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Drug-related problems identified during medication review before and after the introduction of a clinical decision support system

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Ethical guidelines

Author contributions:

All authors contributed to the study design, the study protocol and the manuscript. SV performed the data analysis. All authors approved the final manuscript.

Conflicts of interest

SV was funded by an unconditionally grant for her PhD project to conduct this research, PH worked for Service Apotheek and delivered the data to the other researchers, but did not have any influence on the analysis or interpretation of the data. HFK, MB and JG have no conflicts of interest relevant to the content of this study.

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SUMMARY

What is known and objective

To facilitate the identification of drug-related problems (DRPs) during medication review, several tools have been developed. Explicit criteria, like Beers-criteria or STOPP/START criteria can easily be integrated into a Clinical Decision Support System (CDSS). The aim of this study was to investigate the effect of adding a CDSS to medication review software on identifying and solving DRPs in daily pharmacy practice.

Methods

Pre-post analysis of clinical medication reviews (CMR) performed by 121 pharmacies in 2012 and 2013, before and after the introduction of CDSS into medication review software. Mean number of DRPs per patient, type of DRPs and their resolution rates were compared in the pharmacies pre and post CDSS.

Results and discussion

Pre and post CDSS, respectively 3100 patients and 4303 patients received a CMR. The mean number of identified DRPs per patient was higher after the introduction of CDSS (3.2 vs. 3.6 $p < 0.01$). The resolution rate was lower (50% vs. 44%; $p < 0.01$), which overall resulted in 1.6 resolved DRPs per patient in both groups ($p = 0.93$). After introduction 41% of DRPs were detected by CDSS. The resolution rate of DRPs generated by CDSS was 29% compared to 55% of DRPs identified without the help of CDSS ($p < 0.01$).

What is new and conclusion

The introduction of CDSS to medication review software generated additional DRPs with a lower resolution rate. Structural assessment including a patient interview elicited the most relevant DRPs. Further development of CDSS with more specific alerts is needed to be clinical relevant.

WHAT IS KNOWN AND OBJECTIVE

Older patients with polypharmacy are at risk for drug related problems (DRPs), like overtreatment and suboptimal therapy.¹ A clinical medication review (CMR), consisting of a structured assessment of the pharmacotherapy including a patient interview, is an important instrument to identify and resolve DRPs.¹⁻⁵ This is a time-consuming process.⁶ Given the expected increase of older people with polypharmacy,^{7,8} the amount of medication reviews will increase substantially in the near future. Therefore, standardization and facilitation of the medication review process is needed.⁹

To facilitate the identification of DRPs during medication review, several tools have been developed. These tools can be judgement based (implicit criteria) or criterion based (explicit criteria). An example of implicit criteria is the Medication Appropriateness Index (MAI).^{10,11} Explicit criteria, like the Beers-criteria or STOPP/START criteria aim to identify inappropriate medication and prescribing omissions.¹²⁻¹⁴ An advantage of explicit criteria is that they can be relatively easily integrated into clinical decision support systems (CDSS), whereas implicit criteria typically cannot. CDSS can be described as a computer program designed to help health care professionals to improve the quality of pharmacotherapy.^{15,16}

Most studies describing CDSS investigate only one type of alert; for example, alerts about reducing anticholinergic medication, improving antibiotic prescribing or use of medicines during pregnancy.¹⁶⁻¹⁸ These alerts are usually designed to support physicians during prescribing.^{19,20} Few studies have assessed CDSS in pharmacy practice to support pharmacists.^{9,21-25} One study showed that the use of CDSS during medication review identified more potential DRPs than the pharmacists.²¹ However, this study did not investigate the outcome of interventions aimed at resolving the identified DRPs. Another study suggested that only a minority of DRPs identified during medication review would have been found with explicit criteria. A limitation of this study was that the explicit criteria were applied retrospectively.²⁶

The aim of the study is to investigate the effect of adding a CDSS to medication review software on identifying and solving DRPs in daily pharmacy practice.

METHODS

Study design

This study was a retrospective database study including a pre-post design. Data of clinical medication reviews were extracted from community pharmacies' databases and compared before and after the introduction of a CDSS into medication review software.

Setting

The study was conducted at 121 Dutch community pharmacy franchisees of "Service Apotheek" (SA). Only pharmacies who performed at least five CMR before and after the introduction of the CDSS were included in the study. The pharmacies were distributed over the Netherlands in both rural and urban areas. Per pharmacy, one or more pharmacists performed the medication reviews in community dwelling older patients. The pharmacists used medication review software to register DRPs and interventions during a medication review.^{3,27} In 2013 a CDSS was incorporated into this software program. The CDSS consisted of 46 explicit criteria, which generated alerts to the pharmacist at the start of a medication review.

