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Immediate or deferred adjustment of drug regimens in multidose drug dispensing systems

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ABSTRACT

Background: Multidose drug dispensing (MDD) is used to help patients take their medicines appropriately. Little is known about drug regimen changes within these MDD systems and how they are effectuated by the community pharmacist. Manual immediate adjustments of the MDD system could introduce dispensing errors. MDD guidelines therefore recommend to effectuate drug regimen changes at the start of a new MDD system.
Objective: The aim of this study was to investigate the frequency, type, procedure followed, immediate necessity, and time taken to make MDD adjustments.
Methods: This was a cross-sectional study in eight community pharmacies in the Netherlands. All adjustments to MDD systems were systematically documented for 3 weeks by the community pharmacist.
Results: Overall, 261 MDD adjustments involving 364 drug changes were documented for 250 patients: 127 (35%) drug changes involved the addition of a new drug, 124 (34%) a change in dosage, and 95 (26%) drug discontinuation. Of the MDD adjustments, 135 (52%) were effectuated immediately: 81 (31%) by adjusting the MDD system manually, 49 (19%) by temporarily dispensing the drug separately from the MDD system, and 5 (2%) by ordering a new MDD system. Pharmacists considered that 36 (27%) of the immediate MDD adjustments could have been deferred until the next MDD system was produced. Immediate adjustment took significantly longer than deferred adjustment ($p < 0.001$).
Conclusions: This study shows that in patients using MDD systems, over half of the drug regimen changes are adjusted immediately. The necessity of these immediate changes should be critically evaluated.

1. Introduction

In line with the number of patients on polypharmacy, the number of users of dosing aids has increased rapidly over the past years in the Netherlands.[1] Dosing aids can support patients with their medicine use, but there are also concerns about the prevalence of suboptimal drug treatment, a lower number of medication regimen changes among patients using dosing aids, and rigidity of dosing aids in immediate medication regimen changes.[2–12]

In the Netherlands, automated multidose drug dispensing (MDD) systems are predominately used as dosing aid.[13] In MDD systems, all oral solid medicines are automatically robot-packed in disposable plastic bags, each containing the medicines to be taken on a given day. The disposable bags are labeled with patient data, content, date, and time of intake.[10] Because MDD systems are electronically packed, dispensing error rates are lower compared to manual filled dosing aids[14,15].

In general, MDD systems are prepared by a specialized MDD supplier, based on prescription files forwarded from the pharmacy information system. Completed MDD systems, generally with medication for one week, are returned to the pharmacy for delivery to the patient.[10] The time between the between the order and delivery of MDD systems can take up to 5 days, depending on contractual agreements.

The Dutch guideline for multi-compartment dosing aids recommends that changes to the medicines in MDD systems are deferred until the next MDD system is due to be ordered, to lower the risk of dispensing errors.[13–16] However, this can delay the introduction of a new medicine by several days to more than a week. If immediate

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adjustment is necessary, technicians need to adjust the MDD system manually. This is time consuming and may introduce medication errors, as the proportion of errors is higher after manual adjustments compared to automated adjustments[14,15]. In the case of the addition of a new medicine or an increase in dosage, the new medication can temporarily be dispensed separately from the MDD system. However, separate dispensing can be confusing for patients who have lost the capacity to manage their medication[17,18]. A last option is the order of a new and adjusted MDD system. Completely replacing an MDD system takes a day and has additional costs. The different procedures thus all have their advantages and disadvantages. The pharmacists is responsible for the clinical risk management and final authorization and must weigh these pros and cons of immediate or deferred adjustment for every individual patient. When patients are unable to physically visit the pharmacy, couriers are available for home delivery. Despite the extensive use of MDD systems, little is known about how changes are made to MDD systems. The aim of this study was therefore to examine the frequency, type, followed procedure, immediate necessity, and time needed to effect changes to the medication in MDD systems.

2. Methods

2.1. Setting

This was a cross-sectional study which investigated the adjustments of medicines dispensed via automated MDD system in eight community pharmacies in the Netherlands. The community pharmacies participated on a voluntary basis in a pharmacy practice research course. All participating pharmacies were independent pharmacies and were located in both urban and rural areas.

