
Trailmaking Test B	Connecting numbers and letters in the correct increasing order while alternating between numbers and letters e.g. 1-A-2-B-3-…etc.	Time in seconds to complete	1-600	55-439	Left skewed	logarithmic	N/A	linear	median (IQR)
DSST	Matching of the correct symbol to the correct number for multiple arrays of numbers using a legend displayed above.	Number of symbols correct	133-0	75-7	Normal	5% classes	N/A	linear	mean (SD)
7MS enhanced cued recall	Recalling 16 pictures that participants encoded using cues presented by examiner (e.g. I show you four pictures, which one is a piece of furniture?) followed by cued recall using these cues (e.g. "what piece of furniture did I just show you?	Number of items recalled	16-0	16-5	Ceiling effects	dichotomized	15	logistic	% (n) in best scoring group
7MS Benton temporal orientation	Assessing patient's time orientation.	Number of error points	0-113	0-106	Floor effects	dichotomized	5	logistic	% (n) in best scoring group
7MS clock drawing	Drawing a circle with a clock face including all the numbers and setting the hands to twenty to four.	Number of correct items drawn	7-0	7-1	Ceiling effects	dichotomized	6	logistic	% (n) in best scoring group
7MS category fluency	Naming as many animals as possible in 60 seconds.	Number of animal names produced	45-0	32-5	Normal	N/A	N/A	linear	mean (SD)
Activities of daily living									

Groningen Activity Restriction Scale	Questionnaire assessing problems with activities in daily living e.g. dressing oneself and climbing the stairs.	Severity of problems	18-72	18-66	Left skewed	dichotomized	36	logistic	% (n) in best scoring group
Side effects									
Sedative side effects	Questionnaire assessing sedative side effects.	Severity/number of side effects	0-14	0-12	Negative binomial	N/A	N/A	negative binomial	median (IQR)
UKU	Questionnaire assessing anticholinergic side effects.	Severity/number of side effects	0-144	0-84	Negative binomial	N/A	N/A	negative binomial	median (IQR)
Quality of life									
EQ-5D-3L	Assessing quality of life with regard to mobility, self-care, usual activities, pain discomfort and anxiety/depression.	Utilities	1-0	1-(-)0.204	Right skewed	dichotomized	0,5	logistic	% (n) in best scoring group
EQ-5D-3L: Visual Analogue Scale	Assessing self-related health state on a vertical visual analogue scale.	Points on scale	10-0	10-2	Normal	N/A	N/A	linear	mean (SD)
Risk of falls									
Up&Go test	Stand up from a chair, walk 3m, turn around and sit down.	Time in seconds	<15 - ≥15	6-43	Dichotomous	≥15	N/A	logistic	% (n) in best scoring group

Appendix table 2: Sensitivity analysis of proportion of patients having a decrease in DBI ≥ 0.5

	Proportion with decrease of DBI ≥ 0.5, n/N (%)		Odds ratio (95% CI) *	p-value
	Intervention	Control		
DBI > 1.5	12/64 (18.8)	13/78 (16.7)	1.15 (0.49 to 2.74)	0.746
DBI < 6	12/64 (18.8)	13/79 (16.5)	1.17 (0.49 to 2.78)	0.720
Number of medications at baseline >5	12/61 (19.7)	12/78 (15.4)	1.35 (0.56 to 3.25)	0.508
Number of medications at baseline <20	12/65 (18.5)	13/79 (16.5)	1.15 (0.48 to 2.73)	0.752
Age >66	12/65 (18.5)	12/77 (15.6)	1.23 (0.51 to 2.95)	0.649
Age <93	12/64 (18.8)	13/79 (16.5)	1.17 (0.49 to 2.78)	0.720

* Binary logistic regression, unadjusted, according to second analysis.

Appendix table 3: Patients who had medications started, stopped and changed in dose at follow-up in intervention- and control arm.