All pharmacists previously received training in medication review as this is required by most health insurance companies to be reimbursed for medication review. A helpdesk was available in case pharmacists experienced difficulties with the CDSS.

Ethics and patient confidentiality

Because this was a retrospective analysis of routinely collected anonymized data, that could not be traced back to individual patients and pharmacies, ethical approval was not needed under the Dutch legislation.

Explicit criteria incorporated into the CDSS

An expert team drafted a preliminary list of clinical rules, based on national prescribing guidelines, Beers, STOPP/START criteria, but also on other relevant themes in polypharmacy like inconvenience of use or economic efficiency.^{12,28,29} Based on practical considerations, the developers of the CDSS incorporated 46 of these clinical rules into the CDSS in 2013 (*see Online Appendix A1*).

Clinical Medication Review

Patients aged ≥ 65 years using ≥ 5 chronic oral medications were eligible for a clinical medication review.^{6,11} According to Dutch guidelines, a CMR should involve both pharmacist, GP and patient.⁶ First, the pharmacist collected both clinical and drug dispensing data from the patient. Then the pharmacist interviewed the patient, identified potential DRPs and proposed recommendations (e.g. add or discontinue a drug) in a pharmaceutical care plan. The recommendations in this pharmaceutical care plan were discussed with the patient's general practitioner (GP). Agreed recommendations by the GP were discussed with the patient. After agreement of the patient, recommendations were implemented.

After the introduction of the CDSS, the pharmacists followed the same procedure for CMR, with the exception that the CDSS also automatically generated potential DRPs at the start of the medication review process. The pharmacist could discuss these potential DRPs with the patient and GP during the CMR.

Data collection

Pharmacists were trained to document the results of the CMRs in the software program^{3,27}. The following characteristics were documented: date of the CMR, name and ATC-code (Anatomical Therapeutic Chemical classification) of the drug(s) involved, DRP type, type of recommendation (e.g. recommendation to add a drug) proposed by the pharmacist and type of implemented recommendation (e.g. the drug was added). The medication review software program was linked to the pharmacy information system. In addition, anonymised dispensing records of all included patients, including age and gender, were available for a period of 12 months prior to the CMR date.

Data before CDSS-introduction were collected from January to August 2012. CDSS was introduced at January 2013. Data after introduction of CDSS were collected from January to August 2013.

Measurements

Primary outcome measurements were the mean number of identified and resolved DRPs per patient aggregated per pharmacy before and after the implementation of CDSS. A DRP was considered resolved when the recommendation associated with the DRP was fully or partly implemented as documented by the pharmacists in the software program (e.g. dose reduction when complete discontinuation was proposed). Secondary outcome measurements were: type

of DRPs, type of implemented recommendations and prevalence of the potential DRPs generated by CDSS. The classification of DRPs was adapted from Hepler and Strand and is described in the national guidelines.^{3,6,30}

Data analysis

Duplicate DRPs, incomplete registrations and incomplete patient data were excluded from analysis. To validate the correct classification of DRPs by the pharmacists, a random sample of 100 records per DRP type was checked. The documented classification of DRPs was compared with the description in the free text box by two investigators (SV and HFK). Less than 10% of the classifications deviated from the free descriptions. This percentage was considered acceptable.

Statistical analysis

Descriptive statistics were used for basic characteristics. Frequencies and percentages were reported for categorical variables. Paired t-tests and related samples Wilcoxon signed rank tests were performed to compare differences between pre and post CDSS in the pharmacies, in demographics, mean number and type of identified and solved DRPs per patient and implemented recommendations between pre- and post-CDSS. All the results were aggregated per pharmacy and compared on the pharmacy level pre and post-CDSS. The data were analysed using Microsoft Office Access, Excel Professional 2013 (Microsoft Corporation, Redmond, WA, USA) and IBM SPSS Statistics 22.0 (IBM Corporation, Armonk, NY, USA). A p-value < 0.05 was considered statistically significant.

RESULTS

Descriptive statistics

Clinical medication reviews were performed in 186 pharmacies both before and after the introduction of CDSS in medication review software (pre-CDSS and post-CDSS respectively). We excluded 65 pharmacies because they performed < 5 CMR, either pre- or post CDSS. In the 121 included pharmacies, 3100 patients received a CMR pre-CDSS and 4303 patients post-CDSS. Pharmacies performed less CMR pre-CDSS than post-CDSS (median 16 (IQR 9-36) vs. median 30 (IQR 18-49); $p < 0.01$). Patient characteristics aggregated per pharmacy are shown in table 1.