2.2. Data collection

During three randomly assigned weeks, pharmacists documented all changes to medicines dispensed via a MDD system and how these changes were effectuated. A standardized electronic registration form using Survalyzer software was drafted with the help of the participating community pharmacists and tested in a pilot study. Data collection took place in February and March 2015. Besides the medication changes, basic characteristics about the total number of MDD users per pharmacy, and amount of medicines dispensed via MDD systems were collected.

2.3. Documentation of MDD adjustment

The following data were documented: age, gender, prescriber, type of medication changes (start, stop, dosage adjustment, other), medicines involved, procedure followed to effectuate the medication change, perceived necessity of the immediacy of each MDD adjustment, and time taken by pharmacy staff to effectuate the medication change. The perceived necessity was self-reported by the pharmacist and could be answered with yes or no. As its not common to communicate the reason of medication changes on the prescriptions, pharmacists could consult the patient or prescriber about the reason for the medication change. A free text field was available for additional remarks. Only electronic prescriptions, sometimes presented by the patient were accepted for a medication change.

Each MDD adjustment could involve multiple medication changes (e.g. the addition of one medicine and the discontinuation of a second). Four types of medication changes were registered: (1) addition of a new medicine, (2) discontinuation of a medicine, (3) dose adjustment, (4) other. The procedure to effectuate the MDD adjustment was predefined as (1) immediate manual adjustment of the MDD system in use, (2) dispensing medication separately from the MDD system, (3) production of a new adjusted MDD system, (4) deferred adjustment until the start of the new MDD system. Options one to three were considered immediate adjustments. The time taken to effectuate the change was estimated by the individual staff members (pharmacist, pharmacist technician, and courier). Pharmacists received a study protocol with instructions and attended a joint meeting about the study.

2.4. Ethics and confidentiality

According to the Dutch Medical Research Act Involving Human Subjects, no formal ethical approval was required for this observational study. The research protocol was reviewed by the Institutional Review Board of the Utrecht Pharmacy Panel for Education and Research (UPPER), Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University. In order to protect patients' privacy, only age and gender were recorded.

2.5. Statistical analyses

All data were analyzed using statistical software (SPSS version 23.0; SPSS Inc., Chicago, IL, USA). Medicines were classified according to the Anatomical Therapeutic Chemical (ATC) WHO Classification System level-2 and aggregated on therapeutic use. Descriptive statistics were used for basic characteristics, type, and procedure of MDD adjustment. Mean data ± standard deviation are reported, unless indicated otherwise. Pearson chi-squared (X2) tests were applied for categorical variables. Independent sample *t*-test was applied for continuous variables. Binary logistic regression with immediate or deferred adjustment as dependent variable was performed with adjustment for age, prescriber, one or more medication changes involved (binomial), and type of medication change.

The results have been tested for normality. Differences in time taken were calculated using one-way Anova. If significant outcomes were obtained, a Dunnett's post-hoc test with deferred adjustment as reference group was performed. The median time for the order of a new extra MDD was tested using Mann-Whitney *U* test.

3. Results

3.1. Characteristics

There were 273 ± 138 MDD users per pharmacy (range 61–414), with 6.2 ± 0.67 medicines per MDD user. A total of 261 MDD adjustments were completely documented and involved 250 patients (median age 76 years, interquartile range 60–83) and 1.4 ± 0.9 medication changes per MDD adjustment. Five MDD adjustments were incomplete and discarded. The general practitioner (GP) initiated 138 (53%) MDD adjustments. 123 MDD adjustments were initiated by a variety of medical specialists. Psychiatrist (20%), cardiologists (16%) and internists (14%) were the three most frequent initiators among the medical specialists.

3.2. Procedure

Of the MDD adjustments, 135 (52%) were effectuated immediately (options 1 to 3 as shown in Table 1). Differences were seen between the participating pharmacies in the procedures used to effectuate medication regimen changes (appendix 1). Pharmacists who had a relatively high percentage of deferred adjustment indicated to have agreements with GPs about medication regimen changes among patients using a MDD system. In the opinion of the participating community pharmacists, 36 (27%) of all these adjustments could have been deferred and 3 (2%) of the deferred adjustments should have been made immediately.