ATC code class	Intervention (n=65)		Control (n=80)	
	DBI medication (%, n)	All medication (%, n)	DBI medication (%, n)	All medication (%, n)
Started				
A (alimentary tract and metabolism)	7.7 (5)	20.0 (13)	3.7 (3)	11.3 (9)
R (respiratory system)	4.6 (3)	12.3 (8)	3.7 (3)	7.5 (6)
N (nervous system)	4.6 (3)	6.2 (4)	3.7 (3)	7.5 (6)
M (musculo-skeletal system)	0 (0)	6.2 (4)	3.7 (3)	5.0 (4)
C (cardiovascular system)	4.6 (3)	6.2 (4)	1.3 (1)	2.5 (2)
B (blood and blood forming organs)	0 (0)	10.8 (7)	0 (0)	7.5 (6)
L (antineoplastic and immune-modulating agents)	1.5 (1)	3.1 (2)	0 (0)	0 (0)
H (systemic hormonal preparations, excl. sex hormones and insulins)	0 (0)	1.5 (1)	0 (0)	0 (0)
G (genito urinary system and sex hormones)	0 (0)	0 (0)	1.3 (1)	1.3 (1)
S (sensory organs)	0 (0)	0 (0)	0 (0)	1.3 (1)
Total*	20.0 (13)	43.1 (28)	13.8 (11)	33.8 (27)
Stopped				
A (alimentary tract and metabolism)	9.2 (6)	21.5 (14)	2.5 (2)	6.3 (5)
N (nervous system)	13.8 (9)	15.4 (10)	12.5 (10)	15.0 (12)
C (cardiovascular system)	6.2 (4)	9.2 (6)	7.5 (6)	10.0 (8)
B (blood and blood forming organs)	0 (0)	9.2 (6)	0 (0)	6.3 (5)
R (respiratory system)	0 (0)	7.7 (5)	3.7 (3)	13.8 (11)
M (musculo-skeletal system)	3.1 (2)	4.6 (3)	5.0 (4)	5.0 (4)
G (genito urinary system and sex hormones)	3.1 (2)	4.6 (3)	1.3 (1)	1.3 (1)
D (dermatologicals)	0 (0)	1.5 (1)	0 (0)	0 (0)
H (systemic hormonal preparations, excl. sex hormones and insulins)	0 (0)	0 (0)	0 (0)	2.4 (2)
L (antineoplastic and immune-modulating agents)	0 (0)	0 (0)	1.3 (1)	1.3 (1)
S (sensory organs)	0 (0)	0 (0)	0 (0)	1.3 (1)
Total*	30.8 (20)	46.2 (30)	22.5 (18)	41.3 (33)
Dose change				
N (nervous system)	21.5 (14)	23.1 (15)	21.3 (17)	22.5 (18)
C (cardiovascular system)	10.8 (7)	15.4 (10)	1.3 (1)	2.5 (2)
A (alimentary tract and metabolism)	1.5 (1)	4.6 (3)	3.7 (3)	3.8 (3)
R (respiratory system)	0 (0)	1.5 (1)	1.3 (1)	1.3 (1)
B (blood and blood forming organs)	0 (0)	1.5 (1)	0 (0)	0 (0)
M (musculo-skeletal system)	0 (0)	1.5 (1)	0 (0)	0 (0)
H (systemic hormonal preparations, excl. sex hormones and insulins)	0 (0)	0 (0)	0 (0)	3.8 (3)
J (antiinfectives for systemic use)	0 (0)	0 (0)	1.3 (1)	1.3 (1)
Total*	27.7 (18)	38.5 (25)	23.8 (19)	28.0 (23)
Total interventions	53.8 (35)	72.3 (47)	45.0 (36)	66.3 (53)

ATC = Anatomical Therapeutic Chemical, classification by the WHO Collaborating Centre for Drug Statistics Methodology. Based on second analysis. *Not sum of subtotals, as some patients had several interventions.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2-3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4-5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	4-5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5-6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6-7
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	7
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	5
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	5
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	5
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	5

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	7-8
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	7-8
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	8-9
	13b	For each group, losses and exclusions after randomisation, together with reasons	7-8 + figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	4
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	9
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	8-9 + figure 1
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	9-11
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	9-11
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	9-11
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	11-12
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	12-13
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	12-13
Other information			
Registration	23	Registration number and name of trial registry	3
Protocol	24	Where the full trial protocol can be accessed, if available	5
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	14

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.