Drug-related problems

The mean number of identified DRPs per patient was lower pre-CDSS (3.2 (SD 1.1) vs. 3.6 (SD 1.3); $p < 0.01$), while the proportion of resolved DRPs was higher pre-CDSS (50% (SD 18%) vs 44% (SD 15%); $p < 0.01$). This leads to an equal number of resolved DRPs before and after the introduction of CDSS, (1.6 (SD 0.82) vs. 1.6 (SD 0.79); $p = 0.93$, see Figure 1).

Type of drug-related problems

The two most prevalent type of DRPs before as well as after the introduction of CDSS were: “Overtreatment” and “Suboptimal therapy”. The prevalence of “Overtreatment” was equal in both groups (0.84 (SD 0.66) vs 0.77 (SD 0.34); $p = 0.22$). Suboptimal therapy was identified more frequently after the introduction of CDSS (0.54 (SD 0.38) vs 1.1 (SD 0.44) per patient; $p < 0.01$). The mean number of resolved “Suboptimal therapy” issues per patient, was equal among both groups (0.20 (SD 0.22) vs. 0.24 (SD 0.22); $p = 0.15$). The other differences in type of DRPs are shown in table 2.

Type of implemented recommendations

The mean number of ceased drugs per patient was higher pre-CDSS (0.40 (SD 0.40) vs. 0.31 (SD 0.23); $p = <0.01$) and the mean number of added drugs per patient was higher post-CDSS (0.19 (SD 0.16) vs. 0.25 (SD 0.18); $p <0.01$). Post-CDSS more recommendations led to “no intervention” (1.1 (SD 0.80) vs. 1.4 (SD 0.80); $p = <0.01$). The other differences in types of implemented recommendations are shown in table 3.

Post-CDSS

Post CDSS, 41% of all potential DRPs were detected by the CDSS and 59% were identified by structural assessment by the pharmacists during the CMR. Only 29% (SD 17%) of potential DRPs detected by CDSS were resolved compared to 55% (SD 20%) of DRPs identified by pharmacists ($p < 0.01$).

Table 4 shows the 10 most prevalent alerts based on explicit criteria generated by the CDSS. The most prevalent alert was “Cardiovascular disease without a statin”, which is related to the DRP type: “Suboptimal therapy”. The implementation rate of the associated recommendation to add a statin was 23%. The alert in the CDSS with the lowest implementation rate was “Absence of antiplatelet therapy in cardiovascular disease” (14%) and the alert with the highest implementation rate was: “Lack of vitamin D in osteoporosis” (71%).

DISCUSSION

This study demonstrated the mean number of identified DRPs increased after the addition of clinical decision support system (CDSS) to medication review software. On the contrary, the implementation rate of the recommendations associated with the DRPs decreased resulting in an equal number of resolved DRPs before and after the introduction of the CDSS.

Our finding that a CDSS leads to the identification of more potential but less relevant DRPs is comparable to other studies. A study of Curtain et al. also showed that a CDSS detected more DRPs than a structural assessment by the pharmacist.²¹ A previous study found that only a minority of the DRPs were associated with explicit criteria and a lower resolution rate of these DRPs.²⁶ A limitation of that study was that the investigators applied explicit criteria retrospectively. Our current study investigated the applicability of explicit criteria incorporated into software, by pharmacists during CMR in daily pharmacy practice.

Several reasons for the low implementation rate and limited effectiveness of CDSS alerts have been described in the literature. Some studies have suggested low specificity and alert fatigue as the main reasons for the limited effectiveness of CDSS alerts.^{16,22} There are several comparable explanations for the low resolution rate of DRPs generated by the CDSS in this study. One reason could be that the alerts were not specific enough, like for example the clinical rule that aims to detect heart failure not yet treated with an ACE-inhibitor. This clinical rule is triggered by the presence of a diuretic without concomitant use of an ACE-inhibitor in the drug dispensing records. Probably many patients identified by this clinical rule will use diuretics for other indications. In this case the diagnosis heart failure is derived from the use of a drug (diuretic) and this often leads to false assumptions. It would be better to incorporate a heart failure diagnosis in the system that generates the clinical rule. Another reason that clinical rules often do not lead to medications changes may be that patients are intolerant for the suggested medication. The percentage of implemented recommendations for the alert of the explicit criterion: “Cardiovascular disease without a statin” was very low, namely 23%. Many patients have already discontinued using statins because of myopathy. In general alerts are based on algorithms derived from guidelines developed for use on population level, while CMRs are focused on the needs of individual patients.³¹

Other studies have shown that pharmacists encounter barriers like resistance to change, low consumer contact and lack of time.^{16,22} In our study, low consumer contact and lack of time were no problem, because the CDSS was used during a CMR, where there is a multidisciplinary

collaboration between pharmacist, GP and patient. Robertsen et al. also described that a professional relationship between pharmacist and physician is essential for the benefit of CDSS.²² In this setting, patient and GP are more inclined to cooperate with recommendations for drug changes.