MDD adjustments instigated by medical specialists were more likely to be effectuated immediately (adjusted OR 2.04; CI95% 1.16–3.59) than MDD adjustments instigated by GPs (adjusted for age and number of drugs). MDD adjustments involving more than one medicine were more likely to be effectuated immediately (adjusted OR 1.98; CI95%

Table 1
The procedures followed to effectuate the MDD adjustment and the pharmacist' opinion about the necessity to effectuate the MDD adjustments immediately.

	Number of MDD adjustments % (n)	Necessity of immediate change	
		Yes % (n)	No % (n)
1. Immediate manual adjustment	31 (81)	70 (62)	30 (19)
2. Temporarily separate from MDD system	19 (49)	67 (33)	34 (16)
3. New extra MDD system ordered	2 (5)	80 (4)	20 (1)
4. Deferred until new MDD system	48 (126)	2 (3)	98 (123)
Total	**100 (261)**	**39 (102)**	**61 (159)**

MDD: multidose drug dispensing.

1.04–3.77) than MDD adjustments involving one medicine (adjusted for age and prescriber).

3.3. Type of medication change

The most common medication changes (n = 364) were the addition of a new medicine (35%) and dosage adjustment (34%) (Table 2). Medication changes that involved discontinuation of a medicine were effectuated immediately more often than they were deferred (p = 0.03). In contrast, MDD adjustments classified as 'other' were more likely to be deferred until the new regular MDD system was prepared (p = 0.001).

3.4. Medication classes involved

Changes involving cardiovascular medicines (adjusted OR 1.79; CI95% 1.10–2.93) and medicines used in diabetes (adjusted OR 2.95; CI95% 1.19–7.29) were effectuated immediately more often than they were deferred. In contrast, changes involving vitamins and minerals were predominately deferred (adjusted OR 0.39; CI95% 0.13–0.86) (Table 3). A detailed overview of all the medication classes involved (ATC-2 classification) is presented in appendix 2, together with the type of medication change and procedure used to effectuate the medication change.

3.5. Time taken

The total time needed to adjust an MDD system was in average 15.6 ± 15.8 min (2.4 ± 3.7 min for the pharmacist, 11.1 ± 12.0 min for the pharmacy technician, and 2.2 ± 5.1 min for the home delivery courier). Immediate manual adjustment took pharmacy staff, especially technicians, longer than deferred adjustment (p < 0.001) (see Table 4).

4. Discussion

This study shows that half of the MDD adjustments were effectuated immediately, with the addition of medication and dosage changes being the most common reason for adjustment of MDD systems. Pharmacists were of the opinion that around half of these immediate medication regimen changes could be deferred adjusted. A reduction in immediate adjustments would result in improved dispensing efficacy as immediate adjustments took around twice the time compared to deferred adjustments.

About half of the medication changes were manually effectuated. This high percentage seems in contradiction with the recommendation of the Dutch MDD guideline to minimize manual adjustments in order to decrease the risk of dispensing errors.[13] Besides the risk of dispensing errors, manual adjustment is also labor intensive. The considerable differences in preferred procedure between the participating pharmacies suggest that it is possible to influence the procedure to adjust MDD systems. Reducing the number of immediate adjustments, may render community pharmacists additional time that can be invested in other pharmaceutical care activities from which patients can benefit.[19] Explicit agreements and timely communication between prescribers, patients, and pharmacists about the reason and acuteness of immediate MDD adjustments might decrease the number of immediate MDD adjustments.

According to the participating community pharmacists, approximately one quarter of the immediate adjustments could have been deferred. This is surprising considering that the medication regimen change were effectuated immediately by the pharmacist. The reason why pharmacists effectuated the medication change immediately, against estimation, was not documented for every medication change. In practice, it is the role of the technician to effectuate the medication change. Pharmacists are responsible for the clinical risk management and final authorization. Based on the free text clarifications that were given by the pharmacists, we conclude that practical arguments often influenced the choice between immediate or deferred adjustment (e.g. the patient is already expecting an immediate change, the prescriber cannot be reached or the pharmacy technician has already prepared an immediate change).