Considering the DRPs that were identified by the pharmacists themselves during the CMR, the resolution rate of the DRPs was much higher. Fifty percent or more of these DRPs were resolved, both before and after the introduction of the CDSS. These DRPs were mainly derived by an implicit method of medication review, by a structural assessment and interview between the pharmacist and the patient. Overtreatment, suboptimal therapy, non-compliance and adverse effects are examples of DRPs that mostly derive from information from the patient interview.²⁶ The higher implementation rate of the recommendations associated with these DRPs could be explained by a higher relevance for the patient. Kwint et al. also showed that DRPs identified during patient interviews were more frequently assigned a higher clinical relevance.³² Also Roane et al. showed that consultation with a patient can lead to more appropriate recommendations.³³

This study has several strengths. A major strength is the analysis of the large number of CMRs both before and after the introduction of CDSS. These CMRs represent the daily clinical practice of an average pharmacy in the Netherlands, which make the results likely to be more generalizable. A second strength is that this study is a direct comparison of medication review data before and after the implementation of a CDSS. Another strength is that we used a variety of clinical rules in the CDSS, that focussed both on inappropriate prescribing and suboptimal therapy, but also on other relevant practical aspects for older people with polypharmacy.

There were also some limitations to this study. The first limitation is the potential variability in classifications of the type of DRPs and interventions by the different pharmacists. However, we did check the encodings and we found that less than 10% deviated, which we found acceptable in such a large database. Another limitation is that the resolution of DRPs was based on the partly or full implementation of the associated recommendation registered by the pharmacists in the database. Implementations of medication changes were not checked by either analysis of drug dispensing records or by asking patients if the DRPs were solved.

Finally, the last limitation is more linked to the CDSS itself. There was a lack of clinical information in the generation of specific alerts by the CDDS. The alerts in the CDSS were mainly based on drug dispensing records, because laboratory values and medical information

are often unavailable in the pharmacy information system. This lack of clinical information influenced the implementation rate of the different alerts. This influence was reflected by a broad range in implementation rates between the different alerts in the top 10 potential DRPs identified by the CDSS. The implementation rates ranged from 14% (Absence of antiplatelet therapy in cardiovascular disease)” to 71% (“lack of vitamin D in osteoporosis)”. For the first alert, more clinical information about the patient’s history is needed to give a recommendation about whether an antithrombotic agent should be started. The second alert is based on the use of a bisphosphonate, which is used for osteoporosis and always requires additional supplementation with calcium and vitamin D.³⁴ Another explaining factor for the high implementation rate for this alert could be that there is little resistance to initiate vitamin D.

Our results have several implications for future use and studies of CDSS during CMR. First, we saw that the current CDSS led to the detection of additional potential DRPs, but subsequently a low proportion of these DRPs were resolved. We suggest that the CDSS alerts should be more specific to have added value in detecting clinically relevant DRPs. More specific alerts could be generated by linking dispensing data with clinical diagnoses or laboratory values. Secondly, the aim of a CDSS is to perform a CMR more efficiently by facilitating the identification of potential DRPs. Future studies should include an analysis of the time spent on medication review with and without CDSS is needed to evaluate the added value of the CDSS. Finally, we are of the opinion that a patient interview will always remain essential, because that interview identifies the health issues that are most relevant for the patient.

WHAT IS NEW AND CONCLUSION

This study shows that the introduction of CDSS into medication review software identified more potential DRPs. However, DRPs identified by CDSS were less frequently resolved compared to DRPs identified by a clinical medication review. Probably a structural assessment including a patient interview, facilitated by a CDSS, would identify the most relevant DRPs. Further development of CDSS with more specific alerts, linking dispensing and clinical information, could make the medication review process more efficient.

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REFERENCES

1. Milos V, Rekman E, Bondesson A, et al. Improving the quality of pharmacotherapy in elderly primary care patients through medication reviews: A randomised controlled study. *Drugs Aging*. 2013;30(4):235-246.
2. Lenander C, Elfsson B, Danielsson B, Midlov P, Hasselstrom J. Effects of a pharmacist-led structured medication review in primary care on drug-related problems and hospital admission rates: A randomized controlled trial. *Scand J Prim Health Care*. 2014:1-7.
3. Kempen TG, van de Steeg-van Gompel CH, Hoogland P, Liu Y, Bouvy ML. Large scale implementation of clinical medication reviews in dutch community pharmacies: Drug-related problems and interventions. *Int J Clin Pharm*. 2014.
4. Beuscart JB, Pont LG, Thevelin S, et al. A systematic review of the outcomes reported in trials of medication review in older patients: The need for a core outcome set. *Br J Clin Pharmacol*. 2016.
5. Huiskes VJ, Burger DM, van den Ende CH, van den Bemt BJ. Effectiveness of medication review: A systematic review and meta-analysis of randomized controlled trials. *BMC Fam Pract*. 2017;18(1)
6. Nederlands Huisartsen Genootschap ism andere beroepsorganisaties/ instanties/verenigingen [Dutch College of General Practitioners in collaboration with other professional organisations]. Multidisciplinaire richtlijn polyfarmacie bij ouderen [multidisciplinary guideline polypharmacy in elderly]. 2012;NHG.
7. Hovstadius B, Hovstadius K, Astrand B, Petersson G. Increasing polypharmacy - an individual-based study of the swedish population 2005-2008. *BMC Clin Pharmacol*. 2010;10

8. Payne RA, Avery AJ. Polypharmacy: One of the greatest prescribing challenges in general practice. *Br J Gen Pract.* 2011;61(583):83-84.
9. Bindoff I, Stafford A, Peterson G, Kang BH, Tenni P. The potential for intelligent decision support systems to improve the quality and consistency of medication reviews. *J Clin Pharm Ther.* 2012;37(4):452-458.
10. Spinewine A, Schmader KE, Barber N, et al. Appropriate prescribing in elderly people: How well can it be measured and optimised? *Lancet.* 2007;370(9582):173-184.
11. Hanlon JT, Schmader KE. The medication appropriateness index at 20: Where it started, where it has been, and where it may be going. *Drugs Aging.* 2013;30(11):893-900.
12. Gallagher P, Ryan C, Byrne S, Kennedy J, O'Mahony D. STOPP (screening tool of older person's prescriptions) and START (screening tool to alert doctors to right treatment). consensus validation. *Int J Clin Pharmacol Ther.* 2008;46(2):72-83.
13. By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American geriatrics society 2015 updated beers criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc.* 2015;63(11):2227-2246.
14. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: Version 2. *Age Ageing.* 2015;44(2):213-218.
15. Musen MA, Shahar Y, Shortliffe EH. Clinical decision-support systems. in: Shortliffe EH, Cimino JJ, eds. . . 2006(Biomedical informatics. New York: Springer):698–736.

16. Curtain C, Peterson GM. Review of computerized clinical decision support in community pharmacy. *J Clin Pharm Ther.* 2014;39(4):343-348.
17. Bates DW, Kuperman GJ, Wang S, et al. Ten commandments for effective clinical decision support: Making the practice of evidence-based medicine a reality. *J Am Med Inform Assoc.* 2003;10(6):523-530.
18. Madaras-Kelly KJ, Hannah EL, Bateman K, Samore MH. Experience with a clinical decision support system in community pharmacies to recommend narrow-spectrum antimicrobials, nonantimicrobial prescriptions, and OTC products to decrease broad-spectrum antimicrobial use. *J Manag Care Pharm.* 2006;12(5):390-397.
19. Jaspers MW, Smeulders M, Vermeulen H, Peute LW. Effects of clinical decision-support systems on practitioner performance and patient outcomes: A synthesis of high-quality systematic review findings. *J Am Med Inform Assoc.* 2011;18(3):327-334.
20. Hemens BJ, Holbrook A, Tonkin M, et al. Computerized clinical decision support systems for drug prescribing and management: A decision-maker-researcher partnership systematic review. *Implement Sci.* 2011;6
21. Curtain C, Bindoff I, Westbury J, Peterson G. An investigation into drug-related problems identifiable by commercial medication review software. *Australas Med J.* 2013;6(4):183-188.
22. Robertson J, Walkom E, Pearson SA, Hains I, Williamsone M, Newby D. The impact of pharmacy computerised clinical decision support on prescribing, clinical and patient outcomes: A systematic review of the literature. *Int J Pharm Pract.* 2010;18(2):69-87.