Opposite of the one quarter of immediate medication changes that could have been deferred, in 2% of the deferred adjustments pharmacists were of the opinion that the medication change should have been effectuated immediately. In these cases patients had already identified the medicines that were discontinued and had discarded these from the MDD system themselves. However, identification of the appropriate tablet can be difficult, especially if one bag contains multiple white round tablets. Leaving this difficult task as a responsibility of the

Table 2
Type of medication changes and moment of effectuation.

Type of medication changes	Number of medication changes % (n)	Immediate adjusted % (n)	Deferred until new MDD % (n)	p-value[a]
Addition of new medicine	35 (127)	59 (75)	41 (52)	0.700
Discontinuation of a medicine	26 (95)	67 (64)	33 (31)	0.026
Dosage change	34 (123)	54 (67)	47 (56)	0.374
Addition of previous separate dispensed medicines	4 (14)	14 (2)	86 (12)	0.001
Change in time of intake	1 (3)	0 (0)	100 (3)	
Extra provision of lost medicines	0 (1)	100 (1)	0 (0)	
Manual addition of medication temporarily not in stock at the MDD supplier	0 (1)	100 (1)	0 (0)	
Total	**100 (364)**	**58 (210)**	**42 (154)**	**0.003**

MDD: multidose drug dispensing.
[a] Pearson X^2 test.

Table 3
Medication classes and procedure to effectuate medication changes with adjusted odds ratio.

Medication classes	Immediate adjustments(n = 210)	Deferred adjustments(n = 154)	Adjusted OR[a](95% CI)
Cardiovasculair medication	69% (92)	31% (41)	**1.79 (1.10–2.93)**
Psycho(ana)leptic medication	47% (25)	53% (28)	0.77 (0.39–1.52)
Other medication	56% (18)	44% (14)	0.47 (0.33–1.66)
Medication used in diabetes	68% (19)	32% (9)	**2.95 (1.19–7.29)**
Gastrointestinal medication	58% (14)	42% (13)	0.56 (0.24–1.31)
Vitamins and minerals	36% (9)	64% (16)	**0.39 (0.13–0.86)**
Antibiotics and corticosteroids	77% (17)	23% (5)	1.91 (0.65–5.65)
Antiepileptic and antiparkinson medication	50% (8)	50% (8)	1.21 (0.41–3.58)
Analgetic medication	29% (4)	71% (10)	0.38 (0.11–1.30)
Anti-rheumatics and anti-gout medication	29% (4)	71% (10)	0.33 (0.09–1.14)

OR: Odds Ratio.
[a] Adjusted for age, prescriber, number of medicines involved in medication changes and type of medication change. Statistically significant associations printed in bold.

Table 4
Time taken per MDD adjustment for each staff member per procedure with deferred adjustment as reference group.

	Number of documented MDD adjustments	Pharmacist median time (min) + IQR	Pharmacist technician median time (min) + IQR	Home delivery median time (min) + IQR
Immediate manual adjustment	81	2 (2)[a]	12 (8)[a]	0 (10)[a]
Temporarily separate from MDD system	49	1 (1)	10 (9)[a]	0 (1)[a]
New extra MDD system ordered	5	5 (21)[b]	22 (36)	0 (5)[b]
Deferred until new MDD system	126 (reference group)	1 (0)	4 (5)	0 (0)

MDD: multidose drug dispensing; min: minutes; IQR: interquartile range.
[a] Is significant with p value < 0.05 tested with Anova Dunnett's post-hoc test.
[b] Is significant with p value < 0.05 tested with Mann-Whitney *U* test.

patient, who uses a MDD system to support him with appropriate use of his medication, can introduce new risks.

Besides the high number of manual adjustments, a frequently chosen option was to dispense the newly prescribed or changed medication separately from the MDD system. The provision of medication separate from the used dosing aid could be confusing for patients with a limited medication management capacity[17,18]. Separate dispensing of newly prescribed medication might thus increase the risk of medication errors.[20] Therefore medication should only be dispensed separately from the automated MDD system, when the patient or an informal carer has sufficient medication management capacity. An exception are patients who receive help with medication administration from professional home-care workers. In these circumstances, the provision of separate medication is appropriate provided that the home-care worker is fully informed about the new situation[13,20].