23. Meulendijk MC, Spruit MR, Drenth-van Maanen AC, et al. Computerized decision support improves medication review effectiveness: An experiment evaluating the STRIP assistant's usability. *Drugs Aging*. 2015;32(6):495-503.
24. O'Sullivan D, O'Mahony D, O'Connor MN, et al. Prevention of adverse drug reactions in hospitalised older patients using a software-supported structured pharmacist intervention: A cluster randomised controlled trial. *Drugs Aging*. 2016;33(1):63-73.
25. Bindoff IK, Tenni PC, Peterson GM, Kang BH, Jackson SL. Development of an intelligent decision support system for medication review. *J Clin Pharm Ther*. 2007;32(1):81-88.
26. Verdoorn S, Kwint HF, Faber A, Gussekloo J, Bouvy ML. Majority of drug-related problems identified during medication review are not associated with STOPP/START criteria. *Eur J Clin Pharmacol*. 2015.
27. Chau SH, Jansen AP, van de Ven PM, Hoogland P, Elders PJ, Hugtenburg JG. Clinical medication reviews in elderly patients with polypharmacy: A cross-sectional study on drug-related problems in the netherlands. *Int J Clin Pharm*. 2015.
28. Warle-van Herwaarden MF, Kramers C, Sturkenboom MC, van den Bemt PM, De Smet PA, Dutch HARM-Wrestling Task Force. Targeting outpatient drug safety: Recommendations of the dutch HARM-wrestling task force. *Drug Saf*. 2012;35(3):245-259.
29. American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American geriatrics society updated beers criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2012;60(4):616-631.

30. Hepler CD, Strand LM. Opportunities and responsibilities in pharmaceutical care. *Am J Hosp Pharm.* 1990;47(3):533-543.
31. Goldberger JJ, Buxton AE. Personalized medicine vs guideline-based medicine. *JAMA.* 2013;309(24):2559-2560.
32. Kwint HF, Faber A, Gussekloo J, Bouvy ML. The contribution of patient interviews to the identification of drug-related problems in home medication review. *J Clin Pharm Ther.* 2012;37(6):674-680.
33. Roane TE, Patel V, Hardin H, Knoblich M. Discrepancies identified with the use of prescription claims and diagnostic billing data following a comprehensive medication review. *J Manag Care Pharm.* 2014;20(2):165-173.
34. CBO. Guideline osteoporosis and fracture prevention.
https://www.nhg.org/sites/default/files/content/nhg_org/uploads/osteoporose-en-fractuurpreventie.pdf; 2011.

Table 1: Basic characteristics of patients aggregated per pharmacy pre- and post-CDSS

Characteristic	Pre-CDSS (N=3100)	Post-CDSS(N=4303)	p-value [#]
Age (year, median, IQR)	78 (75 – 82)	77 (75 – 80)	0.02
Number of chronic medicines in use (median, IQR)	8 (7 – 9)	8 (7 – 8)	0.01
Gender, women (% , median, IQR)	59 (50 – 68)	53 (46 – 62)	0.01
10 most prescribed chronic drug classes	% of patients	% of patients	p-value*
Antithrombotic agents	74	72	0.24
Drugs for peptic ulcer and GORD	68	65	0.16
Lipid modifying agents	63	68	0.01
Beta blocking agents	59	58	0.64
ACE inhibitors	35	39	0.02
Oral blood glucose lowering drugs	33	34	0.55
High-ceiling diuretics	30	25	< 0.01
Dihydropyridin calcium channel blockers	29	31	0.29
Laxatives	27	25	0.40
Angiotensin II antagonists (C09C)	24	24	0.67
IQR = interquartile range, CDSS = clinical decision support system; ATC = Anatomical Therapeutical Chemical classification; GORD = gastro-oesophageal reflux disease N = 121 pharmacies; [#] related samples Wilcoxon signed rank test; * = paired t-test;			

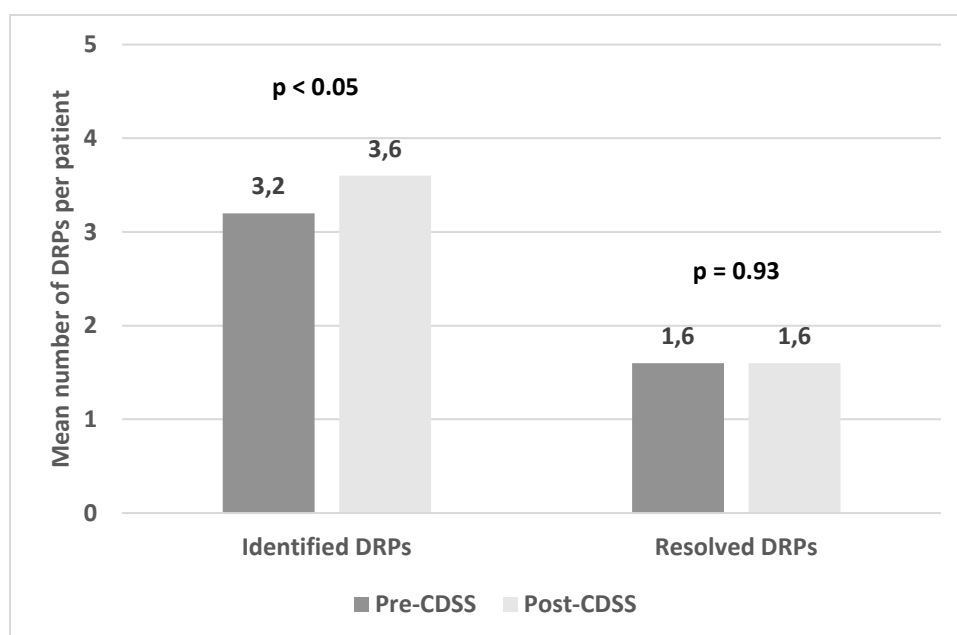


Figure 1: Differences in number of identified and solved DRPs pre and post CDSS
N = 121 pharmacies. Numbers are aggregated per pharmacy; DRP = drug related problem

Table 2: Prevalence and implementation rate of various DRP types pre and post CDSS

DRP type per patient aggregated per pharmacy	Pre-CDSS (N = 3100 patients)		Post-CDSS (N = 4303 patients)		p-value*	
	DRPs identified	Percentage resolved	DRPs identified	Percentage resolved	DRPs identified	Percentage resolved
Overtreatment	0.84	43%	0.77	45%	0.22	0.53
Suboptimal therapy	0.54	38%	1.1	23%	<0.01	0.15
Contra indication	0.28	43%	0.28	45%	0.97	0.85
Drug not effective	0.27	51%	0.22	46%	0.027	0.033
Adverse effect	0.27	58%	0.27	57%	0.85	0.96
Drug interaction	0.22	63%	0.06	44%	<0.01	< 0.01
Inconvenience of use	0.18	70%	0.32	54%	< 0.01	< 0.01
Non-compliance	0.16	71%	0.12	76%	0.017	0.10
Dose too low	0.16	47%	0.13	35%	0.071	0.012
Dose too high	0.16	60%	0.06	53%	< 0.01	< 0.01
Miscellaneous	0.13	44%	0.28	35%	< 0.01	< 0.01
Inappropriate dosage form	0.03	53%	0.07	64%	< 0.01	< 0.01
N = 121 pharmacies. Numbers are aggregated per pharmacy; DRP = drug related problem; CDSS = clinical decision support system; * paired t-test						

Table 3: Differences in type of implemented recommendations pre vs. post CDSS

Type of implemented recommendation per patient	Pre-CDSS (N = 3100 patients)	Post-CDSS (N = 4303 patients)	p-value*
Drug changes			
Drug added	0.19	0.25	<0.01
Drug ceased	0.40	0.31	<0.01
Drug replaced	0.18	0.15	0.23
Dosage (regimen) changed	0.26	0.22	0.18
Dosage form changed	0.03	0.04	0.083
Other changes			
Performed monitoring	0.39	0.54	<0.01
Information/advice provided	0.48	0.50	0.71
Synchronization of all prescriptions	0.06	0.10	0.019
Other	0.15	0.09	0.033
No intervention	1.1	1.4	<0.01
N = 121 pharmacies. Numbers are aggregated per pharmacy; CDSS = clinical decision support system; * paired t-test			