Replacement of the MDD system in use by a completely new MDD system is a convenient and safe way to effectuate medication regimen changes that involve multiple medication changes. However, only 2% of the MDD adjustments were effectuated by ordering a completely new MDD system. The additional costs for the order of a new MDD and the discarded medicines from the MDD system currently in use might deter pharmacists from using this option.

From a pharmacological perspective, medicines for primary or secondary prevention with long-term beneficial effects (e.g. antihypertensive, lipid modifying agents, or vitamins) seem candidates for deferred adjustment. In contrast, if a patient experiences discomfort (e.g. pain medication, antibiotics, or medication withdrawal because of adverse drug events) immediate adjustment of the MDD system is warranted. In this study, 44% of the immediate effectuated medication changes involved cardiovascular medication, while these are frequently used for their long-term effects. However, it is difficult to evaluate the necessity for immediate MDD adjustment if the indication is not available for the pharmacist. For example, metoprolol can be initiated for blood pressure regulation (immediate adjustment not necessary) but also for cardiac arrhythmia (immediate adjustment necessary). In order to be able to appraise the immediate necessity of a MDD adjustment, the pharmacist should be familiar with the reason for a medication change.

This was the first study that prospectively documented changes made to the medicines prescribed to users of MDD systems. Although MDD is used extensively, little has been described about the frequency and type of changes made to medicines dispensed via MDD. Sjöberg et al. reported that, of patients hospitalized for hip fracture, patients using MDD experienced fewer medication changes than patients receiving medicines via manually dispensed medicines after hospital discharge.[3] A cohort study by Wallerstedt et al. found an increased number of medicines in use, more potentially harmful medicines and fewer medication changes after the transition from manual dispensing to MDD.[6] In the current study, an average of 2.1 MDD adjustments per MDD user per year was found. Because of a lack of data on changes in manually dispensed medicines, no comparison could be made with users of manually dispensed medicines, or with data from other studies.

Besides the lack of data on manually dispensed medicines, the study had also some other potential limitations. Secondly, only eight pharmacies participated in the study. The participating pharmacies, however, did differ in size and location (urban and rural community pharmacies). Thirdly, because this was an observational study investigating the procedures followed by community pharmacists, the effect of deferred adjustments on clinical outcomes has not been assessed. As a consequence of the observational design of the study pharmacists received no explicit instructions on how to assess the immediate necessity of MDD adjustments. Whether clear instructions and explicit agreements between prescribers and pharmacists indeed can reduce the number of immediate adjustments must be elucidated in further research combined with the effect on clinical outcomes. Fourthly, the number of days until the deferred adjustment was effectuated was unknown. Theoretically, this might be of influence on the pharmacist's decision to immediately adjust the MDD system. At last, the time needed to make adjustments was self-reported and not recorded by an independent observer. In the meeting before the study, the

importance of accurate recording of the time was emphasized.

5. Conclusion

Half of the adjustments made to MDD systems were effectuated immediately. Immediate effectuated medication regimen changes took twice the time compared to deferred adjustments. Deferred adjustment of changes to MDD systems is preferable when appropriate. Explicit agreements and timely communication between patients, prescribers, and community pharmacists about the necessity of immediate medication changes is therefore needed to improve dispensing efficiency.

Conflicts of interest

B.J. Mertens was funded by an unconditional grant for his PhD project to multidose drug dispensing to conduct this research. The other authors declare no conflict of interest relevant to this study.

Author's contributions

B.J. Mertens, H.F. Kwint, and M.L. Bouvy were responsible for the study concept and design. B.J. Mertens performed the statistical analysis. All authors contributed to the writing of the manuscript and approved the final manuscript for submission.

Compliance with ethical standards

According to the Dutch Medical Research Act Involving Human Subjects, no formal ethical approval was required for this observational study. The research protocol was reviewed by the Institutional Review Board of UPPER, Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University.