Table 4: Top 10 most prevalent potential DRPs generated by the CDSS

Top	Description alert of the CDSS (<i>Potential DRP type</i>)	Prevalence in total number of DRPs (N = 15268 DRPs)		Percentage resolved
		N	%	
1	Cardiovascular disease without a statin (<i>Suboptimal therapy</i>)	669	4.4%	23%
2	Concomitant use of three or more antihypertensives (<i>Overtreatment</i>)	647	4.2%	24%
3	Absence of antiplatelet therapy in cardiovascular disease (<i>Suboptimal therapy</i>)	594	3.9%	14%
4	Inconvenience of use of ACE-inhibitor: once- daily alternative or combination available (<i>Inconvenience of use</i>)	490	3.2%	32%
5	Inappropriate use of inhaled corticosteroids in COPD (<i>Overtreatment</i>)	457	3.0%	26%
6	Concomitant use of two or more antithrombotics (<i>Overtreatment</i>)	397	2.6%	52%
7	Use of aerosol without a spacer (<i>Inappropriate dosage form</i>)	390	2.6%	53%
8	Loop-diuretics as first-line treatment of hypertension (<i>Suboptimal therapy</i>)	324	2.1%	31%
9	Lack of vitamin D in osteoporosis (<i>Suboptimal therapy</i>)	298	2.0%	71%
10	Heart failure without an ACE-inhibitor (<i>Suboptimal therapy</i>)	289	1.9%	17%

ONLINE APPENDIX A1: Overview of explicit criteria incorporated into the CDSS

Description	Type of potential DRP
Concomitant use of three or more antihypertensives	Overtreatment
Concomitant use of two or more antithrombotics	Overtreatment
Inappropriate use of inhaled corticosteroids in COPD	Overtreatment
Concomitant use of ACE-inhibitor and AT-2 antagonist	Overtreatment
Cardiovascular disease without use of a statin	Suboptimal therapy
Absence of antiplatelet therapy in cardiovascular disease	Suboptimal therapy
Loop-diuretics as first-line treatment of hypertension	Suboptimal therapy
Heartfailure without use of an ACE-inhibitor	Suboptimal therapy
Angina Pectoris without use of a statin	Suboptimal therapy
Absence of antiplatelet therapy in angina pectoris	Suboptimal therapy
Chronic heart failure without use of a beta blocker	Suboptimal therapy
Monotherapy with dipyridamole	Suboptimal therapy
Diabetes type 2 without use of a statin	Suboptimal therapy
Diabetes type 2 without use of an antihypertensive	Suboptimal therapy
Two or more short courses with oral corticosteroids per year in patients with asthma or COPD	Suboptimal therapy
Patients using antithrombotic without gastric protection	Suboptimal therapy
Use of opioids without laxatives	Suboptimal therapy
Patients aged 70 years or older using NSAIDs without gastric protection	Suboptimal therapy
Risk for peptic ulcers because of combined use of NSAID's, corticosteroids, anticoagulants, antithrombotics or spironolactone	Suboptimal therapy
Lack of vitamin D in osteoporosis	Suboptimal therapy
Use of non-selective beta blocker (except sotalol) in patients with diabetes	Contra-indication
Use of NSAIDs or salicylates in patients with asthma	Contra-indication
Use of parasympathicomimetics in patients with asthma/COPD	Contra-indication
Use of nitrofurantoin in patients with renal impairment	Contra-indication
Use of betahistine/cinnarizine (Drug not recommended because of inadequate efficacy)	Drug not effective
Use of hydrokinine (seldom effective; only in muscle cramps not for restless legs; evaluate efficacy)	Drug not effective
Metformin and risk of reduced absorption of vitamin B12	Adverse effect
Use of glibenclamide in patients aged 70 years or older	Adverse effect
Use of codeine and an ACE-inhibitor	Adverse effect
Patients aged 65 years or older using cimetidine	Adverse effect
Patients aged 65 years or older using amitriptyline (Beers)	Adverse effect
Patients aged 65 years or older using long-acting benzodiazepines (Beers)	Adverse effect
Patients aged 65 years or older using promethazine (Beers)	Adverse effect
Use of oropharyngeal antifungals when using inhaled corticosteroids	Adverse effect
Phenytoin / phenobarbital and folate deficiency	Adverse effect
Interaction (es)omeprazole with clopidogrel	Drug Interaction
Concomitant use of a RAS inhibitor and another potassium enhancing agent	Drug Interaction
Inconvenience of use of ACE-inhibitor: once-daily alternative or combination available	Inconvenience of use
Inconvenience of use of verapamil twice daily: once-daily alternative or combination available	Inconvenience of use
Inconvenience of use of propranolol twice daily: once-daily alternative or combination available	Inconvenience of use
Dosage simvastatin too low	Dosage too low
Dispensing of methotrexate with incorrect dosage advice	Dosage too high
Use of aerosol without a (new) spacer	Inappropriate dosage form
Concomitant use of a powder inhaler and an aerosol	Inappropriate dosage form
Use of rosuvastatin as first-choice → cheaper alternative available	Economic efficiency
Use of rabeprazole → cheaper alternative available	Economic efficiency