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Appendix 1. Procedure followed by individual pharmacies to effectuate drug regimen changes

	Pharmacy (number of MDD users)								
	1 (414)	2 (345)	3 (236)	4 (128)	5 (397)	6 (194)	7 (61)	8 (410)	Total (2185)
1.Immediate manual adjustment	69% (25)	22% (7)	4% (1)	41% (11)	24% (11)	27% (14)	17% (2)	34% (10)	31% (81)
2.Temporarily separate from MDD system	6% (2)	38% (12)	14% (4)	22% (6)	20% (9)	18% (9)	0% (0)	24% (7)	19% (49)
3.New extra MDD system ordered	0% (0)	0% (0)	0% (0)	4% (1)	9% (4)	0% (0)	0% (0)	0% (0)	2% (5)
4.Deferred until new MDD system	25% (9)	41% (13)	82% (23)	33% (9)	48% (22)	55% (28)	83% (10)	41% (12)	48% (126)
Total	100% (36)	100% (32)	100% (28)	100% (27)	100% (46)	100% (51)	100% (12)	100% (29)	100% (261)

Appendix 2. Individual medication classes on ATC-2 level, type of medication change and procedure used for medication change

ATC classification system	Number of drugs involved (n = 364)	Addition of new medication (n = 127)	Discontinuation of medication (n = 95)	Dose adjustment (n = 123)	Other (n = 19)	Immediate adjusted (n = 210)	Deferred adjusted (n = 154)	p-value *
Cardiovascular medication	**133**	**33% (44)**	**35% (47)**	**26% (35)**	**5% (7)**	**69% (92)**	**31% (41)**	**0.017**
B01 - Antithrombotic agents	17	29% (5)	53% (9)	12% (2)	6% (1)	65% (11)	35% (6)	
C01 - Cardiac therapy	9	11% (1)	33% (3)	33% (3)	22% (2)	78% (7)	22% (2)	
C03 - Diuretics	30	47% (14)	20% (6)	27% (8)	7% (2)	63% (19)	37% (11)	
C07 - Beta blocking agents	26	27% (7)	31% (8)	42% (11)	0% (0)	73% (19)	27% (7)	
C08 - Calcium channel blockers	19	42% (8)	47% (9)	11% (2)	0% (0)	79% (15)	21% (4)	
C09 - Agents acting on the renin-angiotensin system	18	33% (6)	33% (6)	33% (6)	0% (0)	83% (15)	17% (3)	
C10 - Lipid modifying agents	14	21% (3)	43% (6)	21% (3)	14% (2)	43% (6)	57% (8)	
Psycho(ana)leptic medication	**53**	**26% (14)**	**13% (7)**	**53% (28)**	**8% (4)**	**47% (25)**	**53% (28)**	**0.439**

N05 - Psycholeptics	36	22% (8)	11% (4)	56% (20)	11% (4)	56% (20)	44% (16)	
N06 - Psychoanaleptics	17	35% (6)	18% (3)	47% (8)	0% (0)	29% (5)	71% (12)	
Other medication	**32**	**44% (14)**	**31% (10)**	**19% (6)**	**6% (2)**	**56% (18)**	**44% (14)**	**0.546**
G03 - Sex hormones and modulators of the genital system	1	0% (0)	0% (0)	100% (1)	0% (0)	0% (0)	100% (1)	
G04 - Urologicals	8	63% (5)	25% (2)	13% (1)	0% (0)	63% (5)	37% (3)	
H03 - Thyroid therapy	1	0% (0)	0% (0)	100% (1)	0% (0)	100% (1)	0% (0)	
H05 - Calcium homeostasis	2	50% (1)	0% (0)	50% (1)	0% (0)	0% (0)	100% (2)	
L02 - Endocrine therapy	4	50% (2)	50% (2)	0% (0)	0% (0)	100% (4)	0% (0)	
N07 - Other nervous system medicines	2	50% (1)	50% (1)	0% (0)	0% (0)	50% (1)	50% (1)	
R03 - Medication for obstructive airway diseases	1	100% (1)	0% (0)	0% (0)	0% (0)	0% (0)	100% (1)	
R05 - Cough and cold preparations	2	50% (1)	50% (1)	0% (0)	0% (0)	50% (1)	50% (1)	
R06 - Antihistamines for systemic use	8	38% (3)	38% (3)	0% (0)	25% (2)	38% (3)	62% (5)	
V03 - All other therapeutic products	3	0% (0)	33% (1)	67% (2)	0% (0)	100% (3)	0% (0)	
Medication used in diabetes	**28**	**4% (1)**	**18% (5)**	**75% (21)**	**4% (1)**	**68% (19)**	**32% (9)**	**0.043**
A10 - medication used in diabetes	28	4% (1)	18% (5)	75% (21)	4% (1)	68% (19)	32% (9)	
Gastrointestinal medication	**27**	**41% (11)**	**26% (7)**	**22% (6)**	**11% (3)**	**58% (14)**	**42% (13)**	**0.272**
A02 - Medication for acid related disorders	23	48% (11)	22% (5)	17% (4)	13% (3)	52% (12)	48% (11)	
A03 - Medication for functional gastrointestinal disorders	1	0% (0)	100% (1)	0% (0)	0% (0)	100% (1)	0% (0)	
A06 - Medication for constipation	2	0% (0)	0% (0)	100% (2)	0% (0)	0% (0)	100% (2)	
A09 - Digestives, including enzymes	1	0% (0)	100% (1)	0% (0)	0% (0)	100% (1)	0% (0)	
Vitamins and minerals	**25**	**72% (18)**	**24% (6)**	**4% (1)**	**0% (0)**	**36% (9)**	**64% (16)**	**0.032**
A11 - Vitamins	11	91% (10)	0% (0)	9% (1)	0% (0)	22% (2)	78% (9)	
A12 - Mineral supplements	3	67% (2)	33% (1)	0% (0)	0% (0)	67% (2)	33% (1)	
B03 - Antianemic preparations	10	50% (5)	50% (5)	0% (0)	0% (0)	40% (4)	60% (6)	
Y -	1	100% (1)	0% (0)	0% (0)	0% (0)	100% (1)	0% (0)	
Antibiotics and corticosteroids	**22**	**64% (14)**	**5% (1)**	**32% (7)**	**0% (0)**	**77% (17)**	**23% (5)**	**0.823**
J01 - Antibacterials for systemic use	11	91% (10)	9% (1)	0% (0)	0% (0)	78% (9)	22% (2)	
H02 - Corticosteroids for systemic use	11	36% (4)	0% (0)	64% (7)	0% (0)	62% (8)	38% (3)	
Antiepileptic and antiparkinson medication	**16**	**13% (2)**	**25% (4)**	**56% (9)**	**6% (1)**	**50% (8)**	**50% (8)**	**0.524**
N03 - Antiepileptics	12	17% (2)	33% (4)	42% (5)	8% (1)	33% (4)	67% (8)	
N04 - Anti-parkinson medication	4	0% (0)	0% (0)	100% (4)	0% (0)	100% (4)	0% (0)	
Analgetic medication	**14**	**29% (4)**	**215 (3)**	**50% (7)**	**0% (0)**	**29% (4)**	**71% (10)**	**0.091**
N02 - Analgesics	9	22% (2)	22% (2)	56% (5)	0% (0)	33% (3)	67% (6)	
M01 - Anti-inflammatory and antirheumatic products	5	40% (2)	20% (1)	40% (2)	0% (0)	20% (1)	80% (4)	

Anti-rheumatics and antigout medication	**14**	**36% (5)**	**36% (5)**	**21% (3)**	**7% (1)**	**29% (4)**	**71% (10)**	**0.076**
L04 - Immunosuppressants	1	100% (1)	0% (0)	0% (0)	0% (0)	100% (1)	0% (0)	
M04 - Antigout preparations	4	25% (1)	0% (0)	75% (3)	0% (0)	25% (1)	75% (3)	
M05 - Medication for treatment of bone diseases	7	14% (1)	(5) 71%	0% (0)	14% (1)	14% (1)	86% (6)	
P01 - Antiprotozoals	2	100% (2)	0% (0)	0% (0)	0% (0)	50% (1)	50% (1)	

* Adjusted for age, prescriber, number of medicines involved in medication change and type of medication change.